PHARMLINK FDA 警告信翻译系列

Warning Letters

目录 Table of Contents

1. 320-20-01 2019-10-03 Glenmark Pharmaceuticals Limited 印度

Dear Mr. Saldanha:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Glenmark Pharmaceuticals Limited, FEI 3005757050, at Village Kishanpura, Baddi Nalagarh Road, Baddi Solan, Himachal Pradesh, from April 15 to 20, 2019.

美国 FDA 于 2019 年 4 月 15 日至 20 日检查了你们位于印度的 Glenmark PharmaceuticalsLimited 生产场所。

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

本警告信总结了制剂生产严重违反 CGMP 的行为。参见 21CFR 第 210 与 211 部分。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

由于你们的制剂生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的药品根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C. 351(a)(2)(B)被认为是掺假药品。

We reviewed your May 10, 2019, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

我们已详细审核了你公司 2019 年 5 月 10 日的回复，并此告知已收到后续通信。

During our inspection, our investigators observed specific violations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether the batch has already been distributed (21 CFR 211.192).

你公司未能彻底调查所有未解释的差异，或已销售和未销售药品批次及其组份不符合其质量标准的情形（21 CFR 211.192）。

Your firm failed to ensure your investigations identify appropriate root causes and you failed to implement sustainable corrective action and preventive action (CAPA).

你公司未能确保你们的调查识别出适当的根本原因，你们未实施可持续的 CAPA。

a. You failed to thoroughly investigate multiple complaints of grittiness for your topical (b)(4) cream USP, (b)(4)%. Since November 2017, you rejected 20 batches and received at least 38 complaints about product grittiness. Product grittiness has been an ongoing formulation issue since 2010 and was a deficiency cited in the previous inspection of your facility. You proposed specific remediation for this formulation issue in your response at that time. In your response to the most recent inspection, you stated that the product grittiness issue was remediated during product reformulation in November 2018. Your response is inadequate. You did not provide sufficient data to demonstrate the robustness of the new formulation.

你们未能彻底调查多起你们局部 XX 膏的细度投诉。自 2017 年 11 月以来，你们拒收了 20 批次，并且收到了至少 38 起关于药品细度的投诉。自 2010 年以来，产品细度一直就是一个问题，在之前对你工厂的检查中就指出过该缺陷。你们当时在回复中对此提出了具体的补救措施。在你们对最近检查的回复中，你们声称产品细度问题在 2018 年 11 月产品配方修改中已得到改正。你们的回复是不充分的。你们并未提供足够的数据证明新配方的耐用性。

We acknowledge that in July 2019 you recalled all batches within expiry that were manufactured using the original formulation. However, your reformulation and market actions were not performed in a timely manner.

我们了解 2019 年 7 月你们召回了使用原来配方所生产的在效期内的所有批次。但是，你们修改配方和采取市场措施不够及时。

b. You failed to adequately investigate multiple temperature excursions that occurred during shipping of your drug products. Your investigations into the temperature excursions did not include timely actions to prevent their recurrence.

你们未能充分调查多起你们药品在运输途中温度超范围的情况。你们对温度超范围情况的调查未包括采取及时措施防止其再次发生。

For example, in May 2018, (b)(4) cream USP, (b)(4)% batches were exposed to temperature excursions up to (b)(4)°C and (b)(4)°C for (b)(4) while in transit to the United States. (b)(4) cream should be stored between (b)(4)°C. In July 2018, a (b)(4)USP, (b)(4)% batch was exposed to (b)(4)°C for (b)(4) while in transit to theUnited States. (b)(4) should be stored between (b)(4)°C. These (b)(4) batches were distributed to the U.S.

例如，2018 年 5 月，XX 膏 XX 批号暴露于超范围温度中，在运至美国期间温度达 XX°C 和 XX°C。XX 膏应存贮在 XX°C 之间。2018 年 7 月，XX 批号在运输至美国期间暴露于 XX°CXX 时长。XX 应存贮在 XX°C 之间。这些 XX 批次已销售至美国。

Inadequate investigation into temperature excursions is an ongoing issue and was a deficiency cited during the previous inspection of your facility. Notably, you performed a study to determine the impact of elevated temperature on (b)(4) cream USP, (b)(4)%. The study showed phase separation of the product at (b)(4)°C.

对温度超范围调查不充分的问题一直存在，在上次对你公司的现场检查中亦曾引用该缺陷。值得注意的是，你们进行了一项研究来确定 XX 膏在升高温度时受到的影响。研究表明产品在 XX°C 时会有分相。

In your response, you stated that you will performan additional temperature excursion study as well as conduct a long-term stability study. You also stated that you will investigate all confirmed out-of-specification (OOS) results during the temperature excursion studies and will notify the FDA,as appropriate.

在你们的回复中，你们声称你们将执行更多温度超范围研究，并进行长期稳定性研究。你们还声称你们将调查所有在温度超范围研究中已确认的 OOS 结果，并在适当时通知 FDA。

Your response is inadequate. You did not provide an adequate risk assessment for marketed batches exposed to temperatures outside the labeled storage conditions. Also, your response

mentioned the implementation of new shipping practices to protect your products from thermal excursions, but they were not implemented in a timely manner.

你们的回复是不充分的。你们并未提交充分已销售批次暴露于超出标示存贮条件指定温度的风险评估。并且你们的回复提到实施了新的运输方式来保护你们产品，使其温度不会超范围，但该措施执行不够及时。

c. You failed to adequately investigate multiple OOS test results for critical product attributes, such as (b)(4) For example, in April 2018, (b)(4) batch (b)(4) failed (b)(4) Additionally, in February 2019, (b)(4) ointment USP (b)(4)% batch (b)(4) failed (b)(4) These batches were ultimately rejected. However, your investigations into these failures did not determine an appropriate root cause and ensure effective CAPA.

你们未能充分调查多起关键产品属性的 OOS 检测结果，如 XX。例如，2018 年 4 月，XX 批 XX 项不合格。另外，2019 年 2 月，XX 膏 XX 不合格。这些批次最后均被拒收。但是你们对这些不合格的调查并未确定适当的根本原因，确保 CAPA 有效。

In your response, you indicated that you plan to hire a consultant to enhance the quality of your investigations. Your responseis inadequate. You did not assess the potential impact to product quality and the failure to identify potential root causes.

在你们的回复中，你们说你们计划聘请顾问改进你们的调查质量。你们的回复是不充分的。你们并未评估对产品质量的潜在影响，未能识别出可能的根本原因。

d. You failed to adequately investigate more than 70 consumer complaints associated with punctures, cracks, and holes in (b)(4) for various drug products including, but not limited to, (b)(4) ointment USP, (b)(4)%, (b)(4) cream USP, and (b)(4) ointment USP, (b)(4)%. Your investigations failed to adequately address the scope and cause of these serious container/closure system defects and evaluate other drug products that have similar manufacturing quality signals such as complaints, or that use the same supplier.

你们未能充分调查超 70 起关于不同药品包括但不仅限于 XX 膏、XX 霜和 XX 膏的穿孔、裂纹和孔洞方面的客户投诉。你们的调查未能充分界定这些严重的容器密闭器系统缺陷的范围和原因，未评估其它有着相同生产质量信号的药品如投诉，或使用相同供应商的药品。

In your response, you stated that the root cause for the complaints was improper “handling by folding and refolding of the (b)(4)” by consumers. In addition, you stated that because the complaint rate is insignificant, there is no risk to marketed batches. However, you closed more than 50 of the complaints, without CAPA to prevent recurrence of similar quality defects.

在你们的回复中，你们声称投诉的根本原因是客户“XX 折叠和再次折叠”不当。另外，你们声称因为投诉率不高，因此已销售批次没有风险。你们关闭了超 50 起投诉却没有 CAPA 预防类似质量缺陷的重复发生。

Your quality system for investigations is inadequate and does not ensure consistent production of safe and effective products. Your firm has repeatedly failed to determine the root cause and implement CAPA to prevent the recurrence of these serious product quality defects.

你们的调查质量体系不充分，不能确保持续生产出安全有效的药品。你公司多次未能确定根本原因，未能实施 CAPA 以防止这些严重药品质量缺陷的重复发生。

In response to this letter, provide the following:

在回复本函时请提交以下：

- A comprehensive, independent assessment of your overall system for investigating deviations, discrepancies, complaints, OOS results, and failures. Provide a detailed action plan to remediate this system. Your action plan should include, but not be limited to, significant improvements in investigation competencies, scope determination, root cause evaluation, CAPA effectiveness, quality unit oversight, and written procedures. Address how your firm will ensure all phases of investigations are appropriately conducted.

  一份对你公司全面偏差、差异、投诉、OOS 结果和失败调查体系的全面独立评估。提交一份详细的行动计划补救该系统。你们的行动计划应包括但不仅限于大大改进调查能力、范围界定、根本原因评估、CAPA 有效性、质量部门监管和书面程序。说明你们公司要如何确保所有调查阶段均有适当实施。
- An independent assessment and remediation plan for your CAPA program. Summarize how your firm will effectively conduct root cause analysis, assure CAPA effectiveness, regularly review investigation trends, enhance staff competencies, implement improvement to the CAPA program when needed, ensure appropriate quality unit decision rights, and is fully supported by executive management.

  一份对你们 CAPA 程序的独立评估和补救计划。总结你们公司要如何有效执行根本原因分析、确保 CAPA 有效性、定期回复调查趋势、提高员工能力、必要时实施 CAPA 程序改进、确保适当质量部门决策权，以及高级管理人员的全面支持。
- A detailed review of the robustness of the new formulation for (b)(4) cream USP, (b)(4)%, including but not limited to all manufacturing and quality data (e.g., complaints, OOS, deviations, rejects, stability, data to fully assess whether the new formulation is robust or not).

  一份对 XX 膏新配方耐用性的详细审核，包括但不仅限于所有生产和质量数据（例如，投诉、OOS、偏差、拒收、稳定性数据，以全面评估新配方是否耐用）。
- A comprehensive, independent review of your material system to determine whether all suppliers of components, containers, and closures, are each qualified and the materials are assigned appropriate expiration or retest dates. The review should also determine whether incoming material controls are adequate to prevent use of unsuitable components, containers, and closures.

  一份对你们物料体系的全面独立审核，以确定是否所有成分、容器和密闭器的供应商均经过确认，给物料全部给定了有效期或复验期。审核亦应确定对进厂物料的控制是否足以防止使用不适当的成分、容器和密闭器。
- Independent review of all your processes to determine their state ofcontrol. Also, provide your detailed program for designing, validating,maintaining, controlling and monitoring each of your manufacturing processes that includes vigilant monitoring of intra-batch and inter-batch variation to ensure an ongoing state of control. Also include your qualification program for your equipment and facility.

  对你们所有工艺的独立审核，以确定其受控状态。亦请提交一份你们设计、验证、维护、控制和监控你们每个生产工艺的详细计划，其中包括严格监测批间和批内波动性，以确保持续受控状态。亦要包括你们设备和设施的确认程序。

Conclusion 结论

The violations cited in this letter are not intended to be an all-inclusive statement of violations that exist at your facility. You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of other violations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staffalso allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b) and allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

如果你们在考虑要采取的措施可能会导致你们工厂所生产的药品供应中断，FDA 要求你立即联系 CDER 药品短缺负责人员，这样 FDA 可以与你们一起采用最为高效的方式引导你们的操作符合法规要求。联系药品短缺负责人员还能让你满足依据 21U.S.C. 356C(b)你可能必须报告你们药品中止或中断的义务，让 FDA 尽快考虑是否需要采取何种措施来避免短缺，保护依赖于你们药品的患者健康。

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产的新申报和增补申报的批准。

Failure to correct these violations may also result in the FDA refusing admission of articles manufactured at Glenmark Pharmaceuticals Limited, at Village Kishanpura, Baddi Nalagarh Road, Baddi Solan, Himachal Pradesh, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Articles under this authority may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

2. 320-20-02 2019-10-03 Bingbing Pharmaceutical Co., Ltd 兵兵药业有限公司

Dear Mr. Yu:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Bingbing Pharmaceutical (Hubei) Co.Ltd., FEI 3014538973, at No. 698 Bingbing Road, Economic Development Zone,Shiyan, Hubei, from May 7 to 10, 2019.

美国 FDA 于 2019 年 5 月 7 日至 10 日检查了你们位于湖北十堰市郧阳经济开发区兵兵路 698 号的冰冰药业（湖北）有限公司生产场所。

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

本警告信总结了制剂生产严重违反 CGMP 的行为。参见 21CFR 第 210 与 211 部分。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act),21 U.S.C. 351(a)(2)(B).

由于你们的制剂生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的药品根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C. 351(a)(2)(B)被认为是掺假药品。

We reviewed your May 31, 2019, responseto our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

我们已详细审核了你公司 2019 年 5 月 31 日的回复，并此告知已收到后续通信。

During our inspection, our investigator observed specific violations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

1. Your firm failed to maintain written production, control, or distribution records specifically associated with a batch of a drug product for at least one year after the expiration date of the batch (21 CFR 211.180(a)).

你公司未能保存与药品批次有关的具体的书面生产、检测或销售记录至该批次效期后至少 1 年（21CFR 211.180(a)）。

You manufactured drugs at your Wuhan facility at Building (b)(4), No. 5, Kangda Street, Longyang Avenue, Hanyang District, Wuhan, and then transferred drug production to your Hubei facility and closed the Wuhan facility. Your firm failed to maintain manufacturing records, raw material and finished product testing records, retain samples, stability samples, and other CGMP records for your over-the-counter (OTC) (b)(4) drug products manufactured at your Wuhan facility. During the inspection at the Hubei facility, you stated that you lost CGMP manufacturing documentation and drug product samples during the transfer of your manufacturing facility from Wuhan to Hubei in May 2018.

你们在你们的武汉场所武汉市汉阳区龙阳大道康达街 5 号 XX 楼生产药品，然后将药品转移至你们的湖北场所，然后关闭了武汉场所。你们公司未能保存你们在武汉场所生产的 OTC 药品 XX 的生产记录、原料和成品检测记录、留样、稳定性样品和其它 CGMP 记录。在湖北场所检查期间，你们声称你们在 2018 年 5 月将生产场所从武汉转移至湖北时丢失了 CGMP 生产文件和药品样品。

In your response, you stated that you initiated an investigation to assess the scope of impacted product, will attempt to collect samples from the market to evaluate and take “all mandatory and necessary measures,” and will conduct a quality system evaluation using a third-party consultant. Your response is inadequate because you failed to appropriately address the impact of missing records and samples on drug products already on the market. Maintaining all manufacturing and testing records, as well as representative product samples, is critical to establish that your products meet their required quality attributes.

在你们的回复中，你们声称你们已启动了调查来评估受影响药品的范围，将努力从市场上采集样品来评估，并采取“所有法定和必要措施”，以及使用第三方顾问执行质量体系评估。你们的回复是不充分的，因为你们并未适当解决丢失记录和样品对已在市场销售的药品的影响。保存所有生产和检测记录以及代表性产品样品对于确定你们的药品符合其所需质量属性来说是很关键的。

In response to this letter, provide:

在回复本函时请提交

- A complete, independent assessment of documentation systems used throughout your manufacturing and laboratory operations to determine where documentation practices are insufficient. Include a detailed corrective action and preventive action (CAPA) plan that comprehensively remediates your firm’s documentation practices to ensure you retain attributable, legible, complete, original, accurate, contemporaneous records throughout your operation.
  一份在你们生产和实验室操作中所用的文件体系的全面独立评估，以确定文件规范是否不充分。包括详细的 CAPA 计划，全面补救你们公司的文件规范，确保你们保存了你们所有操作的可追溯、清晰、完整、原始、准确、同步的记录。
- A detailed risk assessment of drug products on the market without any manufacturing documentation and without retains or stability samples to support investigations and expiration dating. Specify actions, with timelines, that you will take in response to the risk assessment, such as customer notifications and initiating recalls.
  一份对没有任何生产记录、没有留样或稳定性样品支持调查和有效期的在市场上的药品的详细风险评估。说明你们根据风险评估将要采取的措施以及时间表，例如通知客户和启动召回。

2. Your firm failed to have, for each batch of drug product, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release (21 CFR 211.165(a))。

你公司未对每批药品在放行之前进行适当的实验室检测，确保其符合药品的最终质量标准，包括每种活性成分的鉴别和剂量（21 CFR 211.165(a)）。

Your firm released OTC drug products to the United States market without testing the identity and strength of each active ingredient. For example, your firm failed to test for the active ingredients, (b)(4),in your (b)(4) products. Testing is essential to ensuring that the drug products you manufacture meet established specifications for the required chemical attributes.

你公司未检测每种活性成分的鉴别和剂量即将 OTC 药品放行至美国市场。例如，你公司未检测你们 XX 药品中 XX 活性成分。为确保你们所生产的药品符合所需化学属性的既定标准，必须进行检测。

We acknowledge your commitment to discontinue the manufacture and distribution of (b)(4) products until analytical methods for (b)(4) active ingredients have been established and validated or verified. However, your response is inadequate. You failed to provide details for establishing that your OTC drug products in distribution meet their specifications.

我们知晓你们承诺会停止生产和销售 XX 产品，直到建立 XX 活性成分的分析方法并经过验证或确认。但是你们的回复是不充分的。你们未能提交建立你们在销 OTC 药品符合其质量标准的详细资料。

In response to this letter, provide a list of chemical and microbial specifications, including test methods, used to an alyzeeach lot of your drug products before a lot disposition decision. The list should include:

在回复本函时，请提交一份用于在批处置决策之前分析每批药品的化学和微生物质量标准清单，包括检测方法。该清单应包括：

- An action plan andtimelines for conducting full chemical and microbiological testing of retain samples to determine the quality of all batches of drug product distributed tothe United States within expiry as of the date of this letter.
- 对留样执行全面化学和微生物检测的行动计划和时间表，以确定所有已销售至美国在本函签发时仍在效期内批次的质量。
- A summary of all results obtained from testing retain samples from each batch. If such testing reveals substandard quality drug products, take rapid corrective actions, suchas notifying customers and product recalls.
- 一份对每个批次留样检测所得的所有结果汇总。如果检测显示有不符合质量要求的药品，则采取快速纠正措施，如通知客户和产品召回。

3. Your firm's quality control unit failed to exercise its responsibility to ensure drug products manufactured are in compliance with CGMP, and meet established specifications for identity, strength, quality, and purity (21 CFR 211.22).

你公司质量部门未能履行其职责从而确保所生产的药品符合 CGMP，并且符合既定的鉴别、剂量、质量和纯度标准（21 CFR 211.22）。

During the inspection, our investigator observed that your quality unit (QU) did not provide adequate oversight for the manufacture of your OTC (b)(4). For example, your QU failed to ensure:

在检查中，我们的检查员发现你们质量部门并未对你们的 OTC 生产进行充分的监管。例如你们质量部门未能确保：

- Full testing of drug products and review of their results are performed prior to batch release.
  在批次放行之前药品进行了全面检测并且对其结果进行了审核
- Contract laboratory used for identity testing is qualified following your written procedures.
  用于鉴别测试的合同实验室根据你们的书面程序进行确认
- Cleaning validation of shared (b)(4) tanks include justifications for the worst-case sampling locations following your cleaning validation procedure.
  共用 XX 罐的清洁验证，包括根据你们的清洁验证程序对最差取样位置进行论证
- Written procedures for sampling and testing of the (b)(4) system are followed.
  执行 XX 系统的取样的检测书面程序

- Procedures to review electronic data generated from GC, HPLC, IR, and TOC systems are written and followed.
  具备并遵守书面的 GC、HPLC、IR 和 TOC 系统电子数据审核程序
- Controlled records, including logs, are maintained to track receipt of all components used to manufacture drug products.
  保存并追踪药品生产所用所有组份接收的受控记录，包括日志
- Every OOS resultis appropriately investigated and each investigation is extended to all affected batches, as applicable.
  每个 OOS 结果均经过适当调查，且每次调查均延伸至所有受影响批次（适用时）

In your response, you admitted that due to cash flow problems you "were unable to ensure all products were completely tested and ensure conformance with all pre-determined specification prior to be shipped out". You also submitted numerous CAPA to address each example of your quality unit failures cited above.

在你们回复中，你们承认由于现金流问题，你们"未能确保所有药品在发货之前均经过完整检测，并确保符合所有预定的质量标准"。你们亦提交了大量 CAPA 来解决上面所引用的所有质量部门失败例子。

Because you failed to include supporting documentation, your response is inadequate and cannot be fully evaluated. You also failed to conduct a comprehensive review of your quality unit to identify deficiencies. You did not provide evidence that you have implemented procedures that ensure adequate control over your drug manufacturing processes. In addition, you failed to include a plan to address the quality of your drugs that were manufactured without appropriate quality oversight.

由于你们未能包括支持性文件，你们的回复是不充分的，不能进行全面评估。你们亦未能对你们质量部门执行全面审核以发现缺陷。你们未能提交证据证明你们已执行确保对你们药品生产工艺进行充分控制的程序。另外，你们未能包括一份计划如何解决你们在没有恰当质量监管情况下所生产的药品的质量问题。

In response to this letter, provide:

在回复本函时请提交：

- A comprehensive assessment and remediation plan to ensure your QU is given the authority and resources to effectively function. The assessment should include, but not be limited to:
  一份全面评估和补救计划，确保你们质量部门被授予了权力和资源进行有效工作。该评估应包括但不仅限于：
  - A determination of whether procedures used by your firm are robust and appropriate.
    确定你们公司所用程序是否稳健恰当
  - Provisions for QU oversight throughout your operations to evaluate adherence to appropriate practices.
    质量部门对你们整个运行的监管规定，以评估遵守适当规范的情况
  - A complete and final review of each batch and its related information before the QU disposition decision.
    一份在 QU 处置决策之前对每个批次及其相关信息的完整最终审核
  - Oversight and approval of investigations and discharging of all other QU duties to ensure identity, strength, quality, and purity of all products.

对调查的监管和批准，以及所有其它 QU 为确保所有药品鉴别、剂量、质量和纯度的职责履行情况

- Also describe howtop management supports quality assurance and reliable operations, including but not limited to timely provision of resources to proactively address emerging manufacturing/quality issues and assure a continuing state of control.
  亦请说明最高管理人员如何支持质量保证和可靠运行，包括但不仅限于及时提供资源，主动解决新发生的生产/质量问题，以及确定持续受控状态

- A comprehensive, independent assessment of your overall system for investigating deviations, discrepancies, complaints, OOS results, and failures. Provide a detailed action plan to remediate this system. Your action plan should include, but not be limited to, significant improvements in investigation competencies, scope determination, root cause evaluation, CAPA effectiveness, quality assurance oversight, and written procedures. Describe how your firm will ensure all phases of investigations are appropriately conducted.
  一份对你们偏差、差异、投诉、OOS 结果和失败调查的整体系统的全面独立评估。提交一份详细该系统补救行动计划。你们的行动计划应包括但不仅限于在调查能力、范围确定、根本原因评估、CAPA 有效性、质量保证监管以及书面程序方面的重大改进。说明你们公司要如何确保恰当执行调查的所有阶段

See FDA's guidance document Quality Systems Approach to Pharmaceutical CGMP Regulations for help implementing quality systems and risk management approaches to meet the requirements of CGMP regulations 21 CFR, parts 210 and 211 at https://www.fda.gov/media/71023/download.

参见 FDA 指南文件。

4. Your firm failed to maintain an adequate written record of each complaint (21 CFR211.198(b)).

你公司未保存每个投诉的充分书面记录（21 CFR 211.198(b)）。

You firm failed to maintain a complete and accurate record of your complaint investigations. You opened investigations B-18002 and B-19001 in response to complaints of poor (b)(4) for batches manufactured in Wuhan. In these investigations you stated that you evaluated reserve samples and found no deficiencies. However, you had previously stated that all reserve samples were lost for batches manufactured at your Wuhan site and therefore reserve samples were not available for evaluation.

你公司未能保存你们投诉调查的完整准确记录。你们因武汉所生产的批次不良 XX 投诉事件启动了 B-18002 和 B-19001 调查。在这些调查中你们声称你们评估了留样，没有发现缺陷。但是你们之前声称在你们武汉场所生产批次的所有留样均已丢失，无法取得进行评估。

In your response, you stated that testing was performed on reserve samples manufactured in your Hubei facility. Your responseis inadequate because testing a batch that is different from the complaint batch does not provide you with batch specific information needed to identify potential quality defects in the complaint batch.

在你们的回复中，你们声称该测试使用你们武汉场所生产的留样进行的。你们的回复是不充分的，因为测试批次不同于投诉批次，无法为你们提供特定批次的信息用于识别被投诉批次的潜在质量缺陷。

In response to this letter, provide:

在回复本函时请提交：

- The status of lots identified in investigations B-18002 and B19001.
  在调查 B-18002 和 B19001 中所识别的批次的状态
- Your plan for evaluating complaints for batches manufactured in your Wuhan facility.
  你们评估在武汉场所生产的批次投诉的计划
- The process you will follow if a complaint cannot be appropriately investigated. Indicate the corrective actions you will take including notifying customers and initiating recalls.
  如果无法对投诉进行恰当调查时，你们要遵循的流程。说明你们将采取的纠正措施，包括通知客户和启动召回。

Data Integrity Remediation 数据完整性补救措施

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. See FDA's guidance document Data Integrity and Compliance With Drug CGMP for guidance on establishing and following CGMP compliant data integrity practices at https://www.fda.gov/media/119570/download.

你们的质量体系不能充分确保数据的准确性和完整性，无法支持你们生产的药品的安全性、有效性和质量。参见 FDA 指南文件"数据完整性和药品 GMP 合格"指导建立和遵守 CGMP 合格数据完整性规范。

We strongly recommend that you retain a qualified consultant to assist in your remediation. In response to this letter, provide the following:

我们强烈建议你们聘用一位有资质的顾问协助你们进行补救。在回复此函时请提交以下信息：

- A comprehensive investigation into the extent of the inaccuracies in data records and reporting, including results of the data review for drugs distributed to the United States. Include a detailed description of the scope and root causes of your data integrity lapses.
  一份对数据记录和报告不准确性程度的全面调查，包括销售至美国的药品的数据审核结果。包括对你们数据完整性问题的范围与根本原因的详细说明。
- A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity and analyses of the risks posed by ongoing operations.
  你们药品质量中所发现的不合格情况的潜在影响的当前风险评估。你们的评估应包括由于受到数据完整性问题影响的药品放行导致的患者风险的分析，以及持续运营所具有的风险。
- A management strategy for your firm that includes the details of your global corrective action and preventive action plan. The detailed corrective action plan should describe how you intend to ensure the reliability and completeness of all data generated by your firm including microbiological and analytical data, manufacturing records, and all data submitted to FDA.
  你们公司的管理策略，包括你们全球 CAPA 计划详细情况。详细的整改措施计划应说明你们准备如何确保你们公司所生成的所有数据的可靠性与完整性，包括微生物和分析数据、生产记录以及所有提交给 FDA 的数据。

Conclusion 结论

The violations cited in this letter are not intended to be an all-inclusive statement of violations that exist at your facility. You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of other violations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

FDA placed your firm on Import Alert 66-40 on August 22, 2019.

FDA 已于 2019 年 8 月 22 日将你公司置于进口禁令 66-40 中。

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产的新申报和增补申报的批准。

Failure to correct these violations may also result in the FDA continuing to refuse admission of articles manufactured at Bingbing Pharmaceutical (Hubei) Co., Ltd, at No. 698 Bingbing Road, Economic Development Zone, Shiyan, Hubei, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Articles under this authority may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

3. 320-20-03 2019-10-08 Torrent Pharmaceuticals Limited 印度

Dear Mr. Mehta:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Torrent Pharmaceuticals Limited, FEI 3005029956, at Ahmedabad-Mehsana Highway, Taluka-Kadi, Indrad, Gujarat from April 8 to 16, 2019.

美国 FDA 于 2019 年 4 月 8 日至 16 日检查了你们位于印度的 Torrent Pharmaceuticals Limited 生产场所。

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

本警告信总结了制剂生产严重违反 CGMP 的行为。参见 21CFR 第 210 与 211 部分。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

由于你们的制剂生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的药品根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C. 351(a)(2)(B)被认为是掺假药品。

We reviewed your May 7, 2019, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

我们已详细审核了你公司 2019 年 5 月 7 日对我们 FDA483 表的回复，并此告知已收到后续通信。

During our inspection, our investigators observed specific violations and deviations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

1. Your firm failed to follow written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess (21 CFR211.100(b)).

你公司未能遵守书面的生产和工艺控制程序，这些程序是设计用以确保你们生产的药品具备其理当具备的鉴别、剂量、质量和纯度的（21 CFR 211.100(b)）。

Your firm did not appropriately follow your written and approved process validation (PV) protocol which required quality attributes to be met for “three consecutives” batches to qualify an alternate active pharmaceutical ingredient (API). Several PV batches using a new alternate API were manufactured for Losartan Potassium Tablets USP 50 mg and USP 100 mg without appropriately following your protocol.

你公司并未恰当遵守你们批准的书面工艺验证（PV）方案。该方案要求“连续三批”符合所要求的质量属性，用以确认替代 API。使用新的替代 API 生产的几个 PV 批次氯沙坦钾 50mg 和 100mg 片剂并未恰当遵守你们的方案。

Specifically, after the first of the three PV batches failed for dissolution, assay, and (b)(4), your firm added a fourth batch which was outside of your written protocol. However, the fourth batch also

failed specifications for dissolution. Multiple out-of-specification (OOS) investigations were initiated and quality rejected all four PV batches.

具体来说，在三批 PV 的第一批溶出度、含量和 XX 不合格之后，你公司增加了第 4 批，这不在你们书面方案内。但是第 4 批溶出度亦不合格。你们发起了多起 OOS 调查，质量部门拒收了所有 4 个 PV 批次。

You developed a new interim protocol to justify commercial use of the alternate API and circumvented your original protocol, even though you had data demonstrating your process was not capable of producing quality material using the new alternate API. Numerous Losartan Potassium Tablets USP 50 mg and USP 100 mg commercial batches were manufactured with this new alternate API and released to the U.S. market despite the PV failures. In addition, multiple batches of Losartan Potassium were recalled for unacceptable amounts of nitrosamine impurities.

即使你们有数据证明你们的工艺采用新的替代 API 并不能生产出具备质量的物料，你们制订了新的临时方案，用以论证替代 API 的商业用途，并且替代你们的原始方案。虽然 PV 失败，但你们使用新的替代 API 生产了大量商业批次的氯沙坦钾 50mg 和 100mg 片剂，并且放行至美国市场。另外，多批氯沙坦钾由于亚硝胺杂质数量达到不可接受水平而被召回。

Your response acknowledged that you did not follow your written and approved validation protocols. You also stated the change in API had no impact on the manufacturing process and the quality of the finished drug. Your response is inadequate. You failed to provide adequate root cause for the initial PV batches failures. You also failed to provide adequate justification in your process validation protocols to support approval of the alternate API with known PV failures.

你们的回复承认你们并未遵守所批准的书面验证方案。你们亦声称 API 变更对生产工艺和药品质量并无影响。你们的回复是不充分的。你们并未提供初始 PV 批准失败的充分根本原因。你们亦未对你们工艺验证方案提交足够的论证，以支持批准已知 PV 失败的替代 API。

Process validation evaluates the soundness of design and state of control of a process throughout its lifecycle. Each significant stage of a manufacturing process must be designed appropriately andassure the quality of raw material inputs, in-process materials, and finished drugs. Process qualification studies determine whether an initial state of control has been established.

工艺验证评估的是工艺在其生命周期中设计合理性和受控状态。生产工艺的每个重大阶段均必须经过适当设计，确保原料输入、中间体和成品的质量。工艺确认研究确定是否已建立起初始的受控状态。

Successful process qualification studies are necessary before commercial distribution of drugs. Thereafter, ongoing vigilant oversight of process performance and product quality is necessary to ensure you maintain a stable manufacturing operation throughout the product lifecycle.

在药品商业化销售之前，需要有成功的工艺确认研究。之后要对工艺性能和产品质量进行持续警惕的监管，以确定你们在产品生命周期中能维持稳定的生产操作。

In response to this letter, provide:

在回复本函时请提交：

- A detailed summary of your validation program for ensuring a state of control throughout the product lifecycle, along with associated procedures. Describe your program for process performance qualification and ongoing monitoring of both intra-batch and inter-batch variation to ensure a continuing state of control.
  一份对你们验证程序的详细总结，确保有相关程序时，在产品生命周期中确保工艺处于受控状态。阐述你们的工艺性能确认程序和对批间与批内波动的持续监控，以确保持续受控状态。
- A timeline for performing appropriate process performance qualification (PPQ) for each of your marketed drug products.
  一份对你们所有上市药品执行恰当工艺性能确认（PPQ）的时间。
- A review of all data that supports your process validation for commercially distributed drug products.
  一份对所有支持你们商业化销售药品的工艺验证的数据的回顾。

See FDA's guidance document Process Validation:General Principles and Practices for general principles and approaches that FDA considers appropriate elements of process validation at https://www.fda.gov/media/71021/download.

参见 FDA 指南文件"工艺验证通则"。

2. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

你公司未能彻底调查所有未经解释的差异，或已销售/未销售批次及其组份不符合其质量标准的情况（21 CFR 211.192）。

Your investigations into OOS testing results were inadequate. Multiple OOS investigations related to assay, (b)(4), and dissolution were closed without assignable root cause, or lacked adequate scientific justification for root cause. Despite the inadequate OOS investigations, your firm disregarded initial failing OOS results and released batches based on retested results.

你们对 OOS 检测结果的调查是不充分的。多起与含量、XX 和溶出度的 OOS 调查在没有可归结根本原因或缺乏足够的根本原因科学论证时即被关闭。尽管 OOS 调查不充分，但你公司不顾初始 OOS 结果，仍根据复测的合格结果放行批次。

For example, OOS investigation OOS/IN/F/FP/17/238 for Losartan Potassium and Hydrochlorothiazide (HCTZ) Tablet (b)(4) for batch number BP02D026 was initiated on July 4, 2017, due to a high HCTZ assay value. The result was super potent, (b)(4)%, versus a (b)(4)–(b)(4)% specification. This OOS result was confirmed during your phase I laboratory investigation without establishing a root cause. During your phase I linvestigation, neither a manufacturing nor laboratory error was conclusively identified. Despite no assignable root cause, the initial high OOS results were invalidated and the (b)(4) was released based on retested reserve sample results. The resulting finished product batch was distributed to the U.S.market.

例如，OOS 调查案例 OOS/IN/F/FP/17/238 为氯沙坦钾和 HCTZ 片剂 XX，批号 BP02D026，于 2017 年 7 月 4 日启动，原因是 HCTZ 含量过高。含量结果为 XX%，标准为 XX%。该 OOS 结果在你们第一阶段实验室调查时得到确认，但并没有得出根本原因。在你们第二阶段调查中，既没有识别出可得出结论的生产错误，亦没有识别出可得出结论的实验室错误。尽管并没有复测根本原因，初始过高 OOS 结果仍被宣布无效，基于复测留样结果放行了 XX。该成品批准在美国市场销售。

Multiple examples of improperly invalidating initial failing OOS results were also observed in other drug products. In addition, your firm has a high percentage rate (60–70%) for invalidated initial OOS test results between January 2017 and March 2019.

多起案例中，你们亦不当宣布其它药品初始 OOS 结果无效。另外，你公司在 2017 年 1 月至 2019 年 3 月期间宣布初始 OOS 结果无效的比例非常高（60-70%）。

Your response indicated your awareness of a high percentage rate of invalidated OOS test results without appropriate investigation. Yous tated that between January 2017 to March 2019, you have a downward trend from77% to 41%. Major contributors are human error, instrument/column error, and method error. Your response is inadequate. You failed to provide ar etrospective review of all your drug products to determine if you are attributing root cause appropriately, reporting OOS results correctly, and implementing adequate corrective and preventive actions (CAPA).

你们的回复表示你们了解你们宣布初始 OOS 结果无效的比例过高，没有恰当的调查。你们声称 2017 年 1 月至 2019 年 3 月期间，你们的趋势已从 77%降至 41%。主要原因是人为失误、仪器/柱错误和方法错误。你们的回复是不充分的。你们未能提交对所有你们药品的回顾性审核，以确定你们是否恰当归结根本原因、正确报告 OOS 结果，并且执行了充分的 CAPA。

This is a repeat observation from FDA's April 17–28, 2017, inspection at your Indrad facility. The FDA also cited a similar CGMP observation for inadequate investigations at your Torrent Pharmaceuticals Limited Dahej facility (FEI 3010228235) in Gujarat during a March 11–19, 2019, inspection.

这是 2017 年 4 月 17-28 日对你们 Indrad 场所检查发现的缺陷的重复。FDA 亦在 2019 年 3 月 11-19 日对你们 Dahej 场所检查中发现了类似的调查不充分缺陷。

Repeated failures at multiple sites demonstrate that executive management oversight and control over the manufacture of drugs is inadequate.

多个场所重复缺陷证明你们对于药品生产的高层管理监管和控制是不充分的。

Your executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance. You should immediately and comprehensively assess your company's global manufacturing operations to ensure that systems, processes, and the products manufactured conform to FDA requirements.

你们的高级管理层对全面解决所有缺陷和确保持续 CGMP 合规负有义务。你们应立即全面评估你公司的全球生产动作，以确保系统、工艺和所生产产品符合 FDA 要求。

In response to this letter, provide: 在回复本函时请提交

- A retrospective, third-party review of all invalidated OOS (including in-process and release/stability testing) results for products currently in the U.S. market and within expiry as of the date of this letter, and a report summarizing the findings of the analysis, including the following for each OOS:
  一份对所有宣布无效的当前在美国销售且在本函签发时仍在效期内的药品的 OOS（包括中间体和放行/稳定性检测）结果的第三方回顾性审核，以及一份汇总分析发现问题的报告，包括每个 OOS 的以下内容：

- Determine whether the scientific justification and evidence relating to the invalidated OOS result conclusively or inconclusively demonstrates causative laboratory error.
  确定宣布 OOS 结果无效的科学论证和证据是否能得出结论证明实验室失败可成为原因
- For investigations that conclusively establish laboratory root cause, provide rationale and ensure that all other laboratory methods vulnerable to the same or similar root cause are identified for remediation.
  对于能得出结论的实验室根本原因，提交原因并确保识别出所有其它受到相同或类似根本原因影响的实验室方法并进行补救
- For all OOS results found by the retrospective review to have inconclusive or no root causes identified in the laboratory, include a thorough review of production (e.g., batch manufacturing records, adequacy of the manufacturing steps, suitability of equipment/facilities, variability of raw materials, process capability, deviation history, complaint history, batch failure history). Summarize potential manufacturing root causes for each investigation, and any manufacturing operation improvements.
  对于所有在回顾性审核中发现实验室原因不能得出结论或未识别出化验室根本原因的 OOS 结果，包括一份对生产的彻底审核（例如，批生产记录、生产步骤的充分性、设备/设施的适当性、原料的波动性、工艺能力、偏差历史、投诉历史、批失败历史）。总结每起调查中潜在的生产根本原因，以及所有生产操作改进。
- A comprehensive review and remediation plan for your OOS result investigation systems. The CAPA should include but not be limited to the following:
  一份对你们 OOS 结果调查系统的全面审核和补救计划。CAPA 应包括但不仅限于以下：
  - Quality unit oversight of laboratory investigations.
    质量部门对实验室调查的监管
  - Identification of adverse laboratory control trends.
    识别出不良实验室控制趋势
  - Resolution of causes of laboratory variation.
    实验室波动原因的解决方案
  - Initiation of thorough investigations of potential manufacturing causes whenever a laboratory cause cannot be conclusively identified.
    只要不能识别出可得出结论的实验室原因，要启动对潜在生产原因的彻底调查
  - Adequately scoping of each investigation and its CAPA.
    充分界定每起调查及其 CAPA 的范围
  - Revised OOS investigation procedures with these and other remediations.
    修订 OOS 调查程序，包括这些和其它补救措施

For more information about handling failing, out-of-specification, out-of-trend, or other unexpected results and documentation of your investigations, see FDA's guidance document Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production at https://www.fda.gov/media/71001/download.

失败、OOS、OOT 或其它非预期结果的处理和调查记录更多信息，参见 FDA 指南文件。

CGMP Consultant Recommended CGMP 顾问建议

We acknowledge that you have hired a consultant. Because of your compliance history with inadequate investigations, we recommend that any consultant you engage is qualified as set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements. After your consultant's audit, provide a summary of the report.

我们了解你们已经聘请了一位顾问。由于你们历史上曾有调查不充分的情况，我们建议你们使用一位有 21CFR 211.34 所述资质的顾问来协助你们公司符合 CGMP 要求。在你们顾问审计之后，请提交报告摘要。

Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

你们使用顾问并不能解除你们公司符合 CGMP 的义务。你们公司的高级管理层仍负有义务全面解决所有缺陷，确保持续 CGMP 符合性。

Conclusion 结论

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility/in connection with your products. You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of other violations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C.356C(b). This also allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

如果你们在考虑要采取的措施可能会导致你们工厂所生产的药品供应中断，FDA 要求你立即联系 CDER 药品短缺负责人员，这样 FDA 可以与你们一起采用最为高效的方式引导你们的操作符合法规要求。联系药品短缺负责人员还能让你满足依据 21 U.S.C. 356C(b)你可能必须报告你们药品中止或中断的义务，让 FDA 尽快考虑是否需要采取何种措施来避免短缺，保护依赖于你们药品的患者健康。

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产的新申报和增补申报的批准。

Failure to correct these violations may also result in the FDA refusing admission of articles manufactured at Torrent Pharmaceuticals Limited, Ahmedabad-Mehsana Highway, Taluka-Kadi, Indrad, Gujarat, into the United States under section 801(a)(3) of the FD&C Act, 21U.S.C. 381(a)(3). Articles under this authority may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

4. 320-20-04 2019-10-09 Coral Pharmaceuticals LTD 巴哈马

Dear Ms. Palmer:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Coral Pharmaceuticals Ltd, FEI3003301821, at 20 Longwood Road, Freeport City, from May 20 to 24, 2019.

美国 FDA 于 2019 年 5 月 20 日至 24 日检查了你们位于巴哈马的 Coral Pharmaceuticals Ltd 生产场所。

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

本警告信总结了制剂生产严重违反 CGMP 的行为。参见 21CFR 第 210 与 211 部分。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug product is adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

由于你们的制剂生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的药品根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C. 351(a)(2)(B)被认为是掺假药品。

We reviewed your June 6, 2019, response to our Form FDA 483 in detail. Your response is inadequate because it did not provide sufficient detail or evidence of corrective actions to bring your operations into compliance with CGMP.

我们已详细审核了你公司 2019 年 6 月 6 日的回复，并此告知已收到后续通信。

During our inspection, our investigators observed specific violations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

1. Your firm failed to establish adequate written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess (21CFR 211.100(a).

你公司未建立足够的书面生产和工艺控制程序，其设计用以确保你们生产的药品具备其理当具备的鉴别、剂量、质量和纯度（21 CFR 211.100(a)）。

Under contract, you manufacture a homeopathic drug product, (b)(4), derived from a toxic ingredient, (b)(4). You distributed this homeopathic drug product to the United States without adequate process validation data to demonstrate that your manufacturing process is capable of producing the homeopathic drug product of its purported quality and safety.

根据合同，你们生产顺势疗法药品 XX，其来自一种毒性成分 XX。你们销售该顺势疗法药品至美国，却没有充分的工艺验证数据证明你们的生产工艺能够生产出具备其理当具备的质量和安全性的顺势疗法药品。

Specifically, your data does not support that the drug product you manufacture is the concentration specified on the drug product label. When asked by FDA investigators for data supporting the

finished drug product concentration, you could not provide adequate justification. You contacted your customer, (b)(4), for the information.

具体来说，你们的数据不能支持你们所生产的药品具备药品所标示的浓度。当 FDA 检查员要求查看支持成品浓度的数据时，你们未能提供足够的论证。你们联系了你们的客户 XX 索取信息。

During the inspection you received correspondence from your customer, (b)(4), indicating the manufacturing process utilized at your facility would yield final solution concentration at (b)(4)mcg/mL. This concentration is approximately equivalent to a (b)(4)X homeopathic dilution. However, the label on the homeopathic drug product you distributed is (b)(4)X. This means that you are manufacturing a drug with (b)(4) orders of magnitude, or (b)(4) times, the active concentration of the label that the homeopathic drug is purported to possess. You did not know the true concentration of the homeopathic drug product you distributed, which is especially concerning as it contains the toxic ingredient, (b)(4).

在检查期间，你们收到来自你们客户 XX 的函件，说明在你们场所使用的生产工艺能获得最终溶液浓度 XXmg/ml。该浓度约等于 XX 顺势疗法稀释度。但是，你们销往美国的顺势疗法药品上的标示浓度为 XX。这意味着你们在产药品的浓度为标示浓度的 XX 倍。你们并不知晓你们所发运的顺势疗法药品的真实浓度，尤其是毒性成份 XX 的浓度。

We acknowledge that your response to the Form FDA483 indicated that you are not currently manufacturing drugs for the U.S. market and that it is unlikely you will manufacture products for the U.S. market in the future. FDA placed your firm on import alert 66-40 on September 25, 2019.

我们知晓你们回复了 FDA483 表，说你们目前没有再生产销往美国的药品，未来亦不可能生产销往美国的药品。FDA 已于 2019 年 9 月 25 日将你公司置于进口禁令 66-40 中。

If you intend to resume drug manufacturing for the U.S. market, provide the following in response to this letter.

如果你们准备恢复销往美国的药品生产，请提交以下资料回复本函：

- A detailed summary of your validation plan for ensuring a state of control throughout the product lifecycle, along with associated procedures. Describe your program for process performance qualification (PPQ), and ongoing monitoring of both intra-batch and inter-batch variation to ensure a continuing state of control.
  对你们验证计划的详细总结，确保产品生命周期中受控状态，以及相关程序。阐述你们工艺性能确认计划（PPQ），和对批间与批内波动的持续监控，以确保持续受控状态
- A timeline for performing appropriate PPQ for each of your drug products.
  一份对你们每种药品执行适当 PPQ 的时间表
- A detailed program for designing, validating, maintaining, controlling, and monitoring each of your manufacturing processes that includes vigilant monitoring of intra-batch and inter-batch variation to ensure an ongoing state of control. Also, include your program for qualification of your equipment and facility.
  一份设计、确认、维护、控制和监测你们每种生产工艺的详细计划，其中包括对批间和批内波动严格监测，以确保持续受控状态。还有包括你们设备和设施确认计划。
- An assessment of each drug product process to ensure that there is a data-driven and scientifically sound program that identifies and controls all sources of variability, such that your production processes will consistently meet appropriate specifications and manufacturing standards. This includes, but is not limited to, evaluating suitability of equipment for its

intended use, sufficiency of detectability in your monitoring and testing systems, quality of input materials, and reliability of each manufacturing process step and control.
对每种药品工艺的评估，以确保具备基于数据的科学合理程序识别和控制所有波动源，这样你们的生产工艺能持续满足适当的标准和生产标准。其中包括但不仅限于评估设备满足其既定用途的适用性、你们监测和检测系统可检出性的充分性、输入物料的质量和每个生产工艺步骤与控制的可靠性。

2. Your firm failed to conduct at least one test to verify the identity of each component of a drug product. Your firm also failed to validate and establish the reliability of your component supplier's test analyses at appropriate intervals (21 CFR211.84(d)(1) and (2)).

你公司未能执行至少一种测试来核查药品每种成分的鉴别。你公司亦未以适当周期验证和建立你们成分供应商分析检测的可靠性（21 CFR 211.84(d)(1) 和 (2)）。

You received a component containing a toxic ingredient, (b)(4), from the product owner to manufacture a finished drug product, (b)(4). However, you did not conduct identity testing prior to releasing the component for use in manufacturing.

你们收到了来自产品所有者的含有毒性成份 XX 的组份，用于生产成品 XX。但是你们并未在放行该组份用于生产之前执行鉴别检测。

Additionally, your firm used results from the certificate of analysis (COA) for the component containing (b)(4) without establishing the reliability of the supplier's analyses through appropriate validation. Under 21 CFR 211.84(d)(2), you may not rely on your suppliers' COA to verify the identity of your components. Furthermore, you donot receive COA or certificates of conformance and have not qualified the suppliers for (b)(4) Solution with (b)(4).

另外，你公司使用了含 XX 的组份的 COA 中的结果，却未通过适当验证建立供应商分析的可靠性。根据 21 CFR 211.84(d)(2)，你们不能依赖于供应商的 COA 来验证你们成分的鉴别。另外，你们并未收到 COA 或符合性证书，亦未确认 XX 溶液的供应商。

If you intend to resume drug manufacturing for the U.S. market, provide the following in response to this letter.

如果你们准备恢复生产销往美国的药品生产，请提交以下内容回复本函：

- The chemical and microbiological quality control specifications you use to test and release each incoming lot of component for use in drug manufacturing.
  你们用于检测和放行每批进厂成分用于药品生产的化学和微生物质量控制标准
- A description of how you will test each component lot for conformity with all appropriate specifications for identity, strength, quality, and purity. If you intend to accept any results from your supplier's COA instead of testing each component lot for strength, quality, and purity, specify how you will robustly establish the reliability of your supplier's results through initial validation as well as periodic re-validation. In addition, include a commitment to always conduct at least one specific identity test for each incoming component lot.
  阐述你们将如何检测每种组份符合所有适当鉴别、剂量、质量和纯度标准。如果你们准备接受来自你们供应商 COA 的所有结果，取代你们对每批组份的剂量、质量和纯度的检测，说明你们要如何通过初始验证和后续定期重新验证来稳定建立你们供应商结果的可靠性。另外，要包括一份承诺书，承诺会一直对每批进厂组份执行至少一项专属性鉴别测试。

- A summary of results obtained from testing all components to evaluate the reliability of the COA from each component manufacturer. Include your standard operating procedure (SOP) that describes this COA validation program.
  一份对所有组分检测结果的总结，评估来自每个组份生产商 COA 的可靠性。包括你们描述此种 COA 验证程序的 SOP。
- A summary of your procedures for qualifying and overseeing contract facilities that test the drug products you manufacture.
  一份你们确认和监管检测你们所生产药品的合同场所的程序摘要
- A comprehensive, independent review of your material system to determine whether all suppliers of components, containers, and closures are each qualified and the materials are assigned appropriate expiration or retest dates. The review should also determine whether incoming material controls are adequate to prevent use of unsuitable components, containers, and closures.
  一份对你们物料系统的全面独立审核，确定是否所有组份、容器和密闭器供应商均经过确认，物料被给予有效期或复验期。审核亦应确定是否进厂物料控制足以防止使用不恰当的组份、容器和密闭器。

3. Your firm failed to establish an adequate quality control unit and procedures applicable to the quality control unit with the responsibility and authority to approve orreject all components, drug product containers, closures, in- process materials, packaging materials, labeling, and drug products, including drug products manufactured, processed, packed or held under contract by another company (211.22(a) and (d)).

你公司未建立充分的质量部门和适用于质量部门的程序，赋予其职责和权力批准或拒收所有组份、药品容器、密闭器、中间体、包材、标签和药品，包括根据合同由另一公司所生产、加工、包装或保存的药品（211.22(a) 和 (d)）。

Your firm lacked SOPs to ensure that roles and responsibilities pertaining to manufacturing activities are in writing and clearly detailed for each respective party. Additionally, your firm did not establish clear quality unit (QU) responsibilities for finished drug product approval. Furthermore, your firm did not follow its SOP for reserve samples.

公司缺乏 SOP 确保每个相应方与生产活动有关的角色和职责均有书面详细载明。另外，你公司并未制订成品批准方面清晰的质量部门（QU）职责。并且你公司并未遵守其留样 SOP。

Establishing an adequate QU is essential to ensuring that your operations associated with all systems (facilities and equipment, materials, production, laboratory controls and packaging and labeling) are appropriately planned, approved, conducted, and monitored, and ultimately to ensuring that your firm is capable of consistently producing drug products of acceptable quality.

建立充分的 QU 是确保你们所有系统相关操作（设备和设备、物料、生产、实验室和包装与贴标）经过恰当规划、批准、执行和监测，并最终确保你公司有能力持续生产具备可接受质量药品所必需要。

If you intend to resume drug manufacturing for the U.S. market, provide a comprehensive assessment and remediation plan to ensure your QU is given the authority and resources to effectively function. The assessment should also include, but not be limited to:

如果你们准备恢复为美国市场生产药品，请提交全面评估和补救计划，确保你们 QU 被赋予职责和权力，可有效履责。评估亦应包括但不仅限于：

- A determination of whether procedures used by your firm are robust and appropriate.
  确定你公司所用程序是否稳健和恰当
- Provisions for QU oversight throughout your operations to evaluate adherence to appropriate practices.
  QU 监管整体运作的条款，以评估坚守适当的规范
- A complete and final review of each batch and its related information before the QU disposition decision.
  在 QU 做出处置决策之前对每个批次及其相关信息的完全最终审核
- Oversight and approval of investigations and discharging of all other QU duties to ensure identity, strength, quality, and purity of all products.
  对调查的监管和批准，以及履行所有其它 QU 职责以确保所有产品的鉴别、剂量、质量和纯度

See FDA's guidance document Quality Systems Approach to Pharmaceutical CGMP Regulations for help implementing quality systems and risk management approaches to meet the requirements of CGMP regulations 21 CFR, parts 210 and 211 at https://www.fda.gov/media/71023/download.

参见 FDA 指南文件。

CGMP Consultant Recommended CGMP 顾问建议

Based upon the nature of the violations we identified at your firm, if your firm intends to resume manufacturing drugs for the U.S. market we strongly recommend engaging a consultant qualified as set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements.

鉴于我们在你公司发现的违规情况，如果你公司有意继续为美国市场生产药品，我们强烈建议你们使用一位有 21 CFR211.34 所述资质的顾问来协助你们公司符合 CGMP 要求。

We also recommend that the qualified consultant perform a comprehensive audit of your entire operation for CGMP compliance and that the consultant evaluates the completion and efficacy of your corrective actions and preventive actions before you pursue resolution of your firm's compliance status with FDA.

我们亦建议所确认的顾问对你们整个 CGMP 合规运行进行全面审计，由顾问在你公司寻求符合 FDA 法规要求之前评估你们 CAPA 的完成情况和有效性。

If you intend to resume manufacturing for and shipping drugs to the United States, you should provide comprehensive corrective actions which include systemic remediation as well as a global assessment and remediation of all six systems of your manufacturing operations.

如果你们准备继续生产和运输药品至美国，你们应提交全面 CA，在其中包括系统性补救措施，以及对你们生产操作所有 6 大系统的全球评估和补救措施。

Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

你们使用顾问并不能解除你们公司符合 CGMP 的义务。你们公司的高级管理层仍负有义务全面解决所有缺陷，确保持续 CGMP 符合性。

Responsibilities as a Contractor 作为合同商的义务

Drugs must be manufactured inconformance with CGMP. FDA is aware that many drug manufacturers use independent contractors such as production facilities, testing laboratories, packagers, and labelers. FDA regards contractors as extensions of the manufacturer.

药品生产必须符合 CGMP 要求。FDA 了解许多药品生产商使用独立合同方如生产场所、检测实验室、包装商和贴标商。FDA 将合同商作为生产商的外延部分来对待。

You are responsible for the quality ofdrugs you produce as a contract facility regardless of agreements in place with product owners. You are required to ensure that drugs are made in accordance with section 501(a)(2)(B) of the FD&C Act for safety, identity, strength, quality, and purity. See FDA's guidance document Contract Manufacturing Arrangements for Drugs: Quality Agreements at https://www.fda.gov/media/86193/download.

作为合同场所，虽然你们与药品所有者订有协议，但你们仍对你们所生产的药品负有义务。你们应确保药品生产符合 FDCA 第 501(a)(2)(B)条款对安全性、鉴别、剂量、质量和纯度的要求。参见 FDA 指南文件"药品合同生产安排：质量协议"。

Conclusion 结论

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility.You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of other violations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

FDA placed your firm on Import Alert 66-40 on September 25, 2019.

FDA 已于 2019 年 9 月 25 日将你公司置于进口禁令 66-40 中。

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产的新申报和增补申报的批准。

Failure to correct these violations may also result in the FDA continuing to refuse admission of articles manufactured at Coral Pharmaceuticals Ltd, 20 Longwood Road, Freeport City into the United Statesunder section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Articles under this authority may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C.351(a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

5. 320-20-05 2019-10-29 Cadila Healthcare Limited 印度

Dear Mr. Patel:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Cadila Healthcare Limited, FEI 3002984011, at 419 & 420 8a Village-Moraiya, Ahmedabad, from April 22 to May 3, 2019.

美国 FDA 于 2019 年 4 月 22 日至 5 月 3 日检查了你们位于印度的 Cadila Healthcare Limited，FEI 3002984011 生产场所。

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

本警告信总结了制剂生产严重违反 CGMP 的行为。参见 21CFR 第 210 与 211 部分。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

由于你们的制剂生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的药品根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C. 351(a)(2)(B)被认为是掺假药品。

We reviewed your May 24, 2019 response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

我们已详细审核了你公司 2019 年 5 月 24 日对我们 FDA483 表的回复，并此告知已收到后续通信。

During our inspection, our investigators observed specific violations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

1. Your firm failed to clean, maintain, and, as appropriate for the nature of the drug, sanitize and/or sterilize equipment and utensils at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements (21 CFR 211.67(a))

你公司未能按适当时间间隔对设备和工器具进行清洁、保存，并根据产品属性进行消毒和/或灭菌（适当时）以防止故障或污染改变药品的安全性、鉴别、剂量、质量或纯度使得超出官方或其它既定要求（21 CFR 211.67(a)）。

Your cleaning procedure for non-dedicated equipment, including your (b)(4), is inadequate. Our investigators observed multiple (b)(4), used in the production of potent and non-potent compounds, marked as clean and containing residues of what appeared to be different products. The residues were observed on the back of the (b)(4), after product change-over cleaning. The (b)(4) system of your equipment interacts with the interior of the equipment in which products are processed.

你们对非专用设备包括 XX 的清洁是不充分的。我们的检查员发现多个用于生产活性和非活性化合物的 XX 标示为清洁，但其中有看起来是不同药品的残留。在换产品清洁之后在 XX 背部发现有残留。你们设备的 XX 系统与药品加工的设备内部相互影响。

Significant equipment flaws and cleaning deficiencies resulted in cross-contamination between your drug products. For example, you lacked provisions for inspecting or cleaning the area behind the (b)(4).

严重的设备瑕疵和清洁缺陷导致你们药品之间的交叉污染。例如，你们缺少 XX 后面区域的检查或清洁规定。

After our inspection, your firm observed residues in additional non-dedicated equipment and confirmed the recovery of multiple active ingredients through swab samples and visible (b)(4) residues collected from product-contact surfaces. For example:

在我们检查之后，你们公司在其它非专用设备中也发现了残留，并确认从与产品接触的表面擦拭取样发现多个活性成分和可见 XX 残留。例如：

- Equipment ID #CH/PM/013 – (b)(4) active ingredients were identified in swab and (b)(4) residues out of (b)(4) products processed in the equipment.
  生产 XX 个药品的设备 ID #CH/PM/013 –擦拭取样中检出 XX 活性成分和 XX 残留
- Equipment ID #CH/PP/028 – (b)(4) active ingredients were identified in swab and (b)(4) residues out of (b)(4) products processed in the equipment.
  生产 XX 个药品的设备 ID #CH/PP/028–擦拭取样中检出 XX 活性成分和 XX 残留
- Equipment ID #CH/TS/013 - (b)(4) active ingredients were identified in swab and (b)(4) residues out of (b)(4) products processed in the equipment.
  生产 XX 个药品的设备 ID #CH/TS/013 –擦拭取样中检出 XX 活性成分和 XX 残留
- Equipment ID #CH/MC/TAB/1999/19 - (b)(4) active ingredients were identified in swab and (b)(4) residues out of (b)(4) products processed in the equipment.
  生产 XX 个药品的设备 ID #CH/MC/TAB/1999/19 –擦拭取样中检出 XX 活性成分和 XX 残留
- Equipment ID #CH/MC/TAB/2004/176 - (b)(4) active ingredients were identified in swab and (b)(4) residues out of (b)(4) products processed in the equipment.
  生产 XX 个药品的设备 ID #CH/MC/TAB/2004/176 –擦拭取样中检出 XX 活性成分和 XX 残留

After our inspection, your firm also tested reserve samples of selected batches to assess the potential for cross contamination. Your testing confirmed the presence of active ingredients manufactured in numerous samples tested, including but not limited to:

在我们检查后，你公司亦检测了所选批次的留样，以评估交叉污染的可能性。你们的测试确认了在许多受检样品中检出所生产的活性成分，包括但不仅限于：

- Residues of (b)(4) active ingredients in (b)(4) tablets
  XX 片剂中 XX 活性成分的残留
- Residues of (b)(4) active ingredients in (b)(4) tablets
  XX 片剂中 XX 活性成分的残留
- Residues of (b)(4) active ingredients in (b)(4) tablets
  XX 片剂中 XX 活性成分的残留
- Residues of (b)(4) active ingredients in (b)(4) tablets
  XX 片剂中 XX 活性成分的残留
- Residues of (b)(4) active ingredients in (b)(4) tablets
  XX 片剂中 XX 活性成分的残留
- Residues of (b)(4) active ingredients in (b)(4) tablets

XX 片剂中 XX 活性成分的残留
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  XX 片剂中 XX 活性成分的残留
- Residues of (b)(4) active ingredientsin (b)(4) tablets
  XX 片剂中 XX 活性成分的残留
- Residues of (b)(4) active ingredients in (b)(4) tablets
  XX 片剂中 XX 活性成分的残留

As a result of these inspectional findings your firm initiated a recall of numerous batches manufactured in your (b)(4) #CH/TS/013 (dedicated to potent compounds).

基于检查发现情况，你公司对你们 XX #CH/TS/013（专用于活性化合物）大量批次的启动了召回。

In your response, you committed to corrective and preventive actions (CAPA) for non-dedicated equipment, including revisions to cleaning procedures, mechanical changes to equipment to prevent (b)(4), cleaning validation for all processing equipment, and further testing to analyze reserve samples of batches manufactured using (b)(4) to quantify the potential carryover of previous products.

在你们的回复中，你们承诺了对非专用设备的 CAPA，包括修订清洁程序、对设备进行机械性修改、对所有工艺设备进行清洁验证，以及进行进一步检测从而分析使用 XX 所生产批次的留样以确定前一药品的残留数量。

Your firm's review concluded that the significant cross-contamination identified by your firm does not represent a risk to patients.

你公司的审核结论说你们发现严重的交叉污染，但对患者没有风险。

Your response is insufficient. Your response stated that any potential residue that enters the (b)(4) and contaminates the next drug product can produce a nearly uniform distribution in the (b)(4) and that (b)(4) steps minimize localization of carryover residue. Your rationale is not scientifically sound in that cross-contamination cannot be assumed to be uniformly distributed.

你们的回复是不充分的。你们的回复声称所有进入 XX 的潜在残留和污染下一药品可能在 XX 得到近乎均匀的分布，并且 XX 步骤会降低携入残留的集中。你们的理由不够科学合理，因为不能假定交叉污染会均匀分布。

In addition, your response described failure modesthat may have contributed to the accumulation of residues in the (b)(4). But you failed to explain when the cross-contamination involving numerous products started and why it had not been detected. Your response also stated that testing for cross-contamination in the products provides good assurance that any carryover is detected. However, reserve sample testing alone is insufficient to mitigate associated risks. The extent of the cross-contamination found suggests a lack of assurance that products meet appropriate standards for identity, quality, purity and safety.

另外，你们的回复阐述了可能对 XX 中残留累积起作用的失效模式。但你们并未解释自何时起交叉污染涉及到大量药品，以及为何一直未发现。你们的回复亦声称对药品中交叉污染的检测提供了良好

的保证证明检出所有残留。但是仅仅检测留样是不足以缓解相关风险的。所发现的交叉污染的程度说明不能保证药品符合适当的鉴别、质量、纯度和安全性标准。

In response to this letter provide the following:

在回复本函时请提交以下：

- Your CAPA plan to implement routine, vigilant operations management oversight of facilities and equipment. This plan should ensure, among other things, prompt detection of equipment/facilities performance issues, effective execution of repairs, adherence to appropriate preventive maintenance schedules, timely technological upgrades to the equipment/facility infrastructure, and improved systems for ongoing management review.
  你们对设施和设备实施常规化警觉操作管理监管的 CAPA 计划。该计划应确保（除其它外）快速发现设备/设施性能问题、有效进行修理、遵守适当的预防性维护计划、及时对设备/厂房基础设施进行技术升级，以及改进持续管理审评体系。
- A comprehensive, independent retrospective assessment of your cleaning effectiveness to evaluate the scope of cross-contamination hazards and recalls initiated to determine if additional batches were affected. This should include, but not be limited to:
  一份对你们清洁效果的独立全面回顾评估，以评估交叉污染危害和所启动召回的范围，确定是否还有其它批次受到影响。其中应包括但不仅限于：
  - Identification of any inadequacies of cleaning procedures and practices for each piece of manufacturing equipment used to manufacture more than one product.
    找出多产品生产所用每台生产设备的清洁程序和做法的所有不足；
  - Any updates to your investigation regarding the identity of residues, other manufacturing equipment that may have been improperly cleaned, and an assessment whether additional cross-contaminated products may have been released for distribution.
    对你们残留鉴定方面，其它可能被不当清洁的生产设备，以及评估是否还有其它被交叉污染的药品放行销售调查的任何更新。
- A CAPA plan based on the retrospective assessment, that includes appropriate remediations to your cleaning processes and practices, and timelines for completion. Provide a detailed summary of vulnerabilities in your process for lifecycle management of equipment cleaning. Describe improvements to your cleaning program, including enhancements to cleaning effectiveness; improved ongoing verification of proper cleaning execution for all products and equipment; and all other needed remediations.
  一份基于回顾性评估的 CAPA 计划，其中包括对你们清洁工艺和做法的适当补救措施，以及完成时间表。提交一份对你们设备清洁生命管理工艺中弱点的详细总结。说明你们清洁程序的改进，包括对清洁有效性的改进、改进后的所有药品和设备清洁执行情况持续确认，以及所有其它所需补救措施。
- Appropriate improvements to your cleaning validation program with special emphasis on incorporating conditions identified as worst case in your drug manufacturing operation. This should include but not be limited to identification and evaluation of all worst-case:
  对你们清洁验证程序的适当改进，特别要强调在你们药品生产操作中结合判定为最差情形的条件。其中应包括但不仅限于所有最差情形的识别与评估：
  - drugs with higher toxicities
    较高毒性的药品
  - drugs with higher drug potencies

较高药品效价的药品

- drugs of lower solubility in their cleaning solvents
  在其清洁溶剂中溶解度较低的药品
- drugs with characteristics that make them difficult to clean
  难以清洁的药品
- swabbing locations for areas that are most difficult to clean
  最难清洁区域的擦拭取样位置
- maximum hold times before cleaning
  清洁前最长放置时长

In addition, describe the steps that must be taken in your change management system before introduction of new manufacturing equipment or a new product.

另外，说明你们引入新的生产设备或新产品之前变更管理系统中要采取的步骤。

- A summary of updated SOPs that ensure an appropriate program is in place for verification and validation of cleaning procedures for products, processes, and equipment. Also, include a copy of your cleaning validation report once completed.
  一份更新后的 SOP 的总结，确保具备产品、工艺和设备清洁程序确认和验证程序。另外要包括一份你们清洁验证报告的副本（完成后立即提交）。

2. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

你公司未能彻底调查所有未解释的差异，或已销售或未销售批次或其组份不符合其质量标准的情形（21 CFR 211.192）。

Your investigations into failures during periodic qualification of the (b)(4) cycles are inadequate. For example, investigation DC/2018/381 was initiated on June 9, 2018 for a failure during periodic requalification of the (b)(4) used for (b)(4) Injection (b)(4)ml in (b)(4) ml vial. The required F0 was not achieved and there was significant (b)(4) variation for at least (b)(4). You concluded that the root cause was improper (b)(4). As part of the impact assessment, you evaluated the qualification reports for other products that utilize the same (b)(4) and concluded that there was no impact on other (b)(4) products. Therefore, you did not extend the CAPA to other products.

你们对 XX 回收定期确认过程中的失败调查是不充分的。例如，调查 DC/2018/381 于 20180609 启动，原因是 XX 西林瓶注射剂所用 XX 定期重新确认失败。未达到所需的 F0 值，并且至少有 XX 的严重 XX 波动。你们得出结论说根本原因是 XX 不当。作为影响性评估的一部分，你们评估了使用相同 XX 的其它产品的确认报告，得出结论说对其它 XX 药品没有影响。因此你们并未扩展 CAPA 至其它产品。

However, in March 2019, you initiated investigation DC/2019/190 and DC/2019/195 because of another failure during the periodic requalification of the same (b)(4) used for the (b)(4) of (b)(4) Injection (b)(4) ml in (b)(4) ml vial. Again, several sensors did not achieve the required F0, and one did not reach the (b)(4) temperature. In addition, at the end of the incubation, the biological indicators at multiple locations in the (b)(4) showed microbiological growth. This resulted in the recall of (b)(4) batch of (b)(4) Injection, USP, (b)(4) mg per (b)(4) ml ((b)(4) mg perml), due to lack of (b)(4) assurance.

但是，2019 年 3 月，你们启动了调查 DC/2019/190 和 DC/2019/195，原因是 XX 西林瓶注射剂所用相同 XX 定期重新确认失败。仍然是未达到所需的 F0 值，，并且有一个未到达 XX 温度。另外，在培养结束时，XX 中多个位置的生物指示剂显示有微生物生长。该偏差导致召回 XX 批次 XX 注射剂，理由是缺少 XX 保证。

In this instance you also concluded that the root cause was improper (b)(4). There was no assurance that your assessment of other (b)(4) products using this (b)(4) was thorough and that adequate CAPA were identified and implemented. In addition, your investigation did not sufficiently address why your originally validated cycle parameters were not met and why the process fell out of a state of control.

在此事件中，你们也是得出结论说根本原因是 XX 不当。无法确保你们对使用该 XX 的其它 XX 产品的评估足够彻底，并且识别和执行了充分的 CAPA。另外，你们的调查未充分说明为何不符合你们原来的验证周期参数，以及为何工艺不在受控状态。

Your response adds that there has been some drift in the calibration of the built-in (b)(4) that control the (b)(4) cycle since 2017. However, your response lacks an assessment of the adequacy of the (b)(4) calibration standards, as you acknowledge in the response that the variation observed is within your established acceptance criteria. Also, calibration of (b)(4) was verified as part of your original investigation.

你们的回复补充说自 2017 年以来用于控制 XX 循环的内置 XX 校正有一些漂移。但是你们的回复缺少对 XX 校正标准充分性的评估，因为你们在回复中承认所观察到的波动在你们制订的可接受标准内。另外，XX 的校正作为你们原始调查的一部分是经过了核查的。

According to your firm's investigation report there have been seven deviations during the periodic requalification of this (b)(4) in the past two years. Recurrent failures suggest that you have not adequately identified the root cause and lack (b)(4) assurance.

根据你们公司的调查报告，过去 2 年里该 XX 在定期重新确认中有 7 个偏差。重复发生的失败说明你们并未充分识别根本原因，且缺少 XX 保证。

In response to this letter provide the following:

在回复本函时请提交以下：

- A comprehensive retrospective, independent review of all batches (b)(4) with this (b)(4) that were distributed in the U.S. market and remain within expiry. This review should include, but not be limited, to:
  一份对销售至美国仍在效期内使用本 XX 的所有批次的独立全面回顾审核。该审核应包括但不仅限于：
  - Review of your (b)(4) parameters, including time and (b)(4) settings to ensure a (b)(4) assurance level of (b)(4) or more.
    对你们 XX 参数的审核，包括时间和 XX 设置以确保 XX 或更多 XX 保证水平
  - Evaluations of F-value and Z-value data and any related assumptions; (b)(4); D-value determinations and population enumerations for each biological indicator lot; and commercial batch data to determine whether (b)(4) cycles used for your products were complete/adequate.

对 F 值和 Z 值数据和任何相关假设的评估；XX；每批生物指示剂的 D 值和含菌量的计算；以及商业化批次数据以确定你们药品所用 XX 周期是否完整/充分。

- A comprehensive and independent assessment of your system for investigating deviations, and failures. Your CAPA plan should include, but not be limited to, improvements in investigations, root cause analysis, written procedures, staff competencies (e.g., evaluating potential root causes), and quality unit oversight. Also, include your process for evaluating CAPA plan effectiveness.
  一份对你们调查偏差以及失败的系统的独立全面评估。你们的 CAPA 计划应包括但不仅限于对调查、根本原因分析、书面程序、员工能力（例如评估潜在根本原因）以及质量部门监管的改进。还需包括你们评估 CAPA 计划有效性的流程。

3. Your firm failed to follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR211.113(b)).

你公司未能遵守恰当的书面程序，这些程序应设计用以防止理当无菌药品的微生物污染，以及包括所有无菌和灭菌工艺的验证（21 CFR 211.113(b)）。

Poor Aseptic Behavior 不良无菌行为

- Operators displayed poor aseptic practices during aseptic set-up and filling operations. For example:
  操作员在无菌装配和灌装操作期间显示的不良无菌行为。例如：
- Operators leaned over the open bag of sterilized stoppers. These bags are subsequently introduced into the stopper chute. Also, the operator's hands passed over the sterile stopper chute and over sterilized stoppers already added into the chute. Notably, your procedures specifically prohibit personnel leaning over the product or sterilized containers and closures.
  操作员在无菌塞打开的袋子上方倾斜身体。这些袋子后来被导入胶塞槽。操作员的手还越过无菌塞导槽上，在已加到导槽的灭菌后塞子上方。值得注意的是，你们的程序特别禁止人员在药品或灭菌后容器和密闭器上方倾斜身体。
- Operators used (b)(4) Restricted Access Barrier Systems ((b)(4)RABS) (b)(4) to pick up sterile forceps and remove fallen vials. During that intervention, the (b)(4) extend over open vials without clearing them. According to your procedures, (b)(4)RABS (b)(4) are sterilized only (b)(4). Your firm's staff confirmed that these (b)(4) cannot be considered sterile during this extended use period.
  操作员使用了 XX RABS 捡起无菌钳子，清除倒掉的西林瓶。在此干扰过程中，XX 伸到开口的西林瓶上方却没有清除它们。根据你们的程序，XX RABS XX 仅 XX 灭菌的。你公司的员工确认在此延长使用期间这些 XX 不能认为是无菌。

Inadequate Cleanroom Design and Smoke Study Deficiencies

清洁间设计不足和发烟试验缺陷

Your stopper chute leans (b)(4) of the filling line during stopper loading operations thereby creating turbulence as the air flows (b)(4) filters (b)(4) the chute.

你们的塞子导槽在加塞操作期间倾向灌装线的 XX，因此在空气流动 XX 时导致扰动。

In addition to this inadequate design, your smoke studies performed for your (b)(4) areas also lacked simulation of multiple critical interventions that occur during aseptic manufacturing operations.

除开此设计不足外，你们 XX 区域所实施的发烟试验亦缺乏对无菌生产操作期间发生的多个关键干预的模拟。

Thorough smoke studies are essential to evaluate the effects of such interventions on unidirectional airflow and to ensure design modifications are made wherever necessary.

彻底的发烟试验对于单向流中此类干预影响的评估，以及确保必要时对设计进行修正是必须的。

The (b)(4) area is critical because sterile product is exposed and therefore vulnerable to contamination. Your aseptic filling process should be designed, and operations executed, to prevent contamination hazards to your sterile product. The flawed design of the filling line and execution of the aseptic operations promoted influx of contamination into the critical filling areas.

XX 区域是关键的，因为无菌药品暴露在其中，因此易受污染。你们的无菌灌装工艺的设计以及操作应防止对你们无菌药品的污染危害。灌装线设计和无菌操作执行瑕疵使得关键灌装区域易受污染。

Your firm's response is inadequate. You did not provide a thorough evaluation of all batches produced under inadequate conditions.

你公司的回复是不充分的。你们并未提交对在不充分条件下所生产的所有批次的彻底评估。

In response to this letter, provide the following:

在回复本函时请提交以下：

- A risk assessment of all contamination hazards with respect to your aseptic processes, equipment, and facilities, including an independent assessment that includes, but is not limited to:
  一份对你们无菌工艺、设备和设施方面所有污染危害的风险评估，包括一份独立评估，其中包括但不仅限于：
  - All human interactions within the (b)(4) area
    XX 区域内所有人为扰动
  - Equipment placement and ergonomics
    设备放置和人体工程学
  - Air quality in the (b)(4) area and surrounding room
    XX 区域和周边房间的空气质量
  - Facility layout
    设施平面布局
  - Personnel Flows and Material Flows (throughout all rooms used to conduct and support sterile operations)
    人流和物流（实施和支持无菌操作所用的所有房间）
- A comprehensive, independent retrospective review of all batches that remain within expiry in the U.S. market, which incorporates the knowledge of hazards gained from your risk assessment. Include any additional actions you intend to initiate because of the retrospective review.

一份对在美国市场上仍在效期内的所有批次的独立全面回顾性审核，其中要结合从你们风险评估中所获得的危害性知识。包括所有你们因回顾性审核而准备启动的其它措施。

4. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42(c)(10)(iv)).

你公司未能制订足够的系统监测无菌工艺区域的环境条件（21 CFR 211.42(c)(10)(iv)）。

Your environmental and personnel monitoring programis deficient. For example, your procedures allowed personnel performing aseptic interventions (e.g., (b)(4)) in the (b)(4) area to have (b)(4) colony-forming units (CFU) on their (b)(4) without triggering an appropriate investigation. During our inspection, a firm official indicated that your firm does not consider the (b)(4) to be an (b)(4) intervention and operators are only held to ISO 7 limits.

你们的环境和人员监测计划有缺陷。例如，你们的程序允许人员在 XX 区域执行无菌干预（例如 XX），在其 XX 上有 XX 菌落（CFU）而不会触发适当的调查。在我们检查期间，一位公司官员指出你们公司并未认为 XX 是干预行为，操作员只是遵守 ISO7 限度。

The (b)(4) step in your operation is acritical aseptic intervention, and it is manually intensive. Our inspection noted significant aseptic technique breaches during performance of this intervention.

你们操作中的 XX 步骤为关键的无菌干预，人为动作密集。我们检查注意到在此干预实施期间有严重的无菌技术问题。

Your firm's response is inadequate. We acknowledge your commitment to conduct a protocol-based assessment to evaluate the adequacy of limits of viable monitoring based on the classification of the area and the criticality of the operation. However, your response did not include a retrospective review of your personnel monitoring data to identify the instances in which operators held to ISO 7 limits conducted activities in the (b)(4) area, and if the (b)(4) limits were exceeded. Growth observed on (b)(4) samples taken from personnel performing any activities within the (b)(4) area should, at a minimum, lead to trending and assessment, and could trigger further actions and investigation.

你公司的回复是不充分的。我们知晓你们承诺会根据一份方案基于区域级别和操作关键程度对微生物监测限度充分性进行评估。但是你们的回复并未包括对你们人员监测数据的回顾性审核，以发现操作员遵守 ISO7 限度时所在 XX 区域执行的活动情况，以及是否超出了 XX 限度。从 XX 区域内执行任何活动的人员所采集的 XX 样品中观察到的微生物生长情况至少应进行趋势分析和评估，可能触发进一步措施和调查。

In response to this letter, provide the following for products that remain within expiry in the U.S. market:

在回复本函时，请提交仍在美国市场上且在效期内的药品的以下信息：

- A risk assessment of personnel and environmental monitoring data since April 2017, including but not limited to identification of adverse trends or acute findings, and any potential impact on marketed products. Place special emphasis on data from your aseptic processing rooms, as well as any adverse trends that indicate any loss of environmental control in your facility's overall suite of cleanrooms.

对自 2017 年 4 月以来人员和环境监测数据的风险评估，包括但不仅限于识别不良趋势或严重问题，以及对已销售药品的任何潜在影响。特别要注意你们无菌工艺房间的数据，以及显示出你们设施整体洁净间环境失控的任何不良趋势

- A detailed update to the CAPAs implemented and their current status in light of your decision to permanently close down the injectable manufacturing lines that serve the U.S. market.
  根据你们永久关闭美国市场注射车间线的决定，一份对已实施的 CAPA 的详细更新，及其当前状态
- Describe how your firm will ensure continued accountability and responsibility for all products remaining in distribution from this facility (e.g. complaint evaluation, stability testing, handling of reserve samples, post-marketing reporting activities, OOS investigations and document retention). State who will be performing these duties and procedures that will be followed for all marketed products.
  说明你们公司将如何确保对该设施所生产的所有在市药品的持续义务和责任（例如，投诉评估、稳定性测试、留样处理、上市后报告活动、OOS 调查和文件保存）。说明谁将履行这些义务，以及所有在市药品将要遵守的程序。

Cessation of Sterile Drug Manufacturing for U.S. Marketed Products

停止在美国上市的无菌药品生产

In your October 2, 2019 communication, you informed the FDA that you would permanently cease production of injectable drug products for the United States. It is important to note that full remediation of the related CGMP violations cited will be necessary if you decide to resume the manufacturing of injectable drug products at this site, or if any successor firm assumes responsibility over the site's operation in the future. In your response include your action plan for transferring any of your injectable drug products to other facilities. Notify this office in writing if you decide to revisit your decision and resume manufacturing injectable drugs for the U.S. in the future.

在你们 2019 年 10 月 2 日的沟通中，你们通知 FDA 你们将永久停止生产美国市场的注射药品。需要注意的是，如果你们决定恢复该场所注射药品的生产，如果任何后续公司在将来恢复对该场所的运营责任，则需要全面纠正所引用的相关 CGMP 违规情况。在你们的回复中请包括你们转移任何注射药品至其它设施的行动计划。如果你们决定重新审核你们的决策，在将来恢复美国注射药品的生产，请书面通知本办公室。

Additional Guidance on Aseptic Processing 其它无菌工艺指南

See FDA's guidance document Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practiceto help you meet the CGMP requirements when manufacturing sterile drugs using aseptic processing at https://www.fda.gov/media/71026/download.

参见 FDA 指南文件"无菌工艺生产的无菌药品 CGMP"。

Repeat Violations at Facility 场所重复违规

In previous warning letters (WL 320-11-015 and 320-16-05), FDA cited similar CGMP violations. You proposed specific remediation for these violations in your response. Repeated failures demonstrate that executive management oversight and control over the manufacture of drugs is inadequate.

在之前的警告信（WL 320-11-015 and 320-16-05）中，FDA 引用了相似的 CGMP 违规。你们在回复中对这些违规行为提出了具体的补救措施。重复失败证明执行管理层对药品生产的监管和控制是不充分的。

Conclusion 结论

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of other violations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuancesor interruptions in your drug manufacture under 21 U.S.C. 356C(b). This also allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

如果你们在考虑要采取的措施可能会导致你们工厂所生产的药品供应中断，FDA 要求你立即联系 CDER 药品短缺负责人员，这样 FDA 可以与你们一起采用最为高效的方式引导你们的操作符合法规要求。联系药品短缺负责人员还能让你满足依据 21 U.S.C. 356C(b)你可能必须报告你们药品中止或中断的义务，让 FDA 尽快考虑是否需要采取何种措施来避免短缺，保护依赖于你们药品的患者健康。

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产的新申报和增补申报的批准。

Failure to correct these violations may also result in the FDA refusing admission of articles manufactured at Cadila Healthcare Limited, 3002984011, at 419 & 420 8a Village-Moraiya, Ahmedabad, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Articles under this authority may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C.351(a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

6. 320-20-06 2019-11-05 Mylan Laboratories Limited 印度

Dear Ms. Bresch:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Mylan Laboratories Limited, Unit 8,FEI 3002785310, at G. Chodavaram Village, Vizianagaram, Andhra Pradesh, India, from May 27 to June 5, 2019.

美国 FDA 于 2019 年 5 月 27 日至 6 月 5 日检查了你们位于印度的 Mylan Laboratories Limited，Unit 8，FEI 3002785310 生产场所。

This warning letter summarizes significant deviations from current good manufacturing practice (CGMP) for active pharmaceutical ingredients (API).

本警告信总结了原料药生产严重违反 CGMP 的行为。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your API are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food,Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

由于你们的原料药生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的原料药根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C. 351(a)(2)(B)被认为是掺假药品。

We reviewed your June 26, 2019, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence. Your response is inadequate because it did not provide sufficient detail or evidence of corrective actions to bring your operations into compliance with CGMP.

我们已详细审核了你公司 2019 年 6 月 26 日的回复，并此告知已收到后续通信。

During our inspection, our investigators observed specific deviations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

1. Failure to have adequate written procedures for the receipt, identification, testing and handling of raw materials.

未制订足够的书面程序规定原料的接收、鉴别、检测和处置。

Your procedures for receiving, identifying, testing, and handling raw materials were inadequate to ensure suitability of materials used in manufacturing, including preventing contamination and cross-contamination with (b)(4) impurities such as (b)(4) and (b)(4).Your firm had not anticipated the presence of (b)(4) impurities based on your assessment of the API manufacturing process.

你们的原料接收、鉴别、检测和处置程序不足以确保用于生产的原料的适当性，包括防止 XX 杂质的污染和交叉污染，如 XX 和 XX。你公司未能根据你们 API 生产工艺的评估预测 XX 杂质的出现。

By December 2018, you recalled all your (b)(4) API batches after tests determined that the majority of batches contained (b)(4) contamination at levels above the limit. Your investigation dated November 21, 2018, with addendum dated January 1, 2019, concluded that (b)(4) contamination originated from recovered (b)(4) solvents. Your investigation into (b)(4) contamination also found that another recovered solvent, (b)(4), contained (b)(4) at levels of (b)(4)ppm, more than (b)(4) times your limit of (b)(4) ppm. Without adequate scientific justification, you concluded that the

recovered (b)(4) solvent containing high levels of (b)(4) would not result in significant levels of (b)(4) in your API.

截止 2018 年 12 月，你们在检测确定大部分批次含有 XX 污染高于限度之后召回了你们所有 XX 原料药批次。你们日期为 2018 年 11 月 21 日的调查（补充日期 2019 年 1 月 1 日）得出结论说 XX 污染来源于回收的 XX 溶剂。你们对 XX 污染的调查还发现另一回收溶剂 XX 亦含有 XXppm 的 XX，超出你们限度 XXppm 若干倍。在没有科学论证的情况下，你们得出结论说该含有高水平 XX 的回收 XX 溶剂不会导致你们 API 中显著水平 XX。

In addition, your firm found low levels of (b)(4) in your (b)(4) API. Your investigation concluded this (b)(4) impurity was introduced via contaminated (b)(4) recovered solvents. Notably, you stated in a Field Alert Report (FAR) submitted to FDA on September 13, 2019, that one likely root cause of the (b)(4) contamination found in rejected batches of (b)(4) API was recovered (b)(4) solvent containing (b)(4) at levels as high as (b)(4) ppm.

另外，你公司发现在你们的 XX API 中有低水平 XX。你们调查得出结论说该 XX 杂质是通过受污染的 XX 回收溶剂引入的。值得注意的是，你们在 2019 年 9 月 13 日提交给 FDA 的 FAR 中声称，在拒收的 XXAPI 批次中发现 XX 污染的一个可能根本原因是 XX 回收溶剂含有高达 XXppm 的 XX。

Your firm used recovered solvents such as (b)(4) and (b)(4) from multiple external contract manufacturers, including (b)(4). In January 2019 you restricted the procurement of all (b)(4)-related materials from (b)(4) and in March2019, you removed (b)(4) from your approved manufacturing list. FDA placed (b)(4) on Import Alert 66-40 on June 27, 2019, and issued Warning Letter 320-19-34 on August 8, 2019, due to CGMP deficiencies involving inadequate solvent recovery operations resulting in (b)(4) impurity contamination of solvents supplied to their customers.

你公司使用了来自多个外包生产商的回收溶剂如 XX 和 XX，包括 XX。在 2019 年 1 月，你们限制了采购从 XX 处采购所有 XX 相关物料；在 2019 年 3 月，你们从你们的批准生产商清单中删除了 XX。FDA 于 2019 年 6 月 27 日将 XX 置于进口禁令 66-40 中，并且于 2019 年 8 月 8 日因 CGMP 缺陷签发了警告信 320-19-34，原因是溶剂回收操作不充分导致供应给其客户的溶剂受 XX 杂质污染。

Multiple contract manufacturers supplied solvents that were contaminated with (b)(4), but your firm lacked documentation of which tanks were used to store these solvents. Although you acknowledged that there was no record of usage for each of the recovered solvent tanks, your response did not provide sufficient information on attempts to retrospectively reconcile the number, identification, and usage of the tanks. Furthermore, you did not provide an adequate investigation to determine whether other API could have been impacted by use of storage tanks that held recovered (b)(4) and other (b)(4) API process solvents.

有多个外包生产商供应的溶剂受 XX 污染，但你公司缺乏对存贮这些溶剂的贮罐的文件记录。尽管你们知晓没有记录登记每个回收溶剂贮罐的使用情况，但你们的回复中并未提交充分的信息说明你们努力对贮罐进行回顾性数量、鉴别和用途平衡。另外，你们并未提交一份充分的调查来确定是否有其它 API 可能受到使用贮存回收 XX 和其它 XX API 工艺溶剂的贮罐的影响。

After suspending the use of recovered solvents from contract manufacturers for (b)(4) API,your firm began relying on in-house solvent recovery of (b)(4). While your firm maintained there was no opportunity to produce (b)(4) impurities with your current process, the process performance qualification report for your in-house solvent recovery of (b)(4) found that the solvent contained (b)(4) above your detection limit and (b)(4) at levels above your specification limit.

在停止将来自合同生产商的回收溶剂用于 XX API 之后，你公司开始依赖于自己的 XX 溶剂回收。虽然你们公司当前的生产工艺不会产生 XX 杂质，但你们自己的 XX 溶剂回收工艺性能确认报告显示溶剂中含有的 XX 超出你们的检测限，且 XX 水平超出你们质量标准限度。

In your response, you explained the most probable reason for (b)(4) contamination was theuse of (b)(4) that had been used to store material intended for destruction. You stated you switched to new (b)(4), but your response did not address whether other similar equipment may also need to be replaced or remediated.

在你们的回复中，你们解释说最可能的 XX 污染原因是使用了曾存贮准备销毁的物料的 XX。你们声称你们已换用新的 XX，但你们的回复中并未说明是否有其它类似的设备可能亦需要进行替换或补救。

Furthermore, you stated that you will continue to use fresh solvents until you can validate your in-house solvent recovery process for control of (b)(4) impurities. Your response is inadequate because you did not commit to test fresh and recovered solvents for (b)(4) prior to release for use in API manufacturing.

另外，你们声称你们将继续使用新鲜溶剂直到你们可验证你们自己的溶剂回收工艺可控制 XX 杂质。你们的回复是不充分的，因为你们并未承诺在放行用于 API 生产之前要测试新鲜和回收溶剂中的 XX。

See FDA's guidance document M7 (R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk for approaches to consider where appropriate regarding the presence of mutagenic impurities, at https://www.fda.gov/media/85885/download.

参见 FDA 指南文件 M7（R1）“药品中基因毒性杂质评估和控制以限制潜在致癌风险”。

In response to this letter, provide the following:

在回复本函时请提交以下信息：

- An update on investigations involving recovered solvents, including but not limited to (b)(4) and (b)(4), and corrective action and preventive action (CAPA) plans to avert the presence of (b)(4) and other potential mutagenic impurities in all API manufactured at your firm.
  一份对回收溶剂调查的更新，包括但不仅限于 XX 和 XX，以及避免你公司所生产的所有 API 中出现 XX 和其它潜在诱变性杂质的 CAPA 计划
- Your program for process performance qualification for API and recovered solvents, and ongoing monitoring of both intra-batch and inter-batch variation to ensure a continuing state of control. Include your program for ongoing lifecycle evaluation of impurity profiles for all API.
  你们的 API 和回收溶剂工艺性能确认计划，以及批内和批间波动持续监测计划，以确保持续受控状态。包括你们持续生命周期中所有 API 杂质概况的评估计划。
- Procedures for controlling incoming raw materials, including but not limited to ensuring that they are not co-mingled. In addition, provide an analysis of storage tanks that held contaminated (b)(4) and (b)(4) solvents, and whether material from those tanks was used to manufacture any other API produced by your firm.
  控制进厂原料的程序，包括但不仅限于确保其不会混合的程序。另外，提交一份存贮受污染的 XX 和 XX 溶剂的贮罐的分析，以及是否这些贮罐中物料被你公司用于生产其它任何 API。
- Specifications, including test methods, used to release fresh and recovered solvents in the API manufacturing process. Your response should address capability to detect and quantify a wide array of potential impurities or contaminants, including but not limited to (b)(4).

放行新鲜和回收溶剂用于 API 生产工艺的质量标准，包括检测方法。你们的回复应说明检出和定量较宽范围内潜在杂质或污染物的能力，包括但不仅限于 XX。

- A comprehensive, third-party review of your material system. Provide a report that assesses the adequacy of this system, including but not limited to:
  一份对你们物料系统的第三方全面审核。提交一份该系统的评估报告，包括但不仅限于：
  - incoming lot controls to prevent use of unsuitable materials
    进厂批次控制，以防止使用不适当的物料
  - assignment of appropriate expiration or retest dates
    给定适当的有效期和复验期
  - quality oversight of capability and acceptability of all material suppliers, including qualification standards for initial supplier selection and ongoing lifecycle evaluations to ensure continued supplier acceptability
    对所有物料供应商的能力和可接受度的质量监管，包括供应商初始选择的确认标准，以及生命周期内持续评估标准，以确保供应商持续可接受度
  - all CAPA to be implemented, such as improvements to standard operating procedures (SOPs) and management oversight.
    准备执行的所有 CAPA，如 SOP 改进和管理监管改进

2. Failure to clean equipment and utensils to prevent contamination or carry-over of a material that would alter the quality of the API beyond the official or other established specifications.

未能清洁设备和工器具以防止物料污染或残留改变 API 的质量使得超出官方或其它既定标准。

There is no assurance that your cleaning methods are adequate to clean and prevent contamination or carry-over of drugs manufactured on non-dedicated equipment. Our investigators observed that non-dedicated (b)(4)1102 and (b)(4)1506, were labeled as clean. However, when the interior surfaces of the (b)(4) chutes were wiped with lint-free cloths, (b)(4) stains were observed. Testing you conducted later determined the (b)(4) stains were residual (b)(4) API.

无法确保你们的清洁方法足以清洁和防止非专用设备上所生产药品的污染或残留。我们的检查员发现非专用 XX1102 和 XX1506 被标示为清洁。但是当使用不掉落纤维的布擦拭 XX 导槽的内表面时发现有 XX 污物。你们后来进行的检测确定 XX 污物为残留的 XXAPI。

In your response, you attributed the adherence of residual deposits to rough surfaces on the equipment. Also, as an immediate action, the interior surfaces of the (b)(4) chutes of (b)(4), which were also observed with (b)(4) stains, were ground and polished to smooth surfaces. You also implemented an update to your cleaning procedures.

在你们的回复中，你们将残留物归结于设备表面粗糙。另外，作为即刻措施，也发现了 XX 印迹的 XX 的 XX 导槽的内表面被打磨抛光为光滑表面。你们还更新了你们的清洁程序。

You determined there was minimal impact on product quality based on a review of complaint and out-of-specification investigations. You also stated that all (b)(4) batches and other drugs manufactured were tested for “extraneous matter” and reported no failures. Your response is inadequate. Cross-contamination cannot be assumed to be uniformly distributed and testing alone is insufficient to mitigate the observed contamination hazards.

你们根据对投诉和 OOS 结果调查的回顾认为产品质量影响很小。你们还声称所生产的所有 XX 批次和其它药品均检测了“异物”且报告结果为没有不合格。你们的回复是不充分的。交叉污染是不能假定为均匀分布的，仅是测试不足以缓解所发现的污染危害。

In response to this letter, provide the following:

在回复本函时，请提交以下内容：

- A comprehensive, independent retrospective assessment of your cleaning effectiveness to evaluate the scope of cross-contamination hazards. Include the identity of residues, other manufacturing equipment that may have been improperly cleaned, and an assessment whether cross-contaminated products may have been released for distribution. The assessment should identify any inadequacies of cleaning procedures and practices, and encompass each piece of manufacturing equipment used to manufacture more than one product.
  一份对你们清洁有效性的全面独立回顾性评估，以评估交叉污染危害的范围。包括残留鉴别、其它可能清洁不当的生产设备，以及受到交叉污染的产品是否已被放行销售的评估。该评估应识别清洁程序和做法任何不足，并且指导用于多产品生产的每台设备的清洁。
  - As one element of the risk assessment, describe whether you will be testing all API manufactured on non-dedicated equipment for impurities such as (b)(4) due to your deficient systems for cross-contamination prevention and cleaning. The risk assessment should support your response to this item.
    作为风险评估的一个要素，说明你们是否准备测试非专用设备上生产的所有 API 中由于交叉污染预防和清洁系统缺陷引起的杂质如 XX。该风险评估应能支持你们对此项目的回复。
- Appropriate improvements to your cleaning validation program, with special emphasis on incorporating conditions identified as worst case in your drug manufacturing operation. This should include but not be limited to identification and evaluation of all worst-case:
- 对你们清洁验证程序的适当改进，要特别强调结合你们药品生产操作中认定为最差情形的条件。其中应包括但不仅限于所有最差情形的识别与评估：
  - drugs with higher toxicities
    较高毒性药品
  - drugs with higher drug potencies
    较高活性药品
  - drugs of lower solubility in their cleaning solvents
    在其清洁溶剂中溶解度较低的药品
  - drugs with characteristics that make them difficult to clean
    难以清洁的药品
  - swabbing locations for areas that are most difficult to clean
    最难清洁部位的擦拭取样点
  - maximum hold times before cleaning.
    清洁之前最长放置时间

In addition, describe the steps that must be taken in your change management system before introduction of new manufacturing equipment or a new product.

另外要说明引入新生产设备或新产品之前在你们变更管理系统中必须采取的步骤。

- A summary of updated SOPs that ensure an appropriate program is in place for verification and validation of cleaning procedures for products, processes, and equipment.
  一份更新后的 SOP 摘要，确保具备适当的产品、工艺和设备清洁程序确认和验证程序
- Your CAPA plan to implement routine, vigilant operations management oversight of facilities and equipment. This plan should ensure, among other things, prompt detection of equipment/facilities performance issues, effective execution of repairs, adherence to appropriate preventive maintenance schedules, timely technological upgrades to the equipment/facility infrastructure, and improved systems for ongoing management review.
  你们对设施和设备实施常规化警觉操作管理监管的 CAPA 计划。该计划应确保（除其它外）快速发现设备/设施性能问题、有效进行修理、遵守适当的预防性维护计划、及时对设备/厂房基础设施进行技术升级，以及改进持续管理审评体系。

CGMP Consultant Recommended CGMP 顾问建议

Based upon the nature of the deviations we identified at your firm, we strongly recommend engaging a consultant qualified to evaluate your operations to assist your firm in meeting CGMP requirements.

由于你们未能纠正重复的违规情况，我们强烈建议你们使用一位有 21 CFR211.34 所述资质的顾问来协助你们公司符合 CGMP 要求。

Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for fully resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

你们使用顾问并不能解除你们公司符合 CGMP 的义务。你们公司的高级管理层仍负有义务全面解决所有缺陷，确保持续 CGMP 符合性。

Additional API CGMP Guidance 其它 API CGMP 指南

FDA considers the expectations outlined in ICH Q7 when determining whether API are manufactured in conformance with CGMP. See FDA's guidance document Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredientsfor guidance regarding CGMP for the manufacture of API at https://www.fda.gov/media/71518/download.

FDA 在确定 API 生产是否符合 CGMP 时考虑的是 ICHQ7 里所列要求。参见 FDA 指南文件 Q7"API GMP"。

Conclusion 结论

The deviations cited in this letter are not intended to be an all-inclusive list of deviations that exist at your facility.You are responsible for investigating and determining the causes of these deviations and for preventing their recurrence or the occurrence of other deviations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you

to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C.356C(b). This also allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

如果你们在考虑要采取的措施可能会导致你们工厂所生产的药品供应中断，FDA 要求你立即联系 CDER 药品短缺负责人员，这样 FDA 可以与你们一起采用最为高效的方式引导你们的操作符合法规要求。联系药品短缺负责人员还能让你满足依据 21 U.S.C. 356C(b)你可能必须报告你们药品中止或中断的义务，让 FDA 尽快考虑是否需要采取何种措施来避免短缺，保护依赖于你们药品的患者健康。

Until you correct all deviations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产的新申报和增补申报的批准。

Failure to correct these deviations may also result in FDA refusing admission of articles manufactured at Mylan Laboratories Limited, Unit 8 at G. Chodavaram Village, Vizianagaram, Andhra Pradesh, India into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C.381(a)(3). Under the same authority, articles may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&CAct, 21 U.S.C. 351(a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your deviations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

7. 320-20-07 2019-11-06 Greenbrier International, Inc.美国

Dear Mr. Philbin:

The U.S. Food and Drug Administration (FDA) inspected your corporate headquarters, Greenbrier International, Inc.(Greenbrier) (FEI 3005269673) at 500 Volvo Parkway, Chesapeake, Virginia, fromJanuary 14 to 18, 2019 after FDA inspections revealed violative conditions at multiple foreign drug manufacturers that supplied drugs to your distribution network. Firms inspected by FDA included contract manufacturers used to manufacture Dollar Tree's Assured Brand drugs. The FDA inspections of these foreign facilities revealed significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals, Title21 , Code of Federal Regulations, Pa,is 2 10 and 211 (21 CFR Parts 210 and 211). Additionally, FDA inspected your distribution center warehouse located at 1330 Executive Boulevard (FEI 3004319430). Chesapeake, Virginia, fromJanuary 14 to 17, 2019. This facility operates under the name Dollar Tree Distribution. Inc. and stores your finished drug products, which it then distributes to Dollar Tree and other retail stores.

在 FDA 检查发现为你们分销网络供应药品的多个海外药品生产商违规情况后，美国 FDA 于 2019 年 1 月 14-18 日检查了你们公司总部，位于弗吉利亚切萨皮克沃尔沃公园路 500 号的 Greenbrier International, Inc.(Greenbrier) (FEI 3005269673)。FDA 已检查过的公司包括用于生产 Dollar Tree 品牌药品的合同生产商。FDA 对这些海外工厂的检查发现它们严重违反制剂 CGMP 法规（21 CFR 第 210 和 211 章节）。另外，FDA 于 2019 年 1 月 14-17 日检查了你们位于弗吉利亚切萨皮克行政大道 1330 号（FEI 3004319430）的分销中心仓库。该场所以 Dollar Tree 分销公司的名义运营，存贮你们的制剂成品，这些药品后续被运至 Dollar Tree 和其它零售店。

The inspection revealed that you had limited manufacturing operations at your corporate headquarters. However, the CGMP violations identified at your suppliers caused drug products manufactured by these firms to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Your receipt in interstate commerce of adulterated drugs, and the delivery or proffered delivery thereof,is a violation of section 30 I (c) of the FD&C Act, 21 U.S.C. 33 I (c).

检查发现你们在公司总部有很少部分生产活动，但在你们供应商处发现的 CGMP 违规情况导致这些公司所生产的药品依据 FDCA 第 501(a)(2)(B)条款成为掺假药品。你们在州际贸易中接收掺假药品，然后送往或提供运送违反了 FDCA 第 30 I (c)条款 21 U.S.C. 33 I (c)。

We reviewed your February 5, 20 I 9 response indetail and acknowledge receipt of subsequent correspondence.

我们仔细审核了你们 2019 年 2 月 5 日的回复并此告知已收到后续信函。

Receipt of Adulterated Drugs from Contract Manufacturers and Suppliers

从合同生产商和供应商处接受掺假药品

Our inspection and review of import data revealed the following:

我们检查和审核进口数据发现以下情况：

1. Import records reviewed indicated that your firm received Acne Treatment Pads and (b)(4) from Shanghai Weierya Daily Chemicals Factory, FEI 3010166363, on October 9, 2017 and November 3, 2017, respectively. An inspection of Shanghai Weierya Daily Chemicals in April of 2017 revealed significant CGMP violations, including the failure to conduct component identity testing (21 CFR

211.84(d)(1)) and the failure to test each batch of drug for objectionable microorganisms prior to distribution (21 CFR211.165(b)). As a result of these and other violations, Shanghai Weierya Daily Chemicals was placed on Import Alert 66-40 on September 14, 2017 and issued a warning letter on February 7, 2018. FDA copied your Chief Operating Officer (COO) on the outgoing warning letter.

进口记录显示你公司于 2017 年 10 月 9 日和 2017 年 11 月 3 日分别接收了来自上海唯尔雅日用化学品厂 FEI3010166363 的痤疮治疗垫。2017 年 4 月对上海维尔雅日用化学品厂的检查发现有严重 CGMP 违规情况，包括未能对组份进行鉴别测试（21 CFR 211.84(d)(1)），以及未在销售之前检测每批药品的致病菌（21CFR 211.165(b)）。由于这些和其它违规情况，上海维尔雅日用化学品厂于 2017 年 9 月 14 日被置于进口禁令 66-40 中，并且于 2018 年 2 月 7 日被签发了警告信。FDA 将签发警告信的情况抄送给了你们的首席运营官（COO）。

2. Import records reviewed indicated that your firm received various (b)(4) and (b)(4) drug products from Hangzhou Zhongbo Industrial Company, Ltd., FEI 3008229416, from October through Decemberof 2018. An inspection of Hangzhou Zhongbo Industrial Company, Ltd. in April of 2018 revealed significant CGMP violations, including the failure to test eachbatch of drug for conformance with specifications prior to release (21 CFR 211.165(a)). As a result of this and other violations, Hangzhou Zhongbo Industiial Company, Ltd. was placed on Import Alert 66-40 on September 28, 2018 and was issued a warning letter on November 27, 2018. FDA copied your COO on the outgoing warning letter.

进口记录审核显示你公司于 2018 年 10 月至 12 月间接收了来自杭州中波实业公司 FEI 3008229416 的多个 XX 和 XX 药品。2018 年 4 月对杭州中波实业公司的检查发现严重 CGMP 违规，包括未在放行之前检测每批药品是否符合质量标准（21 CFR 211.165(a)）。由于此项和其它违规情况，杭州中博实业公司于 2018 年 9 月 28 日被置于进口禁令 66-40 中，并且于 2018 年 11 月被签发了警告信。FDA 将签发警告信的情况抄送给了你们的 COO。

We note that during the inspection of your corporate headquarters, you stated that if you were made aware that a warning letter was issued to one of your suppliers or contract manufacturers, you would not purchase over-the-counter (OTC) drug products from that contract manufacturer any longer. Additionally, in your February 5, 2019 response you state, "If a drug product is placed on Import Alert 66-40 (appearing not to comply with drug manufacturing cGMPs), Greenbrier ceases importing drug products from that establishment." The import data detailed above demonstrate this is not always the case.

我们注意到在对你们公司总部检查期间，你们声称如果你们了解你们任何供应商或合同生产商有被签发警告信，你们就不会再向其采购 OTC 药品。另外，在 2019 年 2 月 5 日的回复中你们声称：“如果药品被置于进口禁令 66-40（不符合药品生产 CGMP），Greenbrier 会停止从该场所进口药品”。上述详细进口数据证明并不总是这样的。

We also note that Greenbrier has, at various points in time, used contract manufacturers and suppliers with histories of significant drug CGMP violations. For example, our inspections revealed that beyond the facilities detailed above, your firm has used the following contract manufacturers and suppliers:

我们还注意到 Greenbrier 在不同时间点使用有严重药品 CGMP 违规历史的合同生产商和供应商。例如，我们检查发现除了上述场所外，你公司曾使用过以下合同生产商和供应商：

1. (b)(4), FEI (b)(4), which was issued a warning letter on (b)(4), for, among other things, not testing raw materials prior to use in drug manufacturing and not testing finished drug products prior to distribution.

XX，FEI 号 XX，该场所在 XX 被签发了警告信，违规情况包括未在用于药品生产之前对原料进行检测，以及未在销售之前对原料进行检测，在销售之前未对成品进行检测

2. Bicooya Cosmetics Limited, FEI 3010671652, which was issued a warning letter on August 11, 2017. This firm was also placed on Import Alert 66-40 on June 29, 2017, for, among other things, not testing finished drug products prior to distribution and for rodent feces found throughout the manufacturing facility. FDA copied your COO on the warning letter.

碧蔻雅化妆品有限公司，FEI 3010671652，已于 2017 年 8 月 11 日被签发警告信。该公司亦于 2017 年 6 月 29 日被置于进口禁令 66-40，除其它违规事项外，他们未在销售之前检测药品成品以及在整个生产车间发现啮齿动物粪便。FDA 已将警告信抄送你们 COO。

3. (b)(4), FEI (b)(4), which was issued a warning letter on (b)(4). This firm was also placed on Import Alert 66-40 on (b)(4) for, among other things, falsifying test results and releasing sub-potent drugs to the U.S. market. FDA copied your COO on the warning letter.

XX，FEI 号 XX，该公司于 XX 被签发警告信。该公司亦于 XX 被置于进口禁令 66-40，除其它违规事项外，他们伪造检测结果和放行含量不够的药品至美国市场。FDA 已将警告信抄送你们 COO。

4. Ningbo Pulisi Daily Chemical Products Company, FEI3003727322, which was issued a warning letter on August 13, 2019. This firm wa salso placed on Import Alert 66-40 on June 10, 2019, for, among other things,not testing raw materials for identity prior to use in drug manufacturing, and not testing finished drug products prior to release. FDA copied your COO on the warning letter.

宁波普力丝日用化学品公司 FEI 3003727322，已于 2019 年 8 月 13 日被签发警告信。该公司亦于 2019 年 6 月 10 日被置于进口禁令 66-40，除其它违规事项外，他们在将原料药用于药品生产之前未对原料进行检测，在成品放行之前未进行检测。FDA 已将警告信抄送你们 COO。

For manufacturers that are listed on Import Alert 66-40 for failure to conform to current good manufacturing practices within the meaning of Section 501(a)(2)(B), FDA has evidence that the drugs noted in the Import Alert appear to be adulterated. You are responsible for ensuring that the drugs you distribute are manufactured in compliance with all relevant CGMP requirements for drugs. Up to elate information regarding import alerts can befound at the following FDA website: https://www.accessdata.fda.gov/cms_ia/ialist.html.

对于因不符合第 501(a)(2)(B)条款 CGMP 要求已列入进口禁令 66-40 的生产商，FDA 有证据证明在进口禁令上所列药品为掺假药品。你们有义务确保你们销售的药品在符合所有药品相关 CGMP 要求的条件下生产。关于进口禁令的相关信息可在上述 FDA 官网找到。

Considering that FDA has found a pattern of drug manufacturers with serious CGMP violations in your supply chain, in response to this letter, provide a detailed plan to ensure you do not receive or deliver adulterated drugs in interstate commerce, in violation of section 301 (c) of the FD&C Act, 21 U.S.C. 331(c). Items in your plan should include a full evaluation of your supplier and contract manufacturer evaluation program, including a plan to audit your suppliers. Furthermore, you should also include a full reconciliation of any drugs from the manufacturers listed above, as well as for all firms or drugs currently on FDA import alerts, to determine if you have any remaining drugs in your possession, either in your distribution network or in retail stores under the Dollar Tree, Family

Dollar,or any other retail store brands in your network. FDA encourages entities that engage in manufacturing related solely to drug distribution (e.g.,distributors, brokers, private label distributors, own label distributors) to follow recommendations in FDA's guidance document Contract Manufacturing Arrangements for Drugs: Quality Agreements at https://www.fda.gov/media/86193/download.

考虑到 FDA 已发现你们的供应链中药品生产商有着严重 CGMP 违规的模式，在回复本函时，请提交一份详细的计划，确保你们不会在州际贸易中接受或发运掺假药品，违反 FDCA 第 301 (c)条款 21 U.S.C. 331(c)。在你们计划中的内容应包括对你们供应商和合同生产商评估计划的全面评估，包括审计你们供应商的计划。你们还应包括一份来自上述生产商的所有药品，以及当前列在 FDA 进口禁令的所有公司或药品的全面衡算清单，确定你们是否还持有任何剩余药品，或滞留在你们 Dollar Tree、Family Dollar 名下销售网络或零售店内，或其它任何你们网络的零售店品牌。FDA 鼓励从事仅与药品销售有关的生产实体（例如，分销商、代理商、私人贴标分销商、自有标签分销商）遵守 FDA 指南文件“药品合同生产商安排：质量协议”中的建议。

Use of Bureau Veritas To Conduct Testing of Drug Products

使用必维国际检验集团执行药品检测

You have a contractional relationship with Bureau Veritas (BVS) to conduct testing of articles (including drugs) that you distribute. FDA inspections of the aforementioned contract manufacturers and suppliers revealed that you directed your contract manufacturers and suppliers to use BVS as a contract laboratory. FDA also collected a copy of your quality manual at an FDA inspection of a BVS laboratory that indicates you require your contract manufacturers and suppliers to use BVS to test drugs distributed by Greenbrier International/Dollar Tree.

你们与必维国际（BVS）之间有委托执行你们所销售的产品（包括药品）检测的关系。FDA 对上述合同生产商和供应商的检查发现你们指示你们的合同生产商和供应商使用 BVS 作为合同实验室。FDA 在对一个 BVS 实验室进行检查期间亦采集了你们一份质量手册副本，其中说你们要求你们的合同生产商和供应商使用 BVS 检测 Greenbrier International/Dollar Tree 所销售的药品。

During FDA inspections of your suppliers, some of the firms listed above asserted to FDA that they relied on technical lab reports bearing both Greenbrier International and BVS logos to support release and distribution of drug products to the United States. FDA inspected one BVS location in February 2018 that generated such a technical report and found multiple inadequacies related to test methods BVS employed for the analyses of drugs. Both during this FDA inspection, and in subsequent written correspondence submitted to the FDA, BVS representatives asserted that BVS's test methods were not suitable for drug COMP purposes and that its test results were not suitableto make release decisions of drug products for distribution into the U.S. supply chain.

在 FDA 对你们的供应商检查期间，有些公司列出上述信息向对 FDA 说他们依赖于有 Greenbrier 国际与 BVS 图标的技术实验室报告来支持药品放行和销往美国。FDA 于 2018 年 2 月检查了一个 BVS 实验室，该实验室制作了一份这样的技术报告，并发现多个与 BVS 所用药品检测方法有关的不足。无论是在此次 FDA 检查期间，还是在后续提交给 FDA 的书面沟通中，BVS 代表声称 BVS 的检测方法不适用于药品 CGMP 用途，该检测结果不适合用于做出药品销往美国供应链的放行决策。

Your purchasing agreements require suppliers to use BVS testing for the purpose of acceptance of distributed drugs, despite the fact that BVS could not provide adequate assertion of drug quality.

This testing cannot be used as a substitute for testing required under FDA regulations. You are responsible for ensuring that the drugs you distribute are not adulterated, including ensuring that all drug manufacturers supplying Greenbrier with drugs have had release testing conducted in accordance with COMP requirements.

虽然 BVS 并不提供充分的药品质量保证，但你们的采购协议要求供应商使用 BVS 测试作为所销售药品的接受条件。该检测不能用于替代 FDA 法规所要求的检测。你们有义务确保你们销售的药品不是掺假药品，包括确保所有药品生产商为 Greenbrier 供应依据 CGMP 要求进行了放行检测的药品。

Regulatory Meeting 法规会议

Upon submission of your response to this letter, please contact Ginneh Stowe, by e-mail at Ginneh.Stowe@fda.hhs.gov, to schedule a meeting to discuss the adequacy of the corrective actions you proposed to prevent the continued introduction of adulterated goods into interstate commerce.

在你们提交针对本函的回复时，请通过邮件 Ginneh.Stowe@fda.hhs.gov 联络 Ginneh Stowe 安排一次会议，讨论你们提议防止继续引入掺假产品至州际贸易的纠正措施的充分性。

Conclusion 结论

Violations in this letter are not intended as an all-inclusive list. You are responsible for promptly correcting and addressing the above violations and other violations of the FD&C Act and implement in regulations. Failure to promptly correct the violations may result in legal action without further notice including, without limitation, seizure and injunction.

此函中所引用的违规并不是全部。你们有责任立即纠正和解决上述违规情况和其它违反 FDCA 的情况，并执行法规要求。未能立即改正违规情况可能会导致无进一步通知情况下的无底线强制措施，包括扣留和禁令。

In addition, we note that some of the products that you import are also regulated as cosmetics. For example, you import products from Bicooya Cosmetics Limited that are both OTC drugs and cosmetics. Under section 601(c) of the FD&C Act (21 U.S.C. 361 (c)), a cosmetic shall be deemed to be adulterated if it has been prepared, packed, or held under insanitary conditions whereby they may have become contaminated with filth, or whereby they may have been rendered injurious to health. Some of the sanitation conditions that cause OTC drug products to be adulterated may also cause cosmetic products to be adulterated. Under section 301(a) of the FD&C Act(21 U.S.C. 331 (a)), it is a prohibited act to introduce or deliver for introduction into interstate commerce a cosmetic product that is adulterated. Additionally, the receipt in interstate commerce of adulterated cosmetics, and the delivery or proffered delivery thereof, is a prohibited act under section 301(c) of the FD&C Act.

另外，我们注意到你们进口的一些药品亦作为化妆品被管制。例如，你们从碧蔻雅化妆品有限公司进口的产品既是药品也是化妆品。依据 FDCA 第 601(c)条款，化妆品如果在不卫生条件下制备、包装或保存，则可能受到脏物污染，或对健康造成危害。有些导致 OTC 药品成为掺假药品的卫生条件可能亦会导致化妆品成为掺假产品。依据 FDCA 第 301(a)条款，禁止引入或运输掺假化妆品进入州际贸易。另外，在州际贸易中接收掺假化妆品并运送或提供运送均是 FDCA 第 301(c)条款所禁止的。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you

cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

8. 320-20-08 2019-00-00 FDA 尚未发布

9. 320-20-09 2019-12-03 Henan Kangdi Medical Devices Co. Ltd.河南康迪药械有限公司

Dear Mr. Qi Lei:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Henan Kangdi Medical Devices Co.Ltd., 3009271465, at SME Pioneer Park, No. 4, 2nd Area, Zhoukou, Henan, from March 4 to 7, 2019.

美国 FDA 于 2019 年 3 月 4 日至 7 日检查了你们位于河南周口淮阳县产业集聚区中小企业创业园二区四号的河南康迪药械有限公司生产场所。

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

本警告信总结了制剂生产严重违反 CGMP 的行为。参见 21CFR 第 210 与 211 部分。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

由于你们的制剂生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的药品根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C. 351(a)(2)(B)被认为是掺假药品。

Your firm manufactures "Capsicum Plaster HOT" and " 1st Medx-Patch With 4% Lidocaine." These products are unapproved new drugs in violation of section 505(a) of the FD&C Act, 21U.S.C. 355(a). Introduction or delivery for introduction of such products into interstate commerce is prohibited under section 301(d) of the FD&C Act, 21 U.S.C. 331(d). These violations are described in more detail below.

你公司生产“巴布贴止痛膏药”和“4%利多卡因 1st Medx-Patch”。这些产品为未经批准的新药，违反了 FDCA 第 505(a)条款 21 U.S.C. 355(a)。引入或运输此类药品至州际贸易是 FDCA 第 301(d)条款 21U.S.C. 331(d)所禁止的行为。这些违规情况在以下有详细描述。

We reviewed your March 22, 2019, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

我们已详细审核了你公司 2019 年 3 月 22 日对 FDA 483 表的回复，并此告知已收到后续通信。

During our inspection, our investigator observed specific violations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

1. Your firm failed to have, for each batch of drugproduct, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release (21 CFR 211.165(a)).

你公司未能在放行之前对每批药品进行恰当的实验室检测，确定其符合药品最终质量标准，包括每种活性物质的鉴别（21 CFR 211.165(a)）。

Your firm manufactures and distributes various over-the-counter (OTC) transdermal patch drug products such as "Capsicum Plaster HOT" pain relieving and " (b)(4) for the United States market. Our inspection found that you did not test your finished drug products to determine whether each batch met identity and strength specifications before being released to the U.S. market. Complete testing of each batch before release is an essential part of determining if a drug product batch meets its specifications.

你公司生产和销售不同的 OTC 贴剂，如“巴布贴止痛膏药”和“XX”至美国市场。我们检查发现你们并未在放行至美国市场之前检测你们的成品，确定是否每批均符合鉴定和剂量标准。每批次药品放行之前完成检测是确定药品满足其质量标准的基本要求。

The quality unit must be empowered to make final quality decisions. It is essential that the quality unit be enabled to provide timely oversight of all laboratory and manufacturing data that could impact product quality, whether or not lots have already been distributed. When making batch disposition decisions, the quality unit must be provided with all batch production and control records, including all deviations and test data, to enable a fully informed and appropriate decision regarding suitability for distribution. The quality unit must assure that drug products are fully tested for all critical attributes prior to release.

质量部门必须有能力做出最终质量决策。无论产品是否已销售，质量部门有能力对所有可能影响产品质量的实验室和生产数据进行及时监管是很基本的要求。在做出批处置决策时，必须为质量部门提供所有批生产和检测记录，包括所有偏差和检测数据，使其获得全面信息，做出关于是否适合销售的恰当决策。质量部门必须确保药品在放行之前所有关键属性均经过全面检测。

In your response, you stated that you will searchfor a third-party testing laboratory with adequate capabilities. Additionally, you committed to test for the active ingredient in each batch of finished drug products sold within the U.S. market to ensure product specifications are met.

在你们的回复中，你们声称你们将搜索具有足够能力的第三方检测实验室。另外，你们承诺要检测销往美国市场的每批成品中的活性成分，以确保其符合产品质量标准。

Your response is inadequate because you did not include information about your third-party testing laboratory including nameand location, methods, or a detailed description of the tests they will conduct (e.g., identity, strength and purity). Furthermore, you did not provide how you will evaluate the capability of your third party to perform the intended tests. Additionally, you provided no testing documentation for finished drug product batches currently in the U.S. market.

你们的回复是不充分的，因为你们并未包括你们第三方检测实验室的信息，包括名称和位置、方法，或你们将要执行的检测的详细描述（例如，鉴别、剂量和纯度）。另外，你们并未提交说明你们将如何评估你们第三方执行所需检测的能力。另外，你们未提交当前仍在美国市场的成品批次检测文件。

In response to this letter, provide:

在回复本函时请提交：

- A comprehensive and independent review of your laboratory practices, procedures, methods, equipment, and analyst competencies. Based on this review, provide a detailed corrective action and preventive action (CAPA) plan to fully remediate your laboratory system. Your plan should also include the procedures you will use to evaluate the effectiveness of the implemented CAP A plan.

一份对你们实验室规范、程序、方法、设备和分析资质的全面独立审核。根据此审核，提交一份详细的 CAPA 计划，全面补救你们的实验室系统。你们的计划还应包括你们将用于评估所实施 CAPA 计划的有效性的程序。

- A list of all analytical test methods and specifications used to analyze each batch of your drug products before making the batch disposition decision. Include associated written procedures.
一份在批处置决策之前用于分析你们每批药品的所有分析检测方法和质量标准的清单。包括相关的书面程序。
- A summary of test results obtained from retrospective testing of retain samples of all drug product batches currently in distribution in the U.S. Include test results for identity and strength of active ingredients, and all other appropriate chemical and microbial quality attributes. If you released any batch that was out of specification, indicate the corrective actions you will take, such as customer notifications and product recalls. Provide a timeline for completing this testing expeditiously.
一份对所有当前销售至美国的所有产品批次留样回顾检测所得检验结果总结。包括活性成分的鉴别和剂量检测结果，以及所有其它适当的化学和微生物质量属性。如果你们已放行了任何 OOS 批准，请说明你们将采取的纠正措施，如通知客户和召回产品。提交一份尽快完成该检测的时间表。
- A summary of your program for qualifying and overseeing contract facilities that test the drug products you manufacture.Your summary should include, but not be limited to, your procedure to ensure that any test methods performed by a contract testing laboratory on your behalf are properly validated prior to use for batch analysis. Additionally, include the procedure to evaluate the capability of your third party to accomplish the testing they are contracted to perform.
一份你们确认和监管检测你们生产的药品的合同场所的计划摘要。你们的总结应包括但不仅限于你们用于确保合同检测实验室代表你们所执行所有检测方法在用于批分析之前经过适当验证的程序。另外，要包括评估你们第三方受托完成检测的程序。

2. Your firm failed to conduct at least one test to verify the identity of each component of a drug product. Your firm also failed to validate and establish the reliability of your component supplier's test analyses at appropriate intervals (21 CFR 211.84(d)(1) and (2)).

你公司未能执行至少一项检测来核查药品中每种成分的鉴别。你们公司亦未以恰当的时间间隔验证和建立你们成分供应商的检测分析的可靠性（21 CFR 211.84(d)(1) and (2)）。

You failed to test incoming active pharmaceutical ingredients (API) and other raw materials (e.g., (b)(4)) used to manufacture your drug products to determine their identity, purity, strength, and other appropriate quality attributes. Instead, our investigator observed your firm released API and other materials for use in manufacturing based solely on a visual inspection of the contents of material containers and a review of component suppliers· analyses reports. You did not retain these suppliers' analysis reports, but discarded them after review. Additionally, you did not establish the reliability of your suppliers' analyses through appropriate validation. Your firm did not ensure that at least one specific identify test was conducted for each lot of your incoming materials. This violation was also observed during the December 2016 inspection, after which you committed to test incoming raw material.

你们未检测进厂 API 和其它用于生产你们药品的原料（例如 XX），以确定其鉴别、纯度、含量和其它适当的质量属性。相反，我们调查员发现你公司仅根据对物料包装的目视检查和对成分供应商的

分析报告就放行了 API 和其它生产所用原料。你们并未保存这些供应商的分析报告，而是在审核之后就丢弃了。另外，你们并未通过适当的验证建立你们供应商的分析可靠性。你公司未能确保对你们每批进厂物料至少进行一项鉴别检查。该项违规在 2016 年 12 月的检查中亦有发现，之后你们承诺将对进厂原料进行检测。

In your response, you stated your intent is to finda qualified third-party testing laboratory, revise your procedure for incoming material, and send to the third-party laboratory each lot of active ingredient used in drug products for U.S. supply.

在你们的回复中，你们声称你们准备找一家经过确认的第三方检验实验室，修订你们的进厂原料程序，并将每批用于美国市场药品的 API 送至第三方实验室。

Your response is inadequate because you did not commit to cease manufacturing drugs until the required testing of drug components is in place, and you did not conduct a risk assessment for products already in distribution in the United States. Furthermore, your response did not include the testing of raw materials, other than active ingredients, used in your finished drug products. Additionally, you failed to address how you will establish the reliability of your suppliers' analyses, and provided no documentation to support your CAPA plan.

你们的回复是不充分的，因为你们并未承诺停止生产药品，直到对药品成分进行所需检测；并且你们亦未对已销售至美国的药品进行风险评估。还有，你们的回复并未包括有对 API 以外的药品生产所用原料的检测。另外，你们未说明你们要如何建立你们供应商分析的可能性，亦未提交文件支持你们的 CAPA 计划。

In response to this letter, provide:

在回复本函时请提交：

- A comprehensive, independent review of your material system to determine whether all containers, closures, and ingredients from each supplier are adequately qualified, assigned appropriate expiration or retest dates, and have incoming material controls adequate to prevent use of unsuitable components, containers, and closures.
  一份对你们原料系统的全面独立审核，以确定是否来自每个供应商的所有容器、密闭器和成分均经过充分确认、给定适当的有效期或复验期，并对进厂原料进行充分控制，防止使用不适当的成分、容器和密闭器。
- The chemical and microbiological quality control specifications you will use to determine disposition of each incoming lot of components before use in manufacturing.
  你们在将每批进厂原料用于生产前，用于确定其化学和微生物质量控制标准
- A description of how you will test each component lot for conformity with all appropriate specifications for identity, strength, quality, and purity. If you intend to accept any testing results on your suppliers' certificates of analysis (COA) in lieu of testing each component lot for purity, strength, and quality, specify how you will first establish the reliability and consistency of your suppliers' test results for these attributes through initial validation as well as periodic re-validation. Inaddition, include a commitment to always conduct at least one specific identity test for each incoming component lot.
  说明你们要如何检测每批组份，确认其符合所有适当的鉴别、含量、质量和纯度标准。如果你准备接受你们供应商 COA 上的任何检测结果，取代组份批次的纯度、含量和质量检测，请说明

你们要如何通过初始验证和定期重新验证首先建立你们供应商对这些属性检测结果的可靠性和一致性。另外，请包括一份对每批进厂原料执行至少一项特定鉴别的承诺。

- A summary of test results obtained from full testing of all components to evaluate the reliability of the COA from each component manufacturer. Include your standard operating procedure that describes this COA validation program.
  一份来自所有原料全检的结果总结，用于评估每个原料生产商的 COA 的可靠性。在其中包括你们描述该 COA 验证程序的 SOP。

3. Your firm failed to assure that the drug product bore an expiration date that was supported by appropriate stability testing (21CFR 211.137(a)).

你公司未能确保药品具备由适当的稳定性检测数据支持的有效期（21 CFR 211.137(a)）。

Your firm has not established an adequate stability program to support the (b)(4) expiration date assigned to your drug products. You lack sufficient data to demonstrate that the chemical and microbiological properties of your drug products will remain acceptable throughout their labeled expiry period.

你公司未建立充分的稳定性程序，用于支持为你们药品给定的有效期。你们缺少充分的数据来证明你们药品的化学和微生物属性在其标示的有效期内能够保持在可接受范围内。

In your response, you committed to conduct stability testing on your drug products under accelerated conditions, and to ensure such testing are on samples held under appropriate temperature and humidity control.

在你们的回复中，你们承诺会对你们的药品执行加速条件稳定性检测，并确保此检测样品会放置在适当温湿度控制下。

Your response is inadequate because you failed to provide stability protocols, including all relevant quality attributes and acceptance criteria, and you did not provide assurance that your test methods will be adequate to assess drug stability. In addition, you did not clarifywhether your stability testing will be conducted under real time conditions to support your OTC drug product expiry. Furthermore, you did not indicate any actions to ensure that all distributed drug product batches maintain their quality attributes through their labeled expiry.

你们的回复是不充分的，因为你们未能提交稳定性方案，包括所有相关质量属性和可接受标准，你们亦未能保证你们的检测方法足以评估药品的稳定性。另外，你们并未说明你们的稳定性测试是否会在实时条件下执行，以支持你们的 OTC 药品有效期。还有，你们并未说明为确保所有已销售的药品批次在其标示有效期内能够保持其质量属性而采取的任何措施。

Based upon the lack of material testing, finished testing, and stability testing, there is minimal assurance that your drug manufacturing operations are capable of operating in a state of control.

鉴于物料检测、成品检测和稳定性检测的缺失，你们无法确保你们的的药品生产操作处于受控运行状态。

In response to this letter, provide:

在回复此函时请提交：

- A comprehensive, independent assessment and CAPA plan to ensure the adequacy of your stability program. Your remediated program should include, but not be limited to:
  一份全面独立的评估和 CAPA 计划，用以确保你们的稳定性计划的充分性。你们的补充计划应包括但不仅限于：
  - Stability indicating methods
    稳定性指示性方法
  - Stability studies for each drug product in its marketed container-closure system before distribution is permitted
    在允许销售之前，每种药品的在其上市容器-密闭器系统中的稳定性研究
  - An ongoing program in which representative batches of each product are added each year to the program to determine if the shelf-life claim remains valid
    一份持续计划，确保每年会将每种药品代表性批次增加至计划中以确定是否货架期声明保持有效
  - Detailed definition of the specific attributes to be tested at each station (timepoint)
    详细规定在每个时间点要检测的特定属性
- All procedures that describe these and other elements of your remediated stability program.
  所有描述你们经过弥补的稳定性计划的这些和其它要素的程序
- A detailed program for designing, validating, maintaining, controlling and monitoring each of your manufacturing processes that includes vigilant monitoring of intra-batch and inter-batch variation to ensure an ongoing state of control. Also, include your program for qualification of your equipment and facility.
  设计、验证、维护、控制和监测你们每个生产工艺的详细计划，包括批间和批内波动性警戒监测，以确保持续受控状态。另外，请包括你们设备和设施确认的计划。
- A description how top management will support quality control, quality assurance, and reliable operations, including but not limited to timely provision of oversight and resources to proactively address deficiencies in laboratories and manufacturing in order to support robust operations.
  一份描述高级管理人员要如何支持质量控制、质量保证和可靠操作的说明，包括但不仅限于及时监管和提供资源积极解决实验室和生产缺陷，以支持稳健的运行。

Quality Unit Authority 质量部门权力

Significant findings in this letter indicate that your quality unit is not fully exercising its authority and/or responsibilities. Your firm must provide the quality unit with the appropriate authority and sufficient resources to carry out its responsibilities and consistently ensure drug quality. See FDA's guidance document Quality Systems Approach to Pharmaceutical CGMP Regulations for help implementing qualitysystems and risk management approaches to meet the requirements of CGMP regulations 21 CFR, parts 210 and 211 at https://www.fda.gov/media/71023/download.

在本函中所列的严重缺陷显示你们的质量部门未能全面履行其权力和/或义务。你公司必须为质量部门提供适当的权力和足够的资源，使其可履行其职责，持续确保药品质量。参见 FDA 指南文件“药品 CGMP 法规质量体系方法”，用于帮助实施质量体系和风险管理方法，以符合 CGMP 法规 21CFR 第 210 和 211 部分的要求。

Repeat Observations at Facility 工厂重复缺陷

In a previous inspection, dated December 12 to 14,2016, FDA cited similar CGMP observations. You proposed specific remediation for these observations in your response. Repeated failures demonstrate that executive management oversight and control over the manufacture of drugs is inadequate.

在之前 2016 年 12 月 12-14 日的现场检查中，FDA 发现了类似的 CGMP 缺陷。你们在回复中对这些缺陷提交了补救措施。重复失败证明你们的高级管理层对药品生产的监管和控制是不充分的。

Use of Contract Manufacturers 使用合同生产商

Drugs must be manufactured in conformance with CGMP. FDA is aware that many drug manufacturers use independent contractors such as production facilities, testing laboratories, packagers, and labelers.FDA regards contractors as extensions of the manufacturer.

药品生产必须符合 CGMP 要求。FDA 了解许多药品生产商使用独立合同方如生产场所、检测实验室、包装商和贴标商。FDA 将合同商作为生产商的外延部分来对待。

You are responsible for the quality of your drugs regardless of agreements in place with your contract facilities. You are required to ensure that drugs are made in accordance with section 501(a)(2)(B) of the FD&C Act to ensure safety, identity, strength, quality, and purity. See FDA's guidance document Contract Manufacturing Arrangements for Drugs:Quality Agreements at https://www.fda.gov/media/86193/download.

虽然你们与药品合同场所订有协议，但你们仍对你们的药品质量负有义务。你们应确保药品生产符合 FDCA 第 501(a)(2)(B)条款对安全性、鉴别、剂量、质量和纯度的要求。参见 FDA 指南文件“药品合同生产安排：质量协议”。

CGMP Consultant Recommended CGMP 顾问建议

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualified as set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements if your firm intends to resume manufacturing drugs for the U.S. market. We also recommend that the qualified consultant perform a comprehensive audit of your entire operation for CGMP compliance and that the consultant evaluates the completion and efficacy of your corrective actions and preventive actions before you pursue resolution of your firm's compliance status with FDA.

基于我们在你工厂发现的违规情况，如果你公司有意恢复为美国市场生产药品，我们强烈建议你们使用一位有 21 CFR 211.34 所述资质的顾问来协助你们公司符合 CGMP 要求。我们亦建议该有资质的顾问对你们的整体运行情况进行全面 CGMP 合规审计，并在你们寻求你公司的 FDA 合规状态之前由该顾问对你们 CAPA 的完成情况和有效性进行评估。

Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

你们使用顾问并不能解除你们公司符合 CGMP 的义务。你们公司的高级管理层仍负有义务全面解决所有缺陷，确保持续 CGMP 符合性。

Unapproved New Drug Charges 未获批准的新药指控（略）

Conclusion 结论

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of other violations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

FDA placed your firm on Import Alert 66-40 on October 25; 2019.

FDA 已于 2019 年 10 月 25 日将你公司置于进口禁令 66-40 中。

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产的新申报和增补申报的批准。

Failure to correct these violations may also resultin the FDA continuing to refuse admission of articles manufactured at Henan Kangdi Medical Devices Co. Ltd., SME Pioneer Park, No. 4, 2nd Area, Zhoukou,Henan into the United States under section 801(a)(3) of the FD&C Act, 21U.S.C. 381 (a)(3). Articles under this authority may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

10. 320-20-10 2019-12-05 Tismor Health and Wellness Pty Limited 澳大利亚

Dear Mr. Siracusa:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Tismor Health and Wellness Pty Limited, FEI 3008932054, at 19a Garema Cct, Kingsgrove, from May 20 to 24,2019.

美国 FDA 于 2019 年 5 月 20 日至 24 日检查了你们位于澳大利亚的 Tismor Healthand Wellness Pty Limited（FEI3008932054）生产场所。

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

本警告信总结了制剂生产严重违反 CGMP 的行为。参见 21CFR 第 210 与 211 部分。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

由于你们的制剂生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的药品根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C. 351(a)(2)(B)被认为是掺假药品。

Your firm manufactures “Thursday Plantation Tea Tree Antiseptic Cream." This product is an unapproved new drug in violation of section 505(a) of the FD&C Act, 21 U.S.C. 355(a). Introduction or delivery for introduction of such products into interstate commerce is prohibited under section 301(d) of the FD&C Act, 21U.S.C. 331(d). These violations are described in more detail below.

你公司生产“周四种植园茶树抗菌乳膏”违反 FDCA 第 505(a)条款 21 U.S.C. 355(a)，为未经批准的新药。FDCA 第 301(d)条款 21 U.S.C. 331(d)禁止将此类药品引入或输入州际贸易。以下对此违规情况进行了详细说明。

We reviewed your June 14, 2019, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

我们已详细审核了你公司 2019 年 6 月 14 日对 FDA483 表的回复，并此告知已收到后续通信。

During our inspection, our investigator observed specific violations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

CGMP Violations CGMP 违规

1. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records. (21 CFR 211.68(b).

你公司未对计算机和相关系统进行适当控制，确保仅有经过授权的人员方可修改主生产和检验记录和其它记录（21 CFR 211.68(b)）。

Your firm contract manufactures over-the-counter (OTC) topical drug products (b)(4). Your firm lacked sufficient controls over your gas chromatography (GC) instrument used to test the drug

productprior to release. Specifically, your firm assigned administrative privileges to analysts conducting routine assay tests using your Empower chromatography software data system.

你公司委外生产 OTC 局部药品 XX。你公司对你们的药品放行检测用 GC 仪器缺乏足够控制。具体来说，你公司将管理员权限授予日常使用 EMPOWER 色谱软件数据系统执行含量检测的化验员。

During the review of your Empower chromatography audit trail for your drug product, our investigator observed that you deleted more than 100 test results since October 2017. You also aborted more than 100 sample set results during this same period, although you lacked investigations.

在对你们药品的 EMPOWER 色谱审计追踪进行审核时，我们检查员发现你们自 2017 年 10 月以来删除了 100 多个检测结果。你们在相同时间段还中断了 100 多个样品序列结果，但并未进行调查。

Your quality system does not adequately ensure the accuracy and integrity of the data to support the safety, effectiveness and quality of the drugs you manufacture. Without complete and accurate records,you cannot assure appropriate decisions regarding batch release, product stability, and other matters that are fundamental to ongoing assurance of quality.

你们的质量体系不能充分保证支持你们所生产的药品的安全性、有效性和质量的数据的准确性和完整性。没有完整准确的记录，你们无法确保做出适当的批放行、产品稳定性和其它持续保证质量的基本事务决策。

Your response acknowledged that analysts did not understand the implications of deleting data and attributed the problem to the lack of data integrity training at your firm. You also stated there was nor equirement in your standard operating procedures (SOPs) to regularly review audit trails.

你们在回复中承认化验员并不理解删除数据的意义，将问题归结于你公司缺乏数据完整性培训。你们还声称在你们的 SOP 中不要求对审计追踪进行定期审核。

You stated that procedural updates will include guidance on management of users, assignment of administrative privileges, and the circumstances when administrative privileges can be used. However, your updated procedures still allow analysts to perform “trial work,” which your firm intended to maintain in a separate folder from routine analysis. This is an unacceptable practice. It is essential that all data from the analysis of drug samples be retained and reviewed.

你们声称对程序的更新会包括用户管理指导、管理者权限授权，以及管理者权限可以使用的情景。但是你们更新后的程序仍允许化验员进行“试验性工作”，你公司准备将这部分内容保存在一个与日常分析不同的单独文件夹。这是不可接受的。保存和审核药品样品分析所得所有数据是基本要求。

You committed to investigate previously deleted data and aborted sample sets. Your firm also indicated it will take further actions depending on the outcome of this investigation. Your response is inadequate. You did not assess GC data related to all batches of products distributed to the U.S. to ensure there was no impact to quality or commit to a larger review of all data generated in your laboratory. Your response lacks an independent review including, but not limited to, an evaluation of the origin of behaviors and decisions that led to deletion of quality control data. Your response did not provide adequate detail of your full scope of improvements and management oversight to prevent future data integrity issues.

你们承诺会调查之前删除的数据和中断的样品序列。你们公司亦指出根据该调查的结果可能会采取更多措施。你们的回复是不充分的。你们并未评估与所有销售至美国的批次有关的 GC 数据，以确

保对质量没有影响，或承诺更多审核你们实验室产生的所有数据。你们的回复缺乏独立审核，包括但不仅限于评估导致质量检测数据删除的行为和决策来源。你们的回复并未提交足够的详细的全范围改进和管理监管，以防止未来发生数据完整性问题。

In response to this letter, provide the following:

在回复本函时请提交以下：

- A comprehensive, independent assessment of your laboratory practices, procedures, methods, equipment, documentation, and analyst competencies. Based on this review, provide a detailed plan to remediate and evaluate the effectiveness of your laboratory system.
  一份对你们实验室规范、程序、方法、设备、文件和化验员能力的全面独立评估。基于该项审核，提交一份对你们的实验室系统的详细补救计划并对其有效性进行评估。
- A comprehensive assessment and remediation plan to ensure your quality unit (QU) is given the authority and resources to effectively function. The assessment should also include, but not be limited to:
  一份全面的评估和补救计划，确保你们的 QU 被授予权力和资源可有效运作。评估还应包括但不仅限于：
  - A determination of whether procedures used by your firm are robust and appropriate
    确定你公司所用程序是否稳健恰当
  - Provisions for QU oversight throughout your operations to evaluate adherence to appropriate practices
    QU 监管你们整体运营以评估是否遵守适当规范的条款
  - A complete and final review of each batch and its related information before the QU disposition decision
    在 QU 做出处置决策之前对每批及其相关信息进行完整最终审核
  - Oversight and approval of investigations and discharging of all other QU duties to ensure identity, strength, quality, and purity of all products
    监管和批准调查，履行所有其它 QU 义务，确保所有产品的鉴别、含量、质量和纯度
  - Also describe how top management supports quality assurance and reliable operations, including but not limited to timely provision of resources to proactively address emerging manufacturing/quality issues and to assure a continuing state of control.
    还请描述高级管理层如何支持质量保证和可靠运营，包括但不仅限于及时提供资源积极处理新发生的生产/质量问题，确保持续受控
- A comprehensive, independent assessment of computer system performance and security. Provide a report that identifies vulnerabilities in the design and controls, and a thorough corrective action and preventive action (CAPA) plan for each of your laboratory computer systems, which addresses the following elements.
  一份对计算机系统性能和安保的全面独立评估。提交一份报告识别出设计和控制方面的薄弱点，以及一份对你们实验室所有计算机系统的全面 CAPA 计划，其中应包括以下要素：
  - A list of all hardware (both standalone and networked) and software used by your laboratory.
    一份你们实验室使用的所有硬件（单机和网络）和软件的清单
  - Identify and evaluate vulnerabilities in performance and security of all of these computer systems, including but not limited to their configurations, administrative rights, password controls, audit trails capabilities and state of implementation for each system,

qualification/validation status, deviation history, backup capabilities, network requirements, completeness of data records, suitability of current hardware/software for its intended use(s), change management, and management oversight.
识别和评估所有这些计算机系统的性能和安保薄弱点，包括但不仅限于其参数设置、管理权限、密码控制、审计追踪能力和每个系统的执行状态、确认/验证状态、偏差历史、备份能力、网络要求、数据记录的完整性、当前硬件/软件是否适合其既定用途、变更管理和管理监管

- Detail the associated user privileges for each system.
每个系统的详细用户权限
- Specify user roles and associated user privileges for all staff levels who have access to the laboratory computer system, and provide organizational affiliations, responsibilities, and titles. Clearly specify all staff who have administrator privileges.
为所有可访问实验室计算机系统的员工层次写明用户角色和相关用户权力，提交一份组织隶属关系、职责以及职务
- Fully describe how you will ensure segregation of firm personnel involved with laboratory testing from those with administrator rights. For all staff roles that are permitted to have administrative rights, specify the scope and type of privileges.
全面说明你们要如何确保将公司涉及实验室检测的人员与管理员权力分开。说明所有具备管理员权限的员工角色的权力范围与类型
- Assess each system to determine if unique user names and passwords are used.
评估每个系统是否使用了唯一用户名和密码
- Evaluate policies and procedures regarding computers and data governance, with special emphasis on audit trails, prohibiting data deletion, and appropriate modifications of results. Specify how your firm prevents data deletion and undocumented/inappropriate modifications of data. Also describe how you ensure original data and information is always preserved. Provide your procedures for audit trail review.
评估计算机和数据管理政策与程序，特别要注意审计追踪、禁止数据删除以及对结果的恰当修改。说明你公司要如何防止数据删除和没有文件记录的/不当数据修改。亦请说明你们要如何确保一直会保存原始数据和信息。提交你们的审计追踪审核程序。
- Provide requirements for data retention and backup for all laboratory systems.
提交所有实验室系统数据保存和备份要求。
- Describe how you ensure that all quality control tests are performed by an analyst and receive second-tier review from a separate qualified individual (e.g., lab manager). Provide related procedure(s).
说明你们要如何确保所有 QC 检测由化验员执行，并由单独指定人员（例如实验室经理）进行第二级审核。提交相关程序。
- Summarize your interim controls to assure reliable performance and security while your CAPA plan is being implemented.
总结你们的临时控制措施，确保你们的 CAPA 计划执行时的可靠表现和安全性。

2. Your firm failed to establish written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess (21 CFR 211.100(a)).

你公司未制订书面生产和检测控制，以控制你们生产的药品具备其理当具备或显示具备的鉴别、含量、质量和纯度（21 CFR 211.100(a)）。

Your firm has not qualified the equipment, such as (b)(4), used to manufacture your drug product. In addition, you did not record the (b)(4)of the (b)(4) used at various steps during production in the batch record.

你公司未对药品生产用设备进行确认，例如 XX。另外，你们并未在生产期间各步骤中在批记录里记录所用 XX。

The batch record for the drug product required (b)(4) of components at (b)(4) for (b)(4), but your (b)(4) did not have graduated (b)(4) values, nor does it assure a known (b)(4).Instead, the (b)(4) range from (b)(4), with (b)(4) corresponding to a claimed maximum (b)(4) of (b)(4).

药品批记录要求在 XX 时加入组份 XX，但你们的 XX 并没有刻度 XX 值，亦不能确保已知 XX。相反，XX 范围为 XX，其对应所声明的最大 XX。

In your response, you stated that you will qualify the (b)(4) tank and (b)(4) to demonstrate that the equipment is suitable for its intended use. Specifically, you plan to qualify the (b)(4) to ensure that the operators can set the (b)(4) for the (b)(4) tanks accurately. You qualified the (b)(4) value by using previous process validation work, in which the (b)(4) was set at (b)(4) and was expected to represent a (b)(4) of approximately (b)(4).

在你们的回复中，你们声称你们会确认 XX 罐和 XX，证明设备适合其既定用途。具体来说，你们计划确认 XX 以确保操作员可准确设置 XX 罐。你们使用之前的工艺验证工作确认的 XX 值，该工艺验证中 XX 被设置为 XX，代表的是约 XX。

In your response you stated you have determined speeds at different dial settings and will perform qualification studies to ensure the equipment is suitable for its intended use. Your response is inadequate. Your firm did not assess the potential impact on quality (e.g., (b)(4))if the (b)(4) does not function at the (b)(4) defined during process validation. There is no assurance that previously distributed batches were manufactured with qualified equipment suitable for its intended use.

在你们的回复中，你们声称你们已确定了不同按键设置的速度，并会进行确认研究以确认设备适合其既定用途。你们的回复是不充分的。你公司并未评估如果 XX 在工艺验证中未能在指定的 XX 正确动作对质量（例如 XX）会产生什么潜在影响，因此无法确保之前销售的批次是采用经确认适合其既定用途的设备生产的。

In response to this letter, provide the following:

在回复本函时请提交以下：

- A data driven, scientifically sound qualification program that identifies and controls variability, such that your production and packaging processes meet appropriate manufacturing standards and parameters. This includes, but is not limited to, evaluating suitability of equipment for its intended use, ensuring quality of input materials, and determining the capability and reliability of each manufacturing process step and control.
  一份依据数据的科学合理确认程序，识别和控制波动情况，使得你们的生产和包装工艺符合适当的生产标准和参数。其中包括但不仅限于评估设备是否适合其既定用途，确保输入原料的质量，以及确定每个生产工艺步骤和控制的能力和可靠性
- An assessment of distributed batches of your drug product. Provide your plans for addressing any product quality risks identified for any drug products still in distribution, including notifications or market actions.

一份对你们药品已销售批次的评估。提交你们解决所有已识别仍在销售中的药品质量风险的计划，包括通知客户和市场召回措施。

3. Your firm failed to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans and test procedures designed to assure that components, drug products conform to appropriate standards ofidentity, strength, quality, and purity (21 CFR 211.160(b)).

你公司未制订实验室控制系统，包括科学合理和恰当的质量标准、取样计划和检测程序，用于确保组份和药品符合适当的鉴别、含量、质量和含量标准（21 CFR 211.160(b)）。

Your firm failed to validate the Excel spreadsheet used to perform the assay calculation for your "(b)(4)." Your procedures lacked guidance on how to check and manually verify the calculation sheets.During the inspection, our investigator identified a calculation error within the spreadsheet. The incorrect formula for averaging the Internal Standard peak area was used.

你公司未对你们"XX"含量计算所用的 EXCEL 表格进行验证。你们的程序缺少了如何检查和手动验算表的指南。在检查中，我们检查员发现表格内有计算错误。计算内标峰面积平均值的公式是错误的。

There is no assurance that the associated assay results recorded are reliable and accurate.

这样无法保证所记录的相关含量结果是准确可靠的。

In your response, you stated that you have retrospectively tested products in the market using correct procedures and will update the validation master plan to ensure that spreadsheets are included within the scope of validation efforts. You created a new procedure which details the approach for validating spreadsheets as well as protecting the file from accidental changes. You also stated all Excel spreadsheet calculations for your (b)(4) batches have been retrospectively reviewed.

在你们的回复中，你们声称你们已回顾性检测了采用错误程序计算的已销售产品，并会更新验证主计划以确保验证工作范围包括表格的验证。你们创建了新的程序，在其中详细说明了验证表格的方法，以及保护文件不受意外修改的方法。你们还声称你们的 XX 批次所有 EXCEL 表格计算均已进行了回顾审核。

During the review, you identified another error within your Excel spreadsheets. The assay test result for (b)(4) batch (b)(4) was incorrect due to a transcription entry error for active peak area. Your firm used a new spreadsheet and entered the correct active peak area. The result was recalculated, and the final result was reported. The product had already been released with test results using the incorrect calculation, although the recalculated test result was still within specification. You have committed to manually check calculations until the spreadsheet has been validated.

在审核期间，你们发现你们 EXCEL 表格中的另一个错误。XX 批次的含量检测结果因为转抄录入主峰面积错误导致结果错误。你公司使用了新的表格，录入了正确的主峰面积，重新计算了结果，并且报告了最终的结果。虽然重新计算结果仍在标准范围内，但该产品已采用不正确的计算结果被放行。你们承诺会在完成表格验证之前对计算进行人工检查。

Your firm relied on Excel spreadsheets to calculate assay and determine the reportable result for final batch release. Your computerized systems must perform their functions satisfactorily and that your firm establish a written program to ensure ongoing proper system performance.

你公司依赖 EXCEL 表格计算含量并确定最终批放行的报告结果。你们的计算机化系统必须正确运行函数，你公司应建立书面程序确保系统功能持续正确。

Your response is inadequate. You have not fully assessed the potential impact of using data from unvalidated, unsecured spreadsheets for critical CGMP functions.

你们的回复是不充分的。你们并未全面评估使用未经验证的数据和不安全的表格于关键 CGMP 功能的潜在影响。

In response to this letter, provide the following:

在回复本函时请提交以下内容：

- A comprehensive review of your laboratory practices, procedures, methods, equipment, and analyst competencies. Based on this review, provide a detailed CAPA plan to remedy your laboratory system. Your plan should include the process you will use to evaluate the effectiveness of the implemented CAPA plan.
  一份对你们实验室规范、程序、方法、设备和化验员能力的全面审核。基于此审核，提交一份详细的 CAPA 计划补救你们的实验室系统。你们的计算应包括你们准备用来评估所执行的 CAPA 计划有效性的流程
- A complete assessment of documentation systems used throughout your manufacturing and laboratory operations to determine where documentation practices are insufficient. Include a detailed CAPA plan that comprehensively remediates your firm's documentation practices to ensure you retain attributable, legible, complete, original, accurate, contemporaneous records throughout your operation.
  一份对你们生产和实验室操作所用的文件体系的完整评估，以确定文件规范是否充分。要包括一份详细的 CAPA 计划，全面补救你们公司的文件规范，确保你们会保存可追溯、清晰、完整、原始、准确、整个操作过程中的同步记录。

Responsibilities as a Contractor 作为合同商的义务

Drugs must be manufactured in conformance with CGMP. FDA is aware that many drug manufacturers use independent contractors such as production facilities, testing laboratories, packagers, and labelers.FDA regards contractors as extensions of the manufacturer.

药品生产必须符合 CGMP 要求。FDA 了解许多药品生产商使用独立合同方如生产场所、检测实验室、包装商和贴标商。FDA 将合同商作为生产商的外延部分来对待。

You are responsible for the quality of drugs you produce as a contract facility regardless of agreements in place with product owners. You are required to ensure that drugs are made in accordance with section 501(a)(2)(B) of the FD&C Act for safety, identity, strength,quality, and purity. See FDA's guidance document Contract Manufacturing Arrangements for Drugs: Quality Agreements at https://www.fda.gov/media/86193/download.

作为合同场所，虽然你们与药品所有者订有协议，但你们仍对你们所生产的药品负有义务。你们应确保药品生产符合 FDCA 第 501(a)(2)(B)条款对安全性、鉴别、剂量、质量和纯度的要求。参见 FDA 指南文件“药品合同生产安排：质量协议”。

Data Integrity Remediation 数据完整性补救措施

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. See FDA's guidance document Data Integrity and Compliance With Drug CGMP for guidance on establishing and following CGMP compliant data integrity practices at https://www.fda.gov/downloads/DRUGS/GuidanceComplianceRegulatoryInformation/Guidances/UCM495891.pdf.

你们的质量体系不能充分确保数据的准确性和完整性，无法支持你们生产的药品的安全性、有效性和质量。参见 FDA 指南文件“数据完整性和药品 GMP 合格”指导建立和遵守 CGMP 合格数据完整性规范。

We acknowledge that you are using a consultant to audit your operation and assist in meeting FDA requirements. In response to this letter, provide the following:

我们知悉你们正聘用顾问对你们的操作进行审计并协助你们符合 FDA 要求。在回复此函时请提交以下信息：

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting including results of the data review for drugs distributed to the United States. Include a detailed description of the scope and root causes of your data integrity lapses.

一份对数据记录和报告不准确性程度的全面调查。要包括一份对你们数据完整性问题的范围与根本原因的详细说明。

B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity and analyses of the risks posed by ongoing operations.

你们药品质量中所发现的不合格情况的潜在影响的当前风险评估。你们的评估应包括由于受到数据完整性问题影响的药品放行导致的患者风险的分析，以及持续运营所具有的风险。

C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. The detailed corrective action plan should describe how you intend to ensure the reliability and completeness of all data generated by your firm including microbiological and analytical data, manufacturing records, and all data submitted to FDA.

你们公司的管理策略，包括你们全球 CAPA 计划详细情况。详细的纠正措施计划应说明你们准备如何确保你公司生成的所有数据的可靠性和完整性，包括微生物和分析数据、生产记录以及提交给 FDA 的所有数据。

Products Containing Glycerin 含丙三醇的药品

Your (b)(4) drug product contains glycerin.The use of glycerin contaminated with diethylene glycol (DEG) has resulted invarious lethal poisoning incidents in humans worldwide.

你们的 XX 药品含有丙三醇。使用受二甘醇（DEG）污染的丙三醇已导致全球多次人类因毒致死事件。

See FDA's guidance document Testing of Glycerinfor Diethylene Glycol to help you meet the CGMP requirements when manufacturing drugs containing glycerin at https://www.fda.gov/media/71029/download.

参见 FDA 指南"丙三醇中 EG 检测"，有助于你们满足 CGMP 要求前提下销售使用了丙三醇的药品，以及对 DEG 的检测和供应链完整性的建议。

In responseto this letter, provide the following:

在回复本函时请提交以下内容：

- Results of tests for DEG and EG in retain samples of all glycerin batches used to manufacture your drug products.
  用于生产你们药品的所有丙三醇批次的留样中 DEG 和 EG 的检测结果
- A full risk assessment for drug products that contain glycerin and are within expiry in the U.S. market. Take prompt corrective actions and preventive actions and detail your future actions to ensure appropriate selection of your suppliers, ongoing scrutiny of their supply chain, and appropriate incoming batch controls.
  一份在美国销售且仍在效期内的含丙三醇的药品的全面风险评估。采取快速 CAPA，并详细说明你们未来确保你们适当选择供应商、持续仔细审核其它供应链、以及适当的进厂批次控制的措施。

Any drug marketed by your firm must conform with all applicable requirements of the FD&C Act, including those outlined in the Unapproved New Charges section below.

你公司销售的所有药品必须符合 FDCA 所有适用要求，包括以下未批准新药指控部分所列要求。

Unapproved New Drug Violation 未批准新药违规（略）

Conclusion 结论

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility.You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of other violations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产的新申报和增补申报的批准。

Failure to correct these violations may also result in the FDA refusing admission of articles manufactured at Tismor Health and Wellness Pty Limited at 19a Garema Cct, Kingsgrove, into the United Statesunder section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Articles under this authority may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C.351(a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

11. 320-20-11 2019-12-09 Wild Child WA Pty Ltd. 澳大利亚

Dear Ms. Preston:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Wild Child WA Pty Ltd., FEI 3006210769, at 2 Action Road, Malaga, Western Australia, from May 27 to 31,2019.

美国 FDA 于 2019 年 5 月 27 日至 31 日检查了你们位于澳大利亚的 Wild Child WA Pty Ltd.生产场所。

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See Title 21 Code of Federal Regulations (CFR), parts 210 and 211 (21 CFR parts 210 and 211).

本警告信总结了制剂生产严重违反 CGMP 的行为。参见 21CFR 第 210 与 211 部分。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

由于你们的制剂生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的药品根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C. 351(a)(2)(B)被认为是掺假药品。

We reviewed your response to our Form FDA 483, received on June 12, 2019, in detail and acknowledge receipt of your subsequent correspondence.

我们已详细审核了你公司 2019 年 6 月 12 日对 FDA483 表的回复，并此告知已收到后续通信。

During our inspection, our investigator observed specific violations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

1. Your firm failed to have, for each batch of drug product, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release (21 CFR 211.165(a)).

你公司未能在放行之前对每批药品进行恰当的实验室检测，确定其符合药品最终质量标准，包括每种活性物质的鉴别（21 CFR 211.165(a)）。

Your firm released finished over-the-counter (OTC) drug products, (b)(4), to the U.S. market without adequately testing the identity and strength of the active ingredient, (b)(4). For example,your firm uses an analytical method (residue on ignition) for assay that is inferior to the method established in the United States Pharmacopeia (USP) monograph for (b)(4). In addition, your firm does not perform the minimum fill test, a test specified in the USP monograph.

你公司未充分检测活性成分的鉴别和含量即放行了 OTC 药品 XX 至美国市场。例如，你公司使用了一个分析方法（炽灼残渣）用于含量检测，该方法劣于 USP 中 XX 各论所建立的方法。另外，你公司未执行最小灌装量测试，该测试在 USP 各论中是指定检测项。

Appropriate testing of each batch before release isone of many essential elements necessary to ensure that the drug products you manufacture meet appropriate specifications.

批放行之前对每个批次进行适当的检测是确保你们所生产的药品符合适当的质量标准所必须的许多要素之一。

In your response, you stated that quantitative chemical tests were not performed because your Australian GMP license allows you to perform physical testing only. Your response included a commitment to revise specifications to include the quantitative titration method for (b)(4) contentand minimum fill testing.

在你们的回复中，你们声称未进行定量化学检测，因为你们的澳大利亚 GMP 证书允许你们只进行物理检测。你们的回复中包括有一份承诺，承诺会修订质量标准，在其中包括 XX 含量定量滴定方法和最小灌装量测试。

Your response is inadequate because the corrective actions only apply to future batches and do not include a commitment to evaluate or test retain samples for batches already distributed to the U.S. market. Drug products distributed to the U.S. market must be manufactured in accordance with U.S. drug regulations.

你们的回复是不充分的，因为纠正措施仅用于未来的批次，并未承诺会评估或检测已销售至美国的批次的留样。销售至美国市场的样品必须依据美国药品法规生产。

In response to this letter, provide:

在回复本函时请提交：

- A comprehensive, independent assessment of your laboratory practices, procedures, methods, equipment, documentation, and analyst competencies. Provide your plan to assess laboratory system effectiveness and a subsequent detailed CAPA that ensures full remediation.
  一份对你们实验室规范、程序、方法、设备、文件记录和化验员资质的全面独立评估。提交一份评估实验室系统有效性评估计划，以及之后确保全面补救的详细 CAPA
- A list of chemical and microbial specifications, including test methods, used to analyze each lot of your drug products before a lot disposition decision.
  一份化学和微生物质量标准清单，包括在批处置决策之前用于分析你们每批药品的检测方法
  - An action plan and timelines for conducting full chemical and microbiological testing of retain samples to determine the quality of all batches of drug product distributed to the United States within expiry as of the date of this letter.
    一份对留样执行全面化学和微生物检测以确定所有销售至美国且仍在本函签发时仍在效期内的药品批次质量的行动计划和时间表
  - A summary of all results obtained from testing retain samples from each batch. If such testing reveals substandard quality drug products, take rapid corrective actions, such as notifying customers and product recalls.
    一份对各批次留样检测结果的总结。如果该检测显示药品质量不符合标准，则采取快速纠正措施，如通知客户和召回产品
- An evaluation of all test methods used for the analysis of drug products distributed to the United States. State whether each method used is the USP method. If you use an alternate method, provide your studies showing equivalence or superiority to the compendial method.
- 一份对销售至美国的药品分析所用分析方法的评估。说明所用各方法是否为 USP 方法。如果你们使用了替代方法，需提交你们的研究证明其等同或优于药典方法。

2. Your firm failed to establish adequate written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess (21 CFR 211.100(a)).

你公司未能制订足够的书面生产和工艺控制程序，设计用以确保你们生产的药品具备其理当具备的鉴别、含量、质量和纯度（21 CFR 211.100(a)）。

Your firm does not have an adequate ongoing program for monitoring process control to ensure stable manufacturing operations and consistent drug quality. Specifically, you did not provide documentation to show that the manufacturing processes for OTC (b)(4) drug products have been validated.

你公司不具备足够的持续程序用于监测工艺控制，确保稳定的生产操作和一致的药品质量。具体来说，你们未能提交文件证明 OTC 药品 XX 的生产工艺经过了验证。

Our inspection also found instances where batches of (b)(4) were manufactured using significantly different (b)(4) parameters.

我们检查亦发现生产中使用了相关甚远的 XX 参数。

See FDA's guidance document Process Validation:General Principles and Practices for general principles and approaches that FDA considers appropriate elements of process validation at https://www.fda.gov/media/71021/download.

参见 FDA 指南文件“工艺验证：一般原则和规范”中 FDA 认为是工艺验证恰当要素的原则和方法。

In your response, you provided an action plan to perform validation on (b)(4) formulations for various (b)(4) tanks, which will include (b)(4) sample points after (b)(4) times.You stated that samples would be quantitatively analyzed for (b)(4) content.

在你们的回复中，你们提交了一份在不同 XX 罐中执行 XX 配方验证的行动计划，其中将包括在 XX 时间后的 XX 取样点。你们声称样品会进行 XX 含量定量分析。

Your response is inadequate because it lacked sufficient information on your planned validation activities, including timelines for completion and draft protocols.

你们的回复是不充分的，因为其缺乏足够信息说明你们所计划的验证活动，包括完成和起草方案的时间表。

In response to this letter, provide:

在回复本函时请提交：

- An assessment of each drug product process to ensure that there is a data-driven and scientifically sound program that identifies and controls all sources of variability, such that your production processes will consistently meet appropriate specifications and manufacturing standards. This includes, but is not limited to, evaluating suitability of equipment for its intended use, sufficiency of detectability in your monitoring and testing systems, quality of input materials, and reliability of each manufacturing process step and control.
  一份对每种药品工艺的评估，确保具备由数据支持的科学合理计划，可识别并控制所有变动源，使得你们的生产工艺能持续符合适当的质量标准和生产标准。其中包括但不仅限于，评估设备

适合其既定用途、你们监测和检测系统的检测充分性、输入物料的质量，以及每个生产工艺步骤和控制的可靠性。

- A detailed summary of your validation program for ensuring a state of control throughout the product lifecycle, along with associated procedures. Describe your program for process performance qualification, and ongoing monitoring of both intra-batch and inter-batch variation to ensure a continuing state of control. Also include your program for qualification of your equipment and facility.
  一份你们工艺验证计划的详细总结，确保产品整个生命周期中的受控状态，以及相关程序。说明你们的工艺性能确认计划，以及对批间和批内波动性的持续监测，以确保持续受控状态。亦要包括你们对设备和设施的确认计划。
- A timeline for performing appropriate process performance qualification (PPQ) for each of your marketed drug products.
  一份执行你们所有已上市药品工艺性能确认（PPQ）的时间表。
- Your process performance qualification protocol(s).
  你们的工艺性能确认方案

3. Your firm failed to conduct at least one test to verify the identity of each component of a drug product (21 CFR 211.84(d)(1)).

你公司未能执行至少一项检测来核查药品中每种成分的鉴别。（21 CFR 211.84(d)(1)）。

Your firm failed to test your incoming components for identity, including (b)(4), used to manufacture drug products.

你公司未检测你们用于生产药品的进厂组份包括 XX 的鉴别。

In your response, you stated that individual testing of excipient components is not mandated in Australia for (b)(4), and inactive ingredients are accepted based on the supplier's certificate of analysis (COA). You indicated that a Fourier Transform Infrared (FTIR) instrument would be purchased to implement identification testing for each ingredient.

在你们的回复中，你们声称辅料成分的单项检测在澳大利亚并非强制，非活性成分可根据供应商的 COA 接受。你们说会采购 FTIR 仪器对每种成分进行鉴别测试。

Your response is inadequate because no documentation or timeline was provided to indicate when identity testing of components used in U.S. drug products would begin.

你们的回复是不充分的，因为没有提交文件或时间表说明何时开始对用于美国药品的组份进行鉴定测试。

In response to this letter, provide:

在回复本函时请提交：

- A comprehensive, independent review of your material system to determine whether all suppliers of components, containers, and closures are each qualified, and the materials are assigned appropriate expiration or retest dates. The review should also determine whether incoming material controls are adequate to prevent use of unsuitable components, containers, and closures.

一份对你们物料系统的全面独立审核，确定是否所有组份、容器和密闭器的供应商均经过确认，并且物料均已给定适当的有效期或复验期。该审核亦应确定对进厂物料的控制是否足以防止使用当适当的组份、容器和密闭器。

- Documentation of test results obtained for all lots of (b)(4) active ingredient used to manufacture OTC (b)(4) drug products for the U.S. market showing identification testing performed. Specify the test method used for identification testing and provide the method. If the method used is not the method listed in the USP monograph, provide evidence to show that the method used is equivalent or better than the compendial method.
  对所有用于美国市场 OTC 药品生产的所有批次 XX 活性成分检测所得结果文件，证明所执行的鉴别测试。说明鉴别测试所用检验方法，并提供该方法。如果所用方法并非 USP 各论方法，提交证据证明所用方法等同或优于药典方法。
- Chemical and microbiological quality control specifications you use to test and release each incoming lot of component for use in manufacturing.
  你们用于检测和放行每批生产用进厂组份的化学和微生物质量控制标准。
- A description of how you will test each component lot for conformity with all appropriate specifications for identity, strength,quality, and purity. If you intend to accept any results from your supplier's COA instead of testing each component lot for strength, quality, and purity, specify how you will robustly establish the reliability of your supplier's results through initial validation as well as periodic re-validation. Inaddition, include a commitment to always conduct at least one specific identity test for each incoming component lot.
  一份描述你们如何检测每批组份确认其符合所有适当的鉴别、含量、质量和纯度标准的文件。如果你们准备接受来自你们供应商 COA 的任何结果，取代组份批次剂量、质量和纯度检测，则说明你们要如何通过初始验证和定期重新验证建立你们供应商结果的可靠性。此外，还要承诺你们将一直对每批进厂组份执行至少一项特定鉴别测试。
- A summary of results obtained from testing all components to evaluate the reliability of the COA from each component manufacturer. Include your SOP describing this COA validation program.
  一份所有组份检测所得的结果总结，评估每个组份生产商 COA 的可靠性。提交你们描述该 COA 验证程序的 SOP。
- A summary of your program for qualifying and overseeing contract facilities that test the drug products you manufacture.
  一份你们确认和监管检测你们所生产药品的合同场所的计划摘要。

CGMP Consultant Recommended CGMP 顾问建议

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualifiedas set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements.

由于你们未能纠正重复的违规情况，我们强烈建议你们使用一位有 21 CFR 211.34 所述资质的顾问来协助你们公司符合 CGMP 要求。

Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoingCOMP compliance.

你们使用顾问并不能解除你们公司符合 CGMP 的义务。你们公司的高级管理层仍负有义务全面解决所有缺陷，确保持续 CGMP 符合性。

Conclusion 结论

The violations cited in this letter are not intended to be an all-inclusive list-of violations that exist at your facility.You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of other violations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产的新申报和增补申报的批准。

Failure to correct these violations may also resultin the FDA refusing admission of articles manufactured at Wild Child WA Pty Ltd., 2 Action Road, Malaga, into the United States under section 801(a)(3) ofthe FD&C Act, 21 U.S.C. 381(a)(3). Articles under this authority may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

12. 320-20-12 2019-12-13 Baja Fur S.A. de C.V. 墨西哥

Dear Mr. Chen:

The U.S. Food and Drug Administration (FDA)inspected the site procured by Baja Fur S.A. de C.V., FEI 3012285699, at Avenida Alejandro Graham Bell 19296, Zona Cerril General, C.P. 22163, Tijuana, Mexico from July 8 to 12, 2019. where Mark wins Beauty Brands, Inc. conducts and oversees drug manufacturing operations.

美国 FDA 于 2019 年 7 月 8 日至 12 日检查了你们位于墨西哥的 Baja Fur S.A.de C.V.（FEI 3012285699）生产场所。

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See Title 21 Code of Federal Regulations (CFR), parts 210 and 211 (21 CFR parts 210 and 211).

本警告信总结了制剂生产严重违反 CGMP 的行为。参见 21CFR 第 210 与 211 部分。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food,Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

由于你们的制剂生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的药品根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C. 351(a)(2)(B)被认为是掺假药品。

We reviewed the August 1, 2019 response submitted by Mark wins Beauty Brands to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence. Your response is inadequate becauseit did not provide sufficient detail and evidence of corrective actions to bring your operations into compliance with CGMP.

我们已详细审核了你公司 2019 年 8 月 1 日由 Mark wins Beauty Brands 提交的对我们 FDA483 表的回复，并此告知已收到后续通信。你们的回复是不充分的，因为其中未提交足够详细的信息和证据证明纠正措施可使你们的运营符合 CGMP 要求。

During our inspection, our investigators observed specific violations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

1. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

你公司未能彻底调查已销售和未销售的药品批次所有未经解释的分歧，以及批次或其组份不符合其质量标准的情况（21 CFR 211.192）。

You did not adequately investigate the out-of-specification (OOS) microbiological contamination that caused you to reject (b)(4) batches of your over-the-counter (OTC) drug product (b)(4) including results as high as (b)(4) CFU/g. While you documented these OOS results in you annual product review. you failed to conduct an adequate investigation to prevent recurrence or microbial contamination in the drug products you manufacture for the U.S. market.

你们并未充分调查导致你们拒收 XX 批 OTC 药品 XX 的 OOS 微生物污染事件，包括高达 XX CFU/g 的结果。尽管你们在你们年度产品回顾中记录了这些 OOS 结果，但你们并未执行充分调查以防止你们生产销售至美国的药品重复发生微生物污染。

We also note that your microbiological testing of drug products is listed as "Modified USP61" by your contract testing lab. Your written procedure for microbial testing of drug products specifies incubation of total plate count samples at (b)(4) USP chapter<61> defines incubation parameters for microbiological testing that differ from your procedure. It is essential that each batch of drug product is suitably tested to determine conformance with appropriate microbiological quality specifications.

我们还注意到你们的药品微生物检测被你们的合同检测实验室列为“USP61 修改版”。你们的书面微生物检测程序要求总碟计数样品培养条件与 USP<61>规定的培养参数不同。对每批药品进行适当的检测是确定其是否符合适当的微生物质量标准所必须的。

In your response, you stated that you would establish a written procedure to "fully capture investigation of errors, OOS and rejected products." You further stated that you would investigate "all OOS and rejected products."

在你们的回复中，你们声称你们会建立书面程序“全面发现调查偏差、OOS 和拒收产品”。你们进一步声称你们会调查“所有 OOS 和拒收产品”。

Your response is inadequate. You failed to provide details of your investigation into the source of microbiological contamination. You also did not address any distributed product batches that may be compromised by microbiological contamination.

你们的回复是不充分的。你们未能提交你们对微生物污染来源的详细调查信息。你们亦未解决可能受微生物污染的已销售产品批次问题。

In response to this letter, provide:

在回复本函时请提交：

- A comprehensive assessment of your overall system for investigating deviations, discrepancies, complaints, OOS results, and failures. Provide a detailed action plan to remediate this system. Your action plan should include, but not be limited to, significant improvements in investigation competencies, scope determination, root cause evaluation, corrective action and preventive action (CAPA) effectiveness, quality unit oversight, and written procedures. Address how your firm will ensure that all phases of investigations are conducted appropriately.
  一份对你们偏差、差异、投诉、OOS 结果和失败调查的整体系统的全面评估。提交一份详细的行动计划补救该系统。你们的行动计划应包括但不仅限于对调查能力、范围确定、根本原因评估、CAPA 有效性、质量部门监管和书面程序的重大改进。说明你们公司将如何确保适当完成所有调查阶段。
- Your complete investigations into all batches found to have out-of-specification total counts or objectionable microbes. The updated investigations should detail your findings on the likely root causes of the contamination. Specify actions that you will take in response to the investigation, that may include further customer notifications and product recalls.

你们对发现总计数或致病菌 OOS 的所有批次的完整调查。更新后的调查应详细说明你们对污染可能根本原因的发现。说明你们针对调查结果将采取的措施，可能包括进一步通知客户和召回产品。

- A detailed CAPA plan to ensure that failing drug products are not distributed to the U.S. in the future.
  一份详细的 CAPA 计划，确保未来不会将不合格药品销售至美国。
- Appropriate microbiological batch release specifications (i.e., total counts, identification of bioburden to detect objectionable microbes) for each of your drug products.
  每个药品的适当微生物批放行标准（即总计数、生物负载鉴别以发现致病菌）
- Microbiological testing methods that conform to USP <61> and <62>, which are capable of recovering product bioburden and determining whether any microorganisms are objectionable relative to the product's intended use, route of administration, and patient (i.e., consumer) population.
  符合 USP<61>和<62>的微生物检测方法，应能够回收产品生物负载，确定所检出微生物是否相对产品既定用途、给药方式和患者人群（即消费者）是否为致病菌
- A commitment to test each batch using qualified methods to ensure conformance to finished product specifications before final disposition decision.
  承诺会使用经过确认的方法检测每个批次，在最终批处置决策之前确保药品符合成品标准
- A comprehensive assessment of your firm's manufacturing operations with emphasis on microbiological controls and contamination prevention.
  对你们公司生产操作的全面评估，重点关注微生物控制和污染预防

2. Your firm failed to prepare batch production and control records that include documentation of the accomplishment of each significant step in the manufacture, processing, packing, or holding of the batch, for each batch of drug product (21 CFR 211.188(b)).

你公司没有为每批药品制订批生产和检测记录，在其中包括批生产、加工、包装和保存的每个重要步骤完成情况记录（21 CFR211.188(b)）。

Your batch records do not include adequate production details, including but not limited to identifying significant steps in filling operations and the person(s) performing each significant step in the drugs you manufacture. This documentation is necessary to establish that manufacturing processes were consistently followed and are reproducible.

你们的批记录未包括足够详细的生产信息，包括但不仅限于标明灌装操作中重要步骤，以及注明执行你们药品生产的每个重要步骤的人员信息。持续遵守生产工艺，证明生产工艺的可重复性必须要有这些文件。

In your response, you stated that your "Batch History Record" procedure would be updated and that a "Critical process parameters" form would be created as part of the Batch History Record for your drug products.

在你们的回复中，你们声称你们要更新的“批历史记录”程序，并建立“关键工艺参数”表作为你们药品批历史记录的一部分。

Your response is inadequate. You failed to provide details of your procedural updates to confirm your compliance with batch production and control record requirements. Your response also fails to provide information regarding your review, assessment, and identification of any significant process parameters applicable to drug product packaging and labeling operations.

你们的回复是不充分。你们未能提交你们程序更新的详细信息，确认你们符合批生产和检测记录的要求。你们的回复亦未提交你们审核、评估和标记药品包装和贴标操作所用任何重要工艺参数的信息。

In response to this letter, provide:

在回复本函时请提交以下内容：

- Your master production and control records for your drug products to demonstrate that they fully document each significant and validated manufacturing step.
  你们药品的主生产和检验记录，证明他们能全面记录每个经过验证的重大生产步骤
- A complete assessment of documentation systems used throughout your manufacturing operations to determine where documentation practices are insufficient. Include a detailed CAPA plan that comprehensively remediates your firm's documentation practices to ensure you retain attributable, legible, complete, original, accurate, and contemporaneous records throughout your operation.
  一份对整个生产操作所用文件记录系统的完整评估，确定文件规范是否存在不足。包括一份详细的全面补救你公司文件记录规范的 CAPA 计划，确保你们保存了可追溯的、清晰的、完整的、原始的、准确的和整个操作的同步记录。

3. Your firm failed to establish adequate written procedures for cleaning and maintenance of equipment (21 CFR 211.67(b)).

你公司未建立和执行充分的书面设备清洁和维护程序（21CFR 211.67(b)）。

Your firm fills and packages various drug products using shared equipment. Your firm did not adequately validate your cleaning procedures to ensure that your drug products are not contaminated by other drugs you manufacture on the same equipment.

你公司使用共用设备灌装和包装不同药品。你公司并未充分验证你们的清洁程序，以确保你们的药品不会受到相同设备上所生产的其它药品的污染。

For example, your cleaning validation for the (b)(4) system does not provide adequate assurance that your cleaning procedures for this shared equipment are sufficient to prevent cross-contamination. Inadequate removal of residues from manufacturing equipment during cleaning can cross-contaminate products subsequently manufactured on shared equipment.

例如，你们的 XX 系统清洁验证未提供足够的保障确保你们对该共用设备的清洁程序足以防止交叉污染。在清洁过程中未充分清除残留可能会对后续在共用设备上生产的产品造成交叉污染。

In your response, you stated that you will update your procedure for operating, maintaining, and cleaning the (b)(4), and create a cleaning validation studies checklist.

在你们的回复中，你们声称你们将更新你们的 XX 操作、维护和清洁程序，并建立清洁验证研究检查清单。

Your response is inadequate in that it failed to assess the risk of potential cross-contamination and its effect on product quality and your marketed batches of drug product manufactured on this shared equipment.

你们的回复是不充分的，其中并未评估潜在交叉污染的风险，以及其对在该共用设备上所生产的药品质量和你们已上市批号的影响。

In response to this letter, provide:

在回复本函时请提交以下内容：

- Appropriate improvements to your cleaning validation program, with special emphasis on incorporating conditions identified as worst case in your drug manufacturing operation. This should include but not be limited to identification and evaluation of all worst-case:
  对你们清洁验证程序的恰当改进，特别强调要结合在你们药品生产操作中识别为最差情形的条件。其中应包括但不仅限于识别和评估所有最差情形：
  - drugs with higher toxicities
    高毒性产品
  - drugs with higher drug potencies
    高活性产品
  - drugs of lower solubility in their cleaning solvents
    在清洁剂中低溶解度产品
  - drugs with characteristics that make them difficult to clean
    具有难清洁特性的产品
  - swabbing locations for areas that are most difficult to clean
    最难清洁部位的擦拭取样位置
  - maximum hold times before cleaning
    清洁前的最长放置时间

In addition, describe the steps that must be taken in your change management system before introducing new manufacturing equipment or a new product.

此外，要说明引入新生产设备或新产品之前在你们变更管理体系中必须采取的步骤。

- A summary of updated SOPs that ensure an appropriate program is in place to verify and validate cleaning procedures for products, processes, and equipment.
  更新后 SOP 的总结，确保对产品、工艺和设备清洁程序具备适当的验证和核查计划

CGMP consultant recommended CGMP 顾问建议

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualifiedas set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements. We also recommend that the qualified third party perform a comprehensive audit of your entire operation for CGMP compliance and evaluate the effectiveness of your corrective actions and preventive actions.

鉴于我们在你公司所发现的违规情况，我们强烈建议你们使用一位有 21 CFR 211.34 所述资质的顾问来协助你们公司符合 CGMP 要求。我们亦建议该具备资质的顾问对你们整体运营情况进行药品

CGMP 合规情况全面审计，并由其在你们寻求满足 FDA 合规要求之前对你们 CAPA 的完成情况和有效性进行评估。

Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance.

你们使用顾问并不能解除你们公司符合 CGMP 的义务。你们公司的高级管理层仍负有义务全面解决所有缺陷，确保持续 CGMP 符合性。

Conclusion 结论

Violations cited in this letter are not intended tobe an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of other violations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产的新申报和增补申报的批准。

Failure to correct these violations may also result in the FDA refusing admission of articles manufactured at Baja Fur S.A. de C.V.at Avenida Alejandro Graham Bell 19296, Zona Cerril General, C.P. 22163, Tijuana, Mexico into the United States under section 801(a)(3) of the FD&CAct, 21 U.S.C. 381(a)(3). Articles under this authority may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

13. 320-20-13 2019-12-17 GPT Pharmaceuticals Pvt. Ltd. 印度

Dear Mr. Adityan:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, GPT Pharmaceuticals Pvt. Ltd., FEI 3008311641, at Plot No. 6/3, Road No. 11, Nacharam, Hyderabad, from June 24 to28, 2019.

美国 FDA 于 XXXX 年 XX 月 XX 日至 XX 月 XX 日检查了你们位于 XX 的 XXXX 生产场所。

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See Title 21 Code of Federal Regulations (CFR), parts210 and 211 (21 CFR parts 210 and 211).

本警告信总结了制剂生产严重违反 CGMP 的行为。参见 21CFR 第 210 与 211 部分。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

由于你们的制剂生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的药品根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C. 351(a)(2)(B)被认为是掺假药品。

We reviewed your July 17, 2019, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

我们已详细审核了你公司 XXXX 年 XX 月 XX 日的回复，并此告知已收到后续通信。

During our inspection, our investigators observed specific violations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

1. Your firm's quality control unit failed to exercise its responsibility to ensure drug products manufactured are incompliance with CGMP, and meet established specifications for identity, strength, quality, and purity (21 CFR 211.22).

你公司的质量控制部门未能履行其职责，确保药品生产符合 CGMP 要求，以及符合既定的鉴别、含量、质量和纯度标准（21 CFR 211.22）。

During the inspection, our investigators observed that your quality unit (QU) did not provide adequate oversight for the manufacturing of bulk (b)(4). For example, your QU failed to ensure thefollowing:

在检查期间，我们的检查员发现你们质量部门（QU）没有对散装 XX 的生产进行充分的监控。例如你们 QU 未能确保：

- Out-of-specification (OOS) test results for residual solvents were adequately investigated.
  对残留溶剂 OOS 检测结果进行充分调查
- Test methods for assay and impurities were validated.
  对含量和杂质检测方法进行验证
- Adequate record and report documentation practices, including document control, were in place.

具备充分的记录和报告文件规范，包括文件控制

You receive active pharmaceutical ingredients (API) from suppliers and process them into (b)(4). Your QU failed to adequately investigate OOS results for the residual solvent, (b)(4), for API batches (b)(4). You retested the API, obtained passing results, and released these API batches for use in production. You disregarded the initial OOS results without adequate scientific justification.

你们从供应商处接收了 API，并将其进行加工至 XX。你们的 QU 未能充分调查 API 批号 XX 的残留溶剂的 OOS 结果。你们复测了该 API，获得了合格结果，然后将这些 API 批次放行用于生产。你们在没有充分科学论证前提下就忽略了初始的 OOS 结果。

(b)(4) is a (b)(4) solvent and known (b)(4). Solvents in (b)(4) should not be employed in the manufacture of drug substances, excipients, and drug products because of their unacceptable toxicity. However, if the use of (b)(4) solvents, such as (b)(4), is unavoidable in order to produce a drug, then the levels should be restricted. For more information on residual solvents, see FDA's guidance document Q3C—Tables and List at https://www.fda.gov/media/71737/download.

XX 为 XX 类溶剂，已知 XX。XX 中的 XX 不应用于原料药、辅料和制剂的生产，因为其具有不可接受的毒性。如果使用 XX 溶剂如 XX 是某药品生产所不可避免的，则其水平应受到限制。残留溶剂更多信息参见 FDA 指南文件 Q3C—表格与清单。

Your response stated that you retested each of the batches of (b)(4) API for (b)(4) content and all retest results were within specification. Your response also concluded the original failures for residual (b)(4) were not representative and did not compromise product quality. However, your response failed to provide justification to disregard the initial OOS results or a plan for how your QU will ensure OOS results are adequately investigated. You also did not provide adequate corrective action to ensure appropriate documentation of testing performed as part of your OOS investigations.

你们的回复声称你们复测了 XX API 的所有批次中 XX 含量，所有复测结果均在标准范围内。你们的回复还得出结论说原始检测的残留 XX 结果不具有代表性，对产品质量没有影响。但是，你们的回复未提交忽略初始 OOS 结果的论证，亦未提交你们 QU 要如何确保 OOS 结果会受到充分调查的计划。你们亦未提交充分的纠正措施，以确保适当记录所执行的检测，作为你们 OOS 调查的一部分。

For more information about handling failing,out-of-specification, out-of-trend, or other unexpected results and documentation of your investigations, see FDA's guidance document Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production at https://www.fda.gov/media/71001/download.

处理失败、OOS、OOT 或其它非预期结果和你们调查文件的更多信息，参见 FDA 指南文件"药品 OOS 结果调查"。

In response to this letter, provide a comprehensive assessment and remediation plan to ensure your QU is given the authority and resources to effectively function. The assessment should also include, but notbe limited to:

在回复本函时，请提交一份全面评估和补救计划，以确保你们 QU 被授予权限和提供资源可有效履责。该评估亦应包括但不限于：

- Residual solvents test of retains samples of API you received, as well as (b)(4) you distributed. If such testing reveals substandard quality drugs, take rapid corrective actions, such as notifying customers and product recalls.
  对你们已收到的 API 和你们已销售的 XX 的留样的残留溶剂检测。如果检测发现药品质量不合格，应即刻采取措施，如通知客户和召回产品。
- A list of all residual solvents used in your facility or at your suppliers, and your risk-based plans to strictly limit (or discontinue) any (b)(4) solvents in raw materials you receive and drugs you produce. Include specifications for all residual solvents used in API you receive.
  一份你们工厂或你们供应商所用所有残留溶剂的清单，以及你们基于风险的严格限制（或中断）你们接收的原料和你们生产的药品中的所有 XX 溶剂的计划。包括在你们接收的 API 中所有残留溶剂的标准。
- A retrospective, independent review of all invalidated OOS (including in-process and release/stability testing) results for U.S. drugs, irrespective of whether the batch was ultimately distributed in the U.S. and a report summarizing the findings of the analysis, including the following for each OOS:
  一份对所有宣布无效美国药品（无论该批次是否最终销售至美国）OOS 的独立回顾审核（包括中控和放行/稳定性测试）结果，以及一份分析所发现问题的总结报告，包括每个 OOS 的以下内容：
  - Determine whether the scientific justification and evidence relating to the invalidated OOS result conclusively or inconclusively demonstrates causative laboratory error
    确定宣布无效的 OOS 结果相关的科学论证和证据是否能得出结论，显示有实验室错误导致这些结果
  - For investigations that conclusively establish laboratory root cause, provide rationale and ensure that all other laboratory methods vulnerable to the same or similar root cause are identified for remediation
    如果调查中发现有可得出结论的实验室根本原因，请提交理由，并确保所有受相同或类似根本原因影响的其它实验室方法被识别出来进行补救
  - For all OOS results found by the retrospective review to have an inconclusive or no root cause identified in the laboratory, include a thorough review of production: batch manufacturing records, adequacy of the manufacturing steps, suitability of equipment/facilities, variability of raw materials, process capability, deviation history, complaint history, batch failure history. Summarize potential manufacturing root causes for each investigation, and any manufacturing operation improvements
    如果回顾性审核中发现有 OOS 结果不能得出结论，或未发现实验室根本原因，则包括一份对生产批次生产记录、生产步骤充分性、设备/设施适用性、原料波动性、工艺能力、偏差历史、投诉历史、批失败历史的彻底审核。总结每个调查所发现的可能生产根本原因，以及所有生产操作改进措施。
- A comprehensive review and remediation plan for your OOS result investigation systems. The corrective action and preventive action (CAPA) plan should include but not be limited to the following:
  一份对你们 OOS 结果调查系统的全面审核和补救计划。CAPA 计划应包括但不仅限于：
  - Quality unit oversight of laboratory investigations
    质量部门对实验室调查的监管
  - Identification of adverse laboratory control trends

识别不良实验室控制趋势

- Resolution of causes of laboratory variation
  实验室变动原因的解决方案
- Initiation of thorough investigations of potential manufacturing causes whenever a laboratory cause cannot be conclusively identified
  在未识别出可归因的实验室原因时，对可能的生产原因启动彻底调查
- Adequately scoping of each investigation and its CAPA
  充分划定每个调查及其 CAPA 的范围
- Revised OOS investigation procedures with these and other remediations
  修订后的 OOS 调查程序，包括这些和其它补救措施

- Provisions for QU oversight throughout your operations to evaluate adherence to appropriate practices.
  QU 批准所有操作以评估是否遵守适当规范的条款
- Oversight and approval of investigations and discharging of all other QU duties to ensure identity, strength, quality, and purity of all drugs you manufacture.
  监管和批准调查，履行所有其它 QU 职责，以确保你们生产的所有药品的鉴别、含量、质量和纯度

2. Your firm failed to clean, maintain, and, as appropriate for the nature of the drug, sanitize and/or sterilize equipment and utensils at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements (21 CFR211.67(a)).

你公司未以适当的时间间隔清洁、维护和（药品属性需要时）消毒和/或灭菌设备和工器具，以防止发生故障或污染从而改变药品的安全性、鉴别、含量、质量或纯度使其超出官方或其它既定要求（21 CFR 211.67(a)）。

Our investigator observed that your dedicated equipment such as the (b)(4) and (b)(4) used to manufacture (b)(4) had visible rust, dents, and scratches on product contact surfaces.

我们的调查员发现你们用于生产 XX 的专用设备如 XX 和 XX 与产品接触的表面有肉眼可见铁锈、凹痕和刮痕。

Your response stated that you did not verify the cleanliness of all surfaces because the manufacturing area and entire equipment train is dedicated. You also stated that your Quality Unit would verify equipment cleaning. However, your response did not provide a plan for ensuring routine maintenance of your facility, including equipment maintenance, repairs, and replacement.

你们的回复声称你们并未核查所有表面的清洁情况，因为生产区域和整个设备链是专用的。你们还声称你们 QU 会核查设备的清洁情况。但是你们的回复并未提交一份确保对你们设施进行定期维保的计划，包括设备维护、维修和更换。

In response to this letter, provide:

在回复本函时请提交：

- Your CAPA plan to implement routine, vigilant operations management oversight of facilities and equipment. This plan should ensure, among other things, prompt detection of

equipment/facilities performance issues, effective execution of repairs, adherence to appropriate preventive maintenance schedules, timely technological upgrades to the equipment/facility infrastructure, and improved systems for ongoing management review.
你们执行日常、预警操作管理对设施和设备进行监管的 CAPA 计划。该计划应能确保（除其它事情外）快速发现设备/设施性能问题、有效执行维修、遵守适当的预防性维保计划、及时更新设备/设施基础设施，以及改进系统进行持续管理审核。

- A CAPA plan, based on the retrospective assessment, that includes appropriate remediations to your cleaning processes and practices, and timelines for completion. Provide a detailed summary of vulnerabilities in your process for lifecycle management of equipment cleaning. Describe improvements to your cleaning program, including enhancements to cleaning effectiveness; improved ongoing verification of proper cleaning execution for all products and equipment; and all other needed remediations.
一份基于回顾评估制订的 CAPA 计划，其中包括对你们清洁程序和规范的适当补救，以及完成时间表。提交一份关于你们的设备清洁生命周期管理流程中的弱点的详细总结。说明你们清洁程序的改进，包括改进清洁效果、改进后的所有产品和设备执行适当清洁的持续确认，以及所有需要的补救措施。

3. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).

你公司未对计算机或相关系统执行适当的控制，以确保只有经过授权的人员方可对主生产和检验记录或其它记录进行修改（21 CFR 211.68(b)）。

Our investigator observed your laboratory equipment lacked appropriate controls. For example, from January 1, 2018, to June 25, 2019, audit trails from (b)(4) Agilent 1260 Infinity Series II high-performance liquid chromatography (HPLC) instruments showed a pattern of aborted runs and single run entries for testing (b)(4). Single run entries included analyses of multiple peaks or split peaks without documented investigations or adequate scientific justifications. Your employees used the Agilent Service Account login, with full administrative privileges, to abort HPLC testing runs without being attributable to a specific individual.

我们调查人员发现你们的实验室设备缺乏适当控制。例如，2018 年 1 月 1 日至 2019 年 6 月 25 日，安捷伦 1260 Infinity 系列 II HPLC 审计追踪显示有运行中断和 XX 检测单针运行记录。单针运行记录包括多峰或裂峰分析，但没有调查记录或足够的科学论证。你们的员工使用了安捷伦服务账号登录，具有所有管理权限，可以中断 HPLC 运行，却无法追踪至具体人员。

Your response identified the number of deleted, aborted, and single runs during your HPLC testing. However, your response did not provide adequate investigations or evidence of corrective actions put in place to prevent these data integrity issues from recurring.

你们的回复说找出了你们 HPLC 测试中删除、中断和单针运行的数量。但是你们的回复并未提交足够的调查或制订的纠正措施证据，以防止这些数据完整性问题重复发生。

Data Integrity Remediation 数据完整性补救措施

Your quality system does notadequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. See FDA's guidance document

Data Integrity and Compliance With Drug CGMP for guidance on establishing and following CGMP compliant data integrity practices at https://www.fda.gov/media/119267/download.

你们的质量体系不能充分确保数据的准确性和完整性，无法支持你们生产的药品的安全性、有效性和质量。参见 FDA 指南文件“数据完整性和药品 GMP 合格”指导建立和遵守 CGMP 合格数据完整性规范。

We acknowledge that you are using a consultant to audit your operation and assist in meeting FDA requirements.

我们知悉你们正聘用顾问对你们的操作进行审计并协助你们符合 FDA 要求。

In response to this letter,provide the following:

在回复此函时请提交以下信息：

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include: 一份对数据记录和报告不准确性程度的全面调查。你们的调查应包括

- A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
  详细的调查方案和方法学，所有实验室、生产操作和评估所覆盖的系统的总结，如有除外部分请论证
- Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
  对现有和已离职员工进行面谈，找出数据不准确的程度、范围和根本原因。我们建议这些面谈由有资质的第三方进行。
- An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility’s operations in which you discovered data integrity lapses.
  你们工厂数据完整性缺陷的程度的评估。识别出省略、修改、删除、记录销毁、不同步记录填写和其它缺陷。说明你们已发现的数据完整性问题所涉及的工厂操作。
- A comprehensive retrospective evaluation of the nature of the testing and manufacturing data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses.
  一份对检测和生产数据完整性缺陷情况的全面回顾性评估。我们建议由具备在已发现可能有问题的领域的专业能力的有资质的第三方对所有数据完整性问题进行评估。

B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity and analyses of the risks posed by ongoing operations.
你们药品质量中所发现的不合格情况的潜在影响的当前风险评估。你们的评估应包括由于受到数据完整性问题影响的药品放行导致的患者风险的分析，以及持续运营所具有的风险。

C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include: 你们公司的管理策略，包括你们全球 CAPA 计划详细情况。你们的策略应包括：

- A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all the data you generate including analytical data, manufacturing records, and all data submitted to FDA.
  详细的 CA 计划，描述你们准备如何确保你们生成的所有数据的可靠性和完整性，包括分析数据、生产记录和所有提交给 FDA 的数据。
- A comprehensive description of the root causes of your data integrity lapses, including evidence that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm.
  一份对你们数据完整性问题根本原因的全面描述，包括当前行动计划的范围和深度与调查和风险评估发现相称的证据。说明负责数据完整性的人员是否还有能力影响你公司与 CGMP 有关或药品申报数据。
- Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring.
  临时措施，描述你们已采取或将采取用来保护患者和确保你们药品质量的措施，如通知你们的客户、召回产品、执行额外检测、增加批次至稳定性计划以确保稳定性、药品申报措施和加强投诉监测。
- Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data.
  长期措施，其中描述所有对用以确保你们公司数据完整性的程序、流程、方法、控制、系统、管理监管和人力资源（例如培训、员工提高）的弥补和提升。
- A status report for any of the above activities already underway or completed.
  上述活动已开展或已经完成的状态报告。

Concerns with Drug Suppliers 对药品供应商的担忧

You previously sourced (b)(4) API from (b)(4) who refused FDA inspection and was placed on Import Alert (b)(4) on (b)(4). Accordingly, FDA placed your firm on Import Alert 99-32 until you no longersourced drugs from (b)(4) and you committed to revise your API supplier qualification program.

你们之前从 XX 处采购 XX API，该公司拒绝了 FDA 的现场检查要求，已于 XX 日被放置于进口禁令中。相应地，FDA 已将你公司放置于进口禁令 99-32 中，直到你们不再从 XX 处采购药品，你们已承诺会修订你们的 API 供应商确认程序。

Conclusion 结论

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility.You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of other violations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

If you are considering an action that is likely tolead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C.356C(b). This also allows FDA to consider, as soon as possible, what actions,if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

如果你们在考虑要采取的措施可能会导致你们工厂所生产的药品供应中断，FDA 要求你立即联系 CDER 药品短缺负责人员，这样 FDA 可以与你们一起采用最为高效的方式引导你们的操作符合法规要求。联系药品短缺负责人员还能让你满足依据 21 U.S.C. 356C(b)你可能必须报告你们药品中止或中断的义务，让 FDA 尽快考虑是否需要采取何种措施来避免短缺，保护依赖于你们药品的患者健康。

FDA placed your firm on Import Alert 66-40 on December 16, 2019.

FDA 已于 2018 年 8 月 1 日将你公司置于进口禁令 66-40 中。

Until you correct all violations completely and weconfirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产的新申报和增补申报的批准。

Failure to correct these violations may also result in the FDA continuing to refuse admission of articles manufactured at GPT Pharmaceuticals Pvt. Ltd., FEI 3008311641, at Plot No. 6/3, Road No. 11, Nacharam, Hyderabad into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Articles under this authority may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

14. 320-20-14 2019-12-19 CGA Limited 特立尼达和多巴哥

Dear Mr. Agostini:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, CGA Limited, FEI 3008527957, at Eastern Main Road, Laventille, from May 27 to 31, 2019.

美国 FDA 于 2019 年 5 月 27 日至 31 日检查了你们位于特立尼达和多巴哥的 CGA Limited（FEI 3008527957）生产场所。

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

本警告信总结了制剂生产严重违反 CGMP 的行为。参见 21CFR 第 210 与 211 部分。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

由于你们的制剂生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的药品根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C. 351(a)(2)(B)被认为是掺假药品。

In addition, your firm manufactures “CARIB® Germicidal Soap.” This product is an unapproved new drug in violation of section 505(a) of the FD&C Act, 21 U.S.C. 355(a). Introduction or delivery for introduction of such product into interstate commerce is prohibited under section 301(d) of the FD&C Act, 21U.S.C. 331(d). These violations are described in more detail below.

此外，你公司生产的“CARIB®杀菌皂”是未经批准的新药，违反了 FDCA 第 505(a)条款 21 U.S.C. 355(a)。FDCA 第 301(d)条款 21 U.S.C. 331(d)禁止引入或输送该类药品至州际贸易。此项违规情况在以下详细说明。

We reviewed your June 18, 2019, response to our Form FDA 483 in detail.

我们已详细审核了你公司 2019 年 6 月 18 日对 FDA483 表的回复。

During our inspection, our investigator observed specific violations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

CGMP Violations CGMP 违规

1. Your firm failed to test samples of each component for identity and conformity with all appropriate written specifications for purity, strength, and quality. Your firm also failed to validate and establish the reliability of your component supplier’s test analyses at appropriate intervals (21 CFR 211.84(d)(1) and (2)).

你公司未能检测每种成分的样品的鉴别，未确认其是否符合所有适当的纯度、含量和质量标准。你公司亦未以适当的时间间隔验证和建立你们原料供应商的检测分析可靠性（21 CFR 211.84(d)(1) and (2)）。

You failed to adequately test your incoming components for identity, purity, strength, and other appropriate quality attributes. Specifically, you did not perform the identity test for (b)(4) listed in the

USP monograph. Additionally, you failed to perform impurity testing for (b)(4), also listed in the USP monograph. Your firm released active pharmaceutical ingredients (API) for use in drug manufacturing based on component supplier's analysis reports although you had not established the reliability of the analyses through appropriate validation.

你们未对你们的进厂组份鉴别、纯度、含量和其它适当的质量属性进行充分的检测。具体来说，你们未检测 USP 各论中所列的 XX 鉴别检查。另外，你们未对 XX 进行杂质检测，该项标准亦列在 USP 各论中。虽然你们并未通过适当的验证建立其分析可靠性，但你们公司仍根据组份供应商的分析报告放行了 API 用于药品生产。

In your response, you stated that you do not have the capability to perform the required incoming raw material tests, and contracted an external laboratory to complete testing on the API, (b)(4).

在你们的回复中，你们声称你们没有能力执行所需的进厂原料检测，你们委托外部实验室完成 API XX 的检测。

Your response is inadequate because you did not detail the type of testing you will perform for the API. In addition, you did not describe plans for validation of your raw material suppliers' test results and qualification of your contract testing laboratory.

你们的回复是不充分的，因为你们并未详细列出你们将要对该 API 执行的检测的类型。另外，你们并未说明你们对原料供应商的检测结果进行验证的计划，以及确认你们合同检测实验室的计划。

In response to this letter, provide the following:

在回复本函时，请提交以下内容：

- A comprehensive, independent review of your material system to determine whether all suppliers of components, containers, and closures are each qualified and the materials are assigned appropriate expiration or retest dates. The review should also determine whether incoming material controls are adequate to prevent use of unsuitable components, containers, and closures.
  一份对你们物料系统的全面独立审核，确定是否所有组份、容器和密闭器供应商均经过确认，并且原料有给定适当的有效期或复验期。审核亦应确定进厂物料控制是否足以防止使用不适当的组份、容器和密闭器。
- The chemical and microbiological quality control specifications you use to test and release each incoming lot of component for use in manufacturing.
  你们用于检测和放行每批进厂组份用于生产的化学和微生物质量控制标准。
- A description of how you will test each component lot for conformity with all appropriate specifications for identity, strength, quality, and purity. If you intend to accept any results from your supplier's certificates of analyses (COA) instead of testing each component lot for strength, quality, and purity, specify how you will robustly establish the reliability of your supplier's results through initial validation as well as periodic re-validation. In addition, include a commitment to always conduct at least one specific identity test for each incoming component lot.
  说明你们要如何检测每批组份，确认其符合所有适当的鉴别、含量、质量和纯度标准。如果你们准备接受你们供应商 COA 的所有结果，取代你们对每批组份的含量、质量和纯度检测，则请

说明你们要如何通过初始验证和定期重新验证稳固建立你们供应商结果的可靠性。此外，要包括一份承诺，保证会一直对每批进厂组份执行至少一项专属性鉴别检测。

- Your standard operation procedure (SOP) that describes this COA validation program.
  你们描述 COA 验证程序的 SOP
- A summary of your program for qualifying and overseeing contract facilities that test the drug products you manufacture. Detail how you will ensure that your qualification is completed for these facilities.
  一份你们确认和监管检测你们生产的药品的合同场所的程序摘要。详细说明你们将如何确保你们完成对这些场所的确认。

2. Your firm failed to have, for each batch of drug product, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release (21 CFR 211.165(a)).

你公司未对每批药品在放行前执行适当的实验室检测，确定其符合药品的最终标准，包括每种活性成分的鉴别和含量（21 CFR 211.165(a)）。

Your firm released your topical over-the-counter(OTC) drug product, (b)(4)," to the United States market although your COAs lacked critical tests including but not limited to the (b)(4) active ingredient assay and identity testing. In addition, you lacked stability data to demonstrate that the properties of your drug product remain acceptable throughout its assigned (b)(4) shelf-life.

尽管你们的 COA 缺乏关键检测，包括但不仅限于 XX 活性成分含量和鉴别检测，但你公司放行了你们的局部用 OTC 药品 XX 至美国市场。另外，你们缺乏稳定性数据证明你们的药品性质在其给定的 XX 货架期内保持可接受。

Complete testing of each batch before release is essential part of ensuring that the drug product you manufacture meets established specifications.

在放行之前完成对每个批次的检测是确保你们生产的药品符合既定标准的基本部分。

We acknowledge that you have contracted an external laboratory to retrospectively test batches of finished drug product shipped to the U.S. market for the percent of (b)(4). You also plan to complete an independent stability study of your OTC drug product using an external laboratory. However, your response lacked sufficient details regarding the active ingredient analyses.

我们了解你们已委托了一个外部实验室对销售至美国市场的药品的 XX 百分比进行回顾性检测。你们亦计划采用外部实验室完成你们 OTC 药品的独立稳定性研究。但是你们的回复缺乏关于活性物质分析方面的足够详细内容。

In response to this letter, provide the following:

在回复本函时请提交以下内容：

- A comprehensive, independent assessment of your laboratory practices, procedures, methods, equipment, documentation, analyst competencies. Based on this review, provide a detailed plan to remediate and evaluate the effectiveness of your laboratory system. A similar assessment should be performed to address any functions performed on your behalf by a contract testing laboratory.

一份对你们实验室规范、程序、方法、设备、文件、化验员能力的全面独立评估。根据该回顾，提交一份补救和评估你们实验室系统的详细计划。应进行类似的评估解决代表你们的合同检测实验室所执行的所有职能。

- A list of chemical and microbial test methods and specifications used to analyze each lot of your drug product before making a lot disposition decision, and the associated written procedures.
  一份你们每批药品在批处置决策之前分析所用化学和微生物检测方法和标准清单
- A summary of all results obtained from testing retain samples from each batch. If such testing reveals substandard quality drug products, take rapid corrective actions, such as notifying customers and product recalls.
  对每批留样所有检测结果的总结。如果该检测发现有药品质量不合格，则应采取快速纠正措施，如通知客户和召回产品
- Your plan, with timelines, to develop and implement a complete drug stability program.
  你们开发和执行完整的药品稳定性程序的计划与时间表

3. Your firm failed to establish and follow adequate written procedures for cleaning and maintenance of equipment (21 CFR 211.67(b)).

你公司未建立和执行充分的书面设备清洁和维护程序（21 CFR 211.67(b)）。

We observed apparent rust and peeling paint on product contact surfaces of your non-dedicated equipment, which you use to manufacture drugs and cosmetics. In addition, you have not validated your cleaning methods to demonstrate that they are reproducible to ensure cleaning efficacy.

我们发现你们用于生产药品和化妆品的非专用设备产品接触表面有生锈和掉漆。另外，你们并未验证你们的清洁方法，证明其能确保清洁有效性及可重复性。

In your response, you stated that you will review and revise the relevant written procedures to ensure they comply with FDA regulations.

在你们的回复中，你们声称你们将审核和修订相关的书面程序，确保其符合 FDA 法规要求。

Your response is inadequate because it lacked sufficient details regarding remediations to your equipment cleaning program.

你们的回复是不充分的，因为其中缺乏了足够详细的内容说明要如何补救你们的设备清洁程序。

In response to this letter, provide the following:

在回复本函时请提交以下内容：

- Your corrective actions and preventive actions (CAPA) plan to implement routine, vigilant operations management oversight of facilities and equipment. This plan should ensure, among other things, prompt detection of equipment/facilities performance issues, effective execution of repairs, adherence to appropriate preventive maintenance schedules, timely technological upgrades to the equipment/facility infrastructure, and improved systems for ongoing management review.

你们对设施和设备执行日常、严格操作管理监管的 CAPA 计划。该计划应确保快速发现设备/设施性能问题、有效进行维修、遵守适当的预防性维护计划、及时进行技术升级至设备/设施基础设施，以及改进后的持续管理审评体系

- A comprehensive, independent retrospective assessment of your cleaning effectiveness to evaluate the scope of cross-contamination hazards. Include the identity of residues, other manufacturing equipment that may have been improperly cleaned, and an assessment whether cross-contaminated products may have been released for distribution. The assessment should identify any inadequacies of cleaning procedures and practices, and encompass each piece of equipment used to manufacture more than one product.
一份对你们清洁有效性的全面独立回顾性评价，评估交叉污染危害的范围。其中要包括残留的鉴别、其它可能不当清洁的生产设备，以及被交叉污染的产品是否已被放行销售的评估。该评估应识别清洁程序和规范的任何不充分性，并指导每台共用设备
- A CAPA plan, based on the retrospective assessment, that includes appropriate remediations to your cleaning processes and practices, cleaning validation justification, and timelines for completion. Summarize vulnerabilities in your process for lifecycle management of equipment cleaning in detail. Describe improvements to your cleaning program, including enhancements to cleaning effectiveness; improved ongoing verification of proper cleaning execution for all products and equipment; and all other needed remediations.
一份基于回顾性评估的 CAPA 计划，其中包括对你们清洁工艺和规范的恰当补救、清洁验证论证和完成时间表。详细总结设备清洁生命周期管理过程的薄弱点。阐述对你们清洁程序的改进，包括提升清洁有效性、改进持续监测所有产品和设备的良好清洁执行，以及所有其它所需补救措施
- Appropriate improvements to your cleaning validation program, with special emphasis on incorporating conditions identified as worst case in your drug manufacturing operation. This should include but not be limited to identification and evaluation of all worst-case:
对你们清洁验证程序的恰当改进，特别强调要结合在你们药品生产操作中识别为最差情形的条件。其中应包括但不仅限于识别和评估所有最差情形：
  - products with higher toxicities
高毒性产品
  - products with higher potencies
高活性产品
  - products of lower solubility in their cleaning solvents
在清洁剂中低溶解度产品
  - products with characteristics that make them difficult to clean
具有难清洁特性的产品
  - swabbing locations for areas that are most difficult to clean
最难清洁部位的擦拭取样位置
  - maximum hold times before cleaning
清洁前的最长放置时间

In addition, describe the steps that must be takenin your change management system before introducing new manufacturing equipmentor a new product.

此外，要说明引入新生产设备或新产品之前在你们变更管理体系中必须采取的步骤。

- A summary of updated SOPs that ensure an appropriate program is in place for verification and validation of cleaning procedures for products, processes, and equipment.
  更新后 SOP 的总结，确保对产品、工艺和设备清洁程序具备适当的验证和核查计划

4. Your firm failed to use equipment in the manufacture, processing, packing, or holding of drug products that is of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance (21 CFR 211.63).

你公司未使用经过适当设计、具备足够尺寸和适当定位的设备用于生产、加工、包装和保存药品，以便其操作适合于其既定用途和清洁及维护（21 CFR 211.63）。

Your firm did not assure that the (b)(4) generated from your (b)(4) system used to manufacture drug products wasfit for purpose. You manufactured drug products using (b)(4)" from a (b)(4) system that had not been validated, adequately monitored for objectionable microorganisms, and designed to produce (b)(4). Your (b)(4) system was also routinely (b)(4) which leads to (b)(4) and can cause the system to become insanitary.

你公司未能确保你们用于生产药品的 XX 系统中生成的 XX 适合其用途。你们生产的药品使用了来自未经验证、充分监测致病菌以及设计用以生成 XX 的 XX 系统的 XX。你们的 XX 系统亦日常 XX，这样会导致 XX，可能使得系统不卫生。

In your response, you stated that you will review and revise written procedures including, but not limited to, equipment qualification, validation, and controls for (b)(4). You also stated that your external contactor recommended replacement of the (b)(4) system and that you may also replace your (b)(4).

在你们的回复中，你们声称你们将审核并修订书面程序，包括但不仅限于设备确认、验证和 XX 控制。你们还声称你们的外部合同商建议更换 XX 系统，你们亦可能更换你们的 XX。

Your response is inadequate because you failed to include sufficient remediations to design, monitoring, and control of the system as well as a (b)(4) system validation protocol. It is also unclear if you require (b)(4) used in manufacturing operations to meet (b)(4) USP standards.

你们的回复是不充分的，因为你们未包括对系统设计、监测和控制和 XX 系统验证方案的充分补救。亦不清楚你们是否要求生产操作中所用的 XX 符合 XX USP 标准。

In response to this letter, provide the following:

在回复本函时请提交以下内容：

- A comprehensive, independent assessment of your (b)(4) system design, control, and maintenance.
  一份对你们 XX 系统设计、控制和维护的全面独立评估
- A thorough remediation plan to design and operate a suitable (b)(4) system. Include a robust ongoing control, maintenance, and monitoring program to ensure the new system consistently produces (b)(4) adhering to (b)(4) USP monograph specifications and appropriate microbial limits.
  一份对适用 XX 系统设计和运行的彻底补救计划。包括稳定持续的控制、维护和监测计划，以确保新系统持续产出符合 XX USP 各论标准和适当微生物限度标准的 XX。

- Regarding the latter, ensure that your total microbial count limit for (b)(4) is appropriate in view of the intended use of the products produced by your firm.
  关于后者，要确保你们的 XX 总微生物计数限度适合于你们公司所生产药品的既定用途。
- Validation report for the (b)(4) system obtained after its design has been comprehensively remediated and any maintenance repairs have been completed. Include the system validation protocol, the complete test results, and the final validation report.
  XX 系统设计全面补救和所有维护维修完成之后的验证报告。包括系统验证方案、完成的测试结果以及最终验证报告。
- Revised procedures for routine (b)(4) sampling and analysis for all points-of-use for manufacturing operations.
  修订后的所有生产使用点日常 XX 取样和分析程序
- A detailed risk assessment addressing the potential effects of (b)(4) system deficiencies on the quality of all drug product lots currently in U.S. distribution. Specify actions that you will take in response to the risk assessment.
  一份详细的风险评估，解决 XX 系统缺陷对所有目前在美国销售的药品批次的潜在影响。说明你们应对风险评估将要采取的措施。

CGMP Consultant Recommended CGMP 顾问建议

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualified as set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements. We also recommend that the qualified consultant perform a comprehensive audit of your entire operation for CGMP compliance and that the consultant evaluates the completion and efficacy of your CAPA before you pursue resolution of your firm's compliance status with FDA.

鉴于我们在你公司所发现的违规情况，我们强烈建议你们使用一位有 21 CFR 211.34 所述资质的顾问来协助你们公司符合 CGMP 要求。我们亦建议该具备资质的顾问对你们整体运营情况进行药品 CGMP 合规情况全面审计，并由其在你们寻求满足 FDA 合规要求之前对你们 CAPA 的完成情况和有效性进行评估。

Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for resolving all violations and systemic flaws to ensure ongoing CGMP compliance.

你们使用顾问并不能解除你们公司符合 CGMP 的义务。你们公司的高级管理层仍负有义务全面解决所有缺陷，确保持续 CGMP 符合性。

Unapproved New Drug Charge 未经批准的新药指控（略）

Conclusion 结论

Violations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these violations, for determining the causes, for preventing their recurrence, and for preventing other violations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

FDA placed your firm on Import Alert 66-40 on November 21, 2019.

FDA 已于 2019 年 11 月 21 日将你公司置于进口禁令 66-40 中。

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产的新申报和增补申报的批准。

Failure to correct these violations may also result in FDA continuing to refuse admission of articles manufactured at CGA Limited at Eastern Main Road, Laventille into the United States under section 801(a)(3) of the FD&C Act (21 U.S.C. 381(a)(3)). Under the same authority, articles may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

15. 320-20-15 2019-12-13 Apollo Health And Beauty Care, Inc. 加拿大

Dear Mr. Wachsberg:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Apollo Health and Beauty Care,Inc., FEI: 3003173295, at 1 Apollo Place, North York, Ontario from August 12 to August 16, 2019.

美国 FDA 于 2019 年 8 月 12 日至 16 日检查了你们位于加拿大的 Apollo Healthand Beauty Care, Inc.（FEI:3003173295）生产场所。

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See Title 21 Code of Federal Regulations (CFR), parts210 and 211 (21 CFR parts 210 and 211).

本警告信总结了制剂生产严重违反 CGMP 的行为。参见 21CFR 第 210 与 211 部分。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C.351(a)(2)(B).

由于你们的制剂生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的药品根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C. 351(a)(2)(B)被认为是掺假药品。

We reviewed your September 03, 2019 response to our Form FDA 483 in detail. We acknowledge receipt of your subsequent correspondence. Your response is inadequate because it did not provide sufficient detail or evidence of corrective actions to bring your operationsin to compliance with CGMP.

我们已详细审核了你公司 2019 年 9 月 3 日对我们 FDA483 表的回复，并此告知已收到后续通信。你们的回复是不充分的，因为其中并未提交足够的详细内容和证据证明纠正措施能够使得你们的运作符合 CGMP 要求。

During our inspection, our investigator observed specific violations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

1. Your firm failed to routinely calibrate, inspect, or check according to a written program designed to assure proper performance and to maintain adequate written records of calibration checks and inspections of automatic, mechanical, electronic equipment, or other types of equipment, including computers, used in the manufacture, processing, packing, and holding of a drug product (21 CFR 211.68(a)).

你公司未按照为确保正常运行而设计的书面程序对药品生产、加工、包装和保存所用自动化、机械、电子设备或其它类型设备（包括计算机）进行日常校正、查验或检查，未保存足够书面校正检查和查验记录（21 CFR 211.68(a)）。

Your firm contract manufactures over-the-counter(OTC) drug products, some of which are labeled to be used for children. During a review of an out-of-specification (OOS) investigation for (b)(4) content in your bulk (b)(4) lot (b)(4), our investigator identified multiple discrepancies between the human machine interface (HMI) data, and the entries made by operators into batch records. For

example, the operator recorded (b)(4) the batch during Step (b)(4) for (b)(4) at (b)(4). However, HMI data indicated that (b)(4) were not operational at that time.

你公司委外生产 OTC 药品，其中一些药品标示为儿童专用。在对你们散装批号 XX 的 XX 含量 OOS 调查文件的审核过程中，我们的检查员发现人机界面（HMI）数据与操作员录入批记录中的数据有多处不符。例如，操作员在 XX 步骤中记录的是 XX，但 HMI 数据显示当时 XX 并未运行。

At the time of inspection, your quality unit acknowledged that operators do not (b)(4) the product as the batch record indicates. However, you failed to adequately investigate and resolve these discrepancies.

在检查时，你们的质量部门承诺操作员并未按批记录显示的 XX 产品。但是你们并未对此不符情况进行充分调查并予以解决。

In your response, you stated that you will randomly select batch records to compare against HMI data and will investigate any discrepancies between batch records and HMI data. Your response is inadequate. You did not commit to fully evaluate the scope of the discrepancies between HMI data and batch records or practices of operators not following batch instructions. You did not establish a root cause for these discrepancies. In addition, you did not expand the investigation to include potential records discrepancies in other operational areas or provide an assessment into distributed product. Furthermore, you did not adequately address the failure of operations management and quality unit (QU) oversight over documentation and data integrity.

在你们的回复中，你们声称你们将随机选择批记录与 HMI 数据进行对比，并将调查所有批记录与 HMI 数据之间的不符情况。你们的回复是不充分的。你们并未承诺要全面评估 HMI 数据与批记录或操作员不遵守批指令的做法涉及的范围。你们并未识别出这些不符情况的根本原因。另外，你们没有扩展调查至其它操作区域可能存在的记录不符情况，亦未提交对已销售药品的批评。还有你们并未充分解决操作管理失败问题，以及 QU 对文件和数据完整性监管失败问题。

Your quality system does not adequately ensure the accuracy and integrity of the data to support the safety, effectiveness and quality of the drugs you manufacture. Without complete and accurate records, you cannot assure appropriate. Decisions regarding batch release, product stability, and other matters that are fundamental to ongoing assurance of quality. See FDA's guidance document Data Integrity and Compliance with Drug CGMP, for guidance on establishing and following CGMP compliant data integrity practices at Data Integrity and Compliance with CGMP Guidance for Industry https://www.fda.gov/media/97005/download.

你们的质量体系不能充分保证支持你们所生产药品安全性、有效性和质量的数据的准确性和完整性。没有完整和准确的记录，你们无法确保做出恰当的批放行、产品稳定性和其它事务决策，而这些对于持续质量保证是基本的要求。参见 FDA 指南文件“数据完整性与药品 CGMP 合规”中对于建立和遵守 CGMP 合规数据完整性规范的指南。

In response to this letter, provide the following:

在回复本函时请提交以下：

- A comprehensive investigation into the extent of the inaccuracies in data records and reporting including results of the data review for drugs distributed to the United States. Include a detailed description of the scope and root causes of your data integrity lapses.

一份对数据记录和报告不准确程度的全面调查，包括销售至美国的药品的数据审核结果。包括一份对你们数据完整性问题的范围与根本原因的详细说明

- A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity and analyses of the risks posed by ongoing operations.
  一份对所发现的失败对你们药品质量的潜在影响的目前风险评估。你们的评估应包括受数据完整性问题影响的药品放行所导致的患者风险分析和持续运营风险分析
- A management strategy for your firm that includes the details of your global corrective action and preventive action plan. The detailed corrective action plan should describe how you intend to ensure the reliability and completeness of all data generated by your firm including microbiological and analytical data, manufacturing records, and all data submitted to FDA.
  一份对你们公司的管理策略，包括你们全球 CAPA 计划的详细内容。详细的纠正措施计划应说明你们准备要如何确保你们公司生成的所有数据（包括微生物和分析数据、生产记录和提交给 FDA 的所有数据）的可靠性和完整性
- A complete assessment of documentation systems used throughout your manufacturing and laboratory operations to determine where documentation practices are insufficient. Include a detailed corrective actionand preventive action (CAPA) plan that comprehensively remediates your firm's documentation practices to ensure you retain attributable, legible, complete, original, accurate, contemporaneous records throughout your operation.
  一份对你们生产和实验室操作中所用文件系统的完整评估，确定当前哪些文件做法是不充分的。包括一份全面补救你公司文件做法从而确保你们保存可追溯、清晰、完整、原始、准确、所有操作过程中同步记录的详细 CAPA 计划

2. Your firm failed to establish adequate written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess. (21 CFR 211.100 (a)).

你公司未制订足够的书面生产和工艺控制程序，以确保你们生产的药品具备其理当具备或表述的鉴别、含量、质量和纯度（21 CFR 211.100 (a)）。

Your firm failed to validate multiple processes used to manufacture your drug products. For example, your firm lacked process validation for (b)(4).

你公司未验证多个药品生产所用工艺。例如，你公司缺乏 XX 的工艺验证。

This is a repeat observation that was also cited during our inspection conducted in December 2016.

该缺陷是 2016 年 12 月所执行检查中已列出的重复缺陷。

Additionally, your operators failed to follow batch record instructions or document deviations which may be used to investigate and assess the impact on the finished drug products.

另外，你们的操作员未遵守批记录指令，未记录可能会被用于调查和评估成品所受影响的偏差。

Furthermore, your firm permits a lengthy bulk holdtime of (b)(4) prior to filling drug products. You failed to assure that this practice does not impact the chemical and microbiological quality of your drug products.

还有，你公司允许在成品灌装之前将散装成品保存 XX 时长。你们未能确保该做法不影响你们药品的化学和微生物质量。

Your response lacks specifics on your approach to perform process validation.

你们的回复缺少对执行工艺验证的方法具体说明。

Process validation evaluates the soundness of design and state of control of a process throughout its lifecycle. Each significant stage of a manufacturing process must be designed appropriately and assure the quality of raw material inputs, in-process materials, and finished drugs. Process qualification studies determine whether an initial state of control has been established. Successful process qualification studies are necessary before commercial distribution. Thereafter, ongoing vigilant oversight of process performance and product quality is necessary to ensure you maintain a stable manufacturing operation throughout the product lifecycle. See FDA's guidance document, Process Validation: General Principles and Practices, for general principles and approaches that FDA considers appropriate elements of process validation at http://www.fda.gov/media/71021/download.

工艺验证评估的是一个工艺在其生命周期中的设计合理性和受控状态。生产工艺的每个重要阶段均必须进行适当设计，确保原料输入、中间体和成品的质量。工艺确认研究能确定是否建立了初始的受控状态。商业销售之前必须进行成功的工艺确认研究。之后要进行持续的严格工艺性能和产品质量监测，以确保你们在整个产品生命周期中维持稳定的生产操作。参见 FDA 指南文件“工艺验证一般原则和规范”。

In response to this letter, provide the following:

在回复本函时请提交以下：

- A detailed summary of your validation program for ensuring a state of control throughout the product lifecycle, along with associated procedures.
  一份对你们确保产品在整个生命周期的受控状态的验证计划，以及相关程序的详细总结。
- A timeline for performing appropriate process performance qualification (PPQ) for each of your marketed drug products.
  一份对你们所有已上市药品实施适当 PPQ 的时间表。
- Include your process performance protocol(s), and written procedures for qualification of equipment and facilities.
  你们的工艺性能方案和设备设施确认书面程序。
- Provide a detailed program for designing, validating, maintaining, controlling and monitoring each of your manufacturing processes that includes vigilant monitoring of intra-batch and inter-batch variation to ensure an ongoing state of control. Also, include your program for qualification of your equipment and facility.
  提交一份对你们每个生产工艺进行设计、验证、维护、控制和监测的详细程序，其中应包括严格监控批内和批间波动，以确保其持续受控。还要包括一份你们设备和设施确认的程序。

3. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether the batch has already been distributed (21CFR 211.192).

你公司未对已放行或未放行的产品批次或其组份不符合其任何标准且无解释的情况进行彻底调查（21 CFR 211.192）。

Your firm failed to perform adequate investigations. For example,

你公司未进行彻底的调查。例如：

a. You failed to adequately investigate and document the presence of (b)(4) particles in (b)(4) Lot (b)(4). You concluded that the particles were from a broken belt on the filling line, Your corrective action was to reject approximately (b)(4) units of this lot. However, this corrective action did not expand to cover batches that were previously filled at the same line or preventative maintenance plan to prevent recurrence of similar incidents.

你们未进行充分调查并记录 XX 批中 XX 颗粒物的出现情况。你们得出结论说颗粒物来自灌装线上破碎的传送带。你们的纠正措施是拒收该批次的约 XX 单位。但是该纠正措施并未扩展至之前在相同产线生产的其它批次，亦没有预防措施防止类似事故的重复发生。

b. You failed to conduct an adequate investigation into an OOS test result for low (b)(4) content for your (b)(4) Lot (b)(4). Your investigation stated "as per previous similar OOS on beg [sic] samples, it has been found that at the beginning of filling process, it may be affected for dilution which explain the low results." You then released the units filled after a timepoint of 13:45. You clarified during the inspection that residual water from the (b)(4) process led to rinse water contamination at the beginning of the batch, however, you could not provide a manufacturing investigation to confirm the residual water was the root cause. You lacked assurance that the released units from this batch were not contaminated, and you did expand your investigation to evaluate your (b)(4) process.

你们未对你们 XX 批号 XX 中含量 XX 过低的 OOS 结果进行充分调查。你们的调查声称“根据之前 XX 样品的类似 OOS，已发现在灌装工艺开始时可能会受到稀释的影响，这就解释了为何结果会偏低”。然后你们放行了在 13：45 之后灌装的单位。你们在检查期间澄清说来自 XX 工艺的残留水分导致在批开始时淋洗水污染，但你们不能提供生产调查来确认残留水是根本原因。你们不能保证该批中所放行单位未受影响，你们亦未扩展你们的调查对你们的 XX 工艺进行评估。

In your response you indicated that you will improve your investigation process. Your response is inadequate. You did not commit to perform a retrospective review of all your drug products to ensure you are attributing root cause appropriately, reporting OOS results correctly, and implementing adequate CAPA.

在你们的回复中，你们说你们将改进你们的调查流程。你们的回复是不充分的。你们并未承诺要对你们所有药品执行回顾性审核，确保你们适当归因根本原因、正确报告 OOS 结果，以及执行充分的 CAPA。

This is a repeat observation that was also cited during the inspection conducted in December 2016.

该缺陷是 2016 年 12 月检查所发现的重复缺陷。

In response to this letter, provide the following:

在回复本函时请提交以下内容：

- A comprehensive, independent assessment of your overall system for investigating deviations, discrepancies, complaints, OOS results, and failures. Provide a detailed action plan to remediate this system. Your action plan should include, but not be limited to, significant improvements in investigation competencies, scope determination, root cause evaluation, CAPA effectiveness, quality assurance oversight, and written procedures. Address how your firm will ensure all phases of investigations are appropriately conducted.
  一份对你们整个偏差、差异、投诉、OOS 结果和失败调查体系的全面独立评估。提交一份详细的行动计划对该系统进行补救。你们的行动计划应包括但不仅限于对调查能力、范围确定、根本原因评估、CAPA 有效性、质量保证监管和书面程序的重大改进。说明你们公司要如何确保适当执行所有的调查阶段。
- An independent assessment and remediation plan for your CAPA program. Provide a report that evaluates if it includes staff with proper investigation competencies, effectively conducts root cause analysis, assures CAPA effectiveness, regularly reviews investigations trends, implements improvements to the CAPA program when needed, ensures appropriate quality assurance decision rights, and is fully supported by executive management.
  一份对你们 CAPA 程序的独立评估和补救计划。提交一份报告，评估其中是否包括了具备适当调查能力的人员、有效执行根本原因分析、确保 CAPA 有效性、定期审核调查趋势、执行 CAPA 计划的改进（必要时）、确保适当的质量保证决策权力，以及得到执行管理人员的全面支持。
- A comprehensive assessment and remediation plan to ensure your QU is given the authority and resources to effectively function.The assessment should also include, but not be limited to:
  一份全面评估和补救计划，确保你们的 QU 被授予权力和给予资源能有效运行。评估还应包括但不仅限于：
  - A determination of whether procedures used by your firm are robust and appropriate
    确定你公司所用程序是否稳健和恰当
  - Provisions for QU oversight throughout your operations to evaluate adherence to appropriate practices
    QU 监管你们所有操作从而评估是否遵守适当规范的条款
  - A complete and final review of each batch and its related information before the QU disposition decision
    QU 在处置决策之前对每个批次及其相关信息进行全面最终审核
  - Oversight and approval of investigations and discharging of all other QU duties to ensure identity, strength, quality, and purity of all products. Also describe how top management supports quality assurance and reliable operations, including but not limited to timely provision of resources to proactively address emerging manufacturing/quality issues and to assure a continuing state of control.
    监管和批准调查，履行所有其它 QU 义务，确保所有产品的鉴别、含量、质量和纯度。亦请说明高级管理人员如何支持质量保证和可靠运营，包括但不仅限于及时提供资源，主动解决新发现的生产/质量问题，以及确保持续受控状态

CGMP Consultant Recommended CGMP 顾问建议

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualified as set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements if your firm intends to resume manufacturing drugs for the U.S.market. We also recommend that the qualified consultant perform a comprehensive audit of your entire operation for

CGMP compliance and that the consultant evaluates the completion and efficacy of your corrective actions and preventive actions before you pursue resolution of your firm 's compliance status with FDA.

鉴于我们在你公司所发现的违规情况，我们强烈建议你们使用一位有 21 CFR 211.34 所述资质的顾问来协助你们公司符合 CGMP 要求。我们亦建议该具备资质的顾问对你们整体运营情况进行药品 CGMP 合规情况全面审计，并由其在你们寻求满足 FDA 合规要求之前对你们 CAPA 的完成情况和有效性进行评估。

Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm 's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

你们使用顾问并不能解除你们公司符合 CGMP 的义务。你们公司的高级管理层仍负有义务全面解决所有缺陷，确保持续 CGMP 符合性。

Conclusion 结论

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the·causes of these violations and for preventing their recurrence or the occurrence of other violations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

If you are considering an action that is likely tolead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C.356C(b). This also allows FDA to consider, as soon as possible, what actions,if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

如果你们在考虑要采取的措施可能会导致你们工厂所生产的药品供应中断，FDA 要求你立即联系 CDER 药品短缺负责人员，这样 FDA 可以与你们一起采用最为高效的方式引导你们的操作符合法规要求。联系药品短缺负责人员还能让你满足依据 21 U.S.C.356C(b)你可能必须报告你们药品中止或中断的义务，让 FDA 尽快考虑是否需要采取何种措施来避免短缺，保护依赖于你们药品的患者健康。

FDA placed your firm on Import Alert 66-40 on December 16, 2019.

FDA 已于 2019 年 12 月 16 日将你公司置于进口禁令 66-40 中。

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer. ·

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产的新申报和增补申报的批准。

Failure to correct these violations may also result in the FDA continuing to refuse admission of articles manufactured at Apollo Health and Beauty Care, Inc., at 1 Apollo Place, North York, Ontario into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Articles under this authority may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501 (a)(2)(B) of the FD&C Act, 21 U.S.C.351 (a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

16. 320-20-16 2020-01-09 Huaian Zongheng Bio-Tech Co., Ltd 淮安纵横生物科技有限公司

Dear Mr. Li:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Huaian Zongheng Bio-Tech Co., Ltd., FEI 3007628845, at No. 615 North Xiangyu Road, Huaian, from July 1 to 5, 2019.

美国 FDA 于 2019 年 7 月 1 日至 5 日检查了你们位于江苏淮安市淮阴区翔宇北道 615 号的淮安纵横生物科技有限公司生产场所。

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

本警告信总结了制剂生产严重违反 CGMP 的行为。参见 21CFR 第 210 与 211 部分。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

由于你们的制剂生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的药品根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C. 351(a)(2)(B)被认为是掺假药品。

We reviewed your July 25, 2019, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

我们已详细审核了你公司 2019 年 7 月 25 日的回复，并此告知已收到后续通信。

During our inspection, our investigator observed specific violations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

1. Your firm failed to have, for each batch of drug product, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release (21 CFR 211.165(a)).

你公司未对每批药品进行适当的实验室检测，确定其符合药品最终质量标准，包括每种活性成分的鉴别和含量（21 CFR 211.165(a)）。

Your firm contract manufactures over-the-counter(OTC) (b)(4) drug products, including versions specifically marketed for children. You released your drug products without adequate testing, including identity and strength testing for each active ingredient. For example, you did not test drug products (b)(4) for their labeled active ingredient, (b)(4), prior to release.

你公司委外生产 OTC 药品 XX，包括儿童专用版本。你们未进行足够的检测，包括每种活性成分的鉴别和含量检测即放行了药品。例如，你们在放行之前并未检测药品 XX 中其所标示的活性成分 XX。

Complete testing of each batch before release is essential to determine if the drug products you manufacture meet appropriate specifications.

放行前对每批进行完整检测以确定你们生产的药品是否满足适当的标准是很重要的。

In your response, you provided third-party testing results for assay of (b)(4) contained in (b)(4) drug product lotof (b)(4) and (b)(4) drug product lot of (b)(4). You also provided the revised finished product specifications for both drug products to add the requirements for (b)(4) assay testing prior to release in the future.

在你们的回复中，你们提交了 XX 药品批次中 XX 含量第三方检测结果。你们亦提交了修订后的 2 个成品质量标准，增加了未来放行前检测 XX 含量的要求。

Your response is inadequate. Your testing was limited to assay, and you failed to specify and perform at least one test to verify the identity of (b)(4) in (b)(4) batch of drug product you manufacture containing the active ingredient. Further, you failed to test all of your retain samples of drug products containing (b)(4) within expiry to determine whether they meet established specifications for identity and assay. Your response is also inadequate because you did not include sufficient information about your testing procedures, methods, or a detailed description of the tests you will conduct (e.g., identity, strength, and purity).

你们的回复是不充分的。你们的检测仅限于含量，你们并未说明并执行至少一项检查以确定你们所生产的含有 XX 的 XX 药品批次中 XX 的鉴别。另外，你们未能检测你们含 XX 的仍在效期内的药品的留样，确定其是否满足既定的鉴别和含量标准。你们的回复不充分还因为你们并未包括关于你们检测程序、方法或详细阐述你们将要执行的检测（例如，鉴别、含量和纯度）的足够信息。

In response to this letter, provide the following:

在回复本函中，请提交：

- A list of chemical and microbial specifications, including test methods, used to analyze each lot of your drug products before a lot disposition decision.
  一份在批处置决策之前用于分析每批药品的化学和微生物标准清单，包括检测方法
- An action plan and timelines for conducting full chemical and microbiological testing of retain samples to determine the quality of all batches of drug product distributed to the United States within expiryas of the date of this letter
  一份对留样执行全面化学和微生物检测的行动计划和时间表，以确保销售至美国仍在效期内的所有批次药品的质量
- A summary of all results obtained from testing retain samples from each batch. If such testing reveals substandard quality drug products, take rapid corrective actions, such as notifying customers and product recalls
  一份对每批留样检测所得结果的总结。如果该检测结果显示药品质量不合格，则应采取快速纠正措施，如通知客户和召回产品
- A comprehensive, independent assessment of your laboratory practices, procedures, methods, equipment, documentation, and analyst competencies. Based on this review, provide a detailed plan to remediate and evaluate the effectiveness of your laboratory system.
  一份对你们实验室做法、程序、方法、设备、文件和化验员能力的全面独立评估。基于该回顾，提交一份详细的计划，对你们实验室系统进行补救，并评估其有效性
- Your procedure to ensure that any test methods performed by a contract testing laboratory on your behalf are properly validated before use.
  你们确保合同检测实验室执行的所有检测方法在使用前均经过适当验证的程序

2.Your firm failed to conduct at least one test to verify the identity of each component of a drug product (21 CFR 211.84(d)(1)).

你公司未能执行至少一项检查确认药品每种组份的鉴别（21CFR 211.84(d)(1)）。

You failed to test incoming components used to manufacture your drug products to determine their identity. For example, your firm did not ensure that at least one specific identity test was conducted for each lot of active ingredients (b)(4).

你公司未检测药品生产所用组份的鉴别。例如，你公司未能确保对每批活性成分 XX 执行至少一项专属鉴别检查。

In your response, you stated that you revised the specifications for incoming active ingredients (e.g., (b)(4)) to include an identification test. You also provided an example of the revised specification sheet for (b)(4), in addition to an example of a third-party laboratory test report for the (b)(4) content in (b)(4) lot of (b)(4) raw material.

在你们的回复中，你们声称你们修订了进厂活性成分（例如 XX）的质量标准，加入了一项鉴别检查。除了一份 XX 批次 XX 原料 XX 含量的第三方检测报告样例外，你们还提交了一份 XX 修订后质量标准表的样例。

Your response is inadequate. You failed to specify and perform at least one test to verify the identity of all of the components you use to manufacture your drug products. Further, you failed to test your retain samples of active ingredients used in the manufacture of drug products to determine whether they meet established specifications for identity.

你们的回复是不充分的。你们未对药品生产所用组份指明和执行至少一项鉴别检查。另外，你们并未检测你们药品生产所用的活性成分留样，确定其是否满足既定的鉴别标准。

In response to this letter, provide the following:

在回复本函时请提交以下：

- The chemical and microbiological quality control specifications you use to test and release each incoming lot of component foruse in manufacturing.
  你们用于检测和放行每批生产用进厂组份的化学和微生物质量控制标准
- An action plan and timelines for conducting full. chemical and microbiologicaltesting of API retain samples to determine the quality of all batches of active ingredients used in the manufacture of drug products distributed to the United States within expiry.
  一份对 API 留样执行全面化学和微生物检测，确定销售至美国且仍在有效期内的药品生产所用所有批次活性成分质量的行动计划和时间表
- A summary of all results obtained from testing API retain samples from eachbatch. If such testing reveals substandard quality drug substances, take rapidcorrective actions, such as notifying customers and product recalls
  一份对每批 API 留样进行检测的结果总结。如果该结果显示原料药质量不合格，则应采取快速纠正措施，如通知客户和召回产品
- A description of how you will test each componentlot for conformity with all appropriate specifications for identity, strength, quality, and purity. If you intend to accept any results from your supplier's Certificates of Analysis (COA) instead of testing each component lot for

strength, quality, and purity, specify how you will robustly establish the reliability of your supplier's results through initial validation as well as periodic re-validation. In addition, include a commitment to always conduct at least one specific identity test for each incoming component lot.

一份阐述你们将如何检测每批进厂组份，确保其符合所有适当的鉴别、含量、质量和纯度标准的说明。如果你们准备接受你们供应商 COA 的所有结果，取代你们对每批组份的含量、质量和纯度检测，说明你们要如何通过初次验证和定期再验证稳固建立你们供应商结果的可靠性。此外，还要承诺会一直对每批进厂组份执行至少一项专属鉴别

- A summary of results obtained from testing all components to evaluate the reliability of the COA from each component manufacturer. Include your standard operating procedure (SOP) that describes this COA validation program.

  一份对所有组份进行检测所得的结果汇总，评估来自每个组份生产商的 COA 的可靠性。包括你们描述该 COA 验证计划的 SOP
- A summary of your program for qualifying and overseeing contract facilities that test the drugs you manufacture.

  一份对你们检测你们所生产的药品的合同场所进行确认和监管的程序摘要

3. Your firm failed to establish and follow an adequate written testing program designed to assess the stability characteristics of drug products and to use results of stability testing to determine appropriate storage conditions and expiration dates (21 CFR211.166(a)).

你公司未建立并遵守足够的书面检测计划，以评估药品的稳定性特性，并使用稳定性检测结果确定适当的存贮条件和有效期（21 CFR 211.166(a)）。

Your firm did not have an adequate stabilitytesting program to demonstrate that the chemical and (b)(4) properties of your drug products remain acceptable throughout their labeled expiry period. Your firm does not have adequate stability data to support the assigned expiration date of up to 36 months.

你公司没有足够的稳定性检测计划来证明你们药品的化学和 XX 特性在其标示的有效期内保持可接受水平。你公司没有足够的稳定性数据支持 36 个月的有效期。

In your response, you committed to revising your stability procedures to include extending your accelerated stability studies from three months to six months with new drug samples, requiring 36 months of real-time stability for drug products, and conducting stability studies at the appropriate humidity and temperatures with respective monitoring. You also purchased an (b)(4).

在你们的回复中，你们承诺要修订你们的稳定性程序，其中包括采用新药品样品将你们加速稳定性研究从 3 个月延长至 6 个月，对药品进行 36 个月的实时稳定性，在适当的温湿度执行稳定性研究并进行相应监测。你们还购买了 XX。

Your response is inadequate. While you state inyour response you have real time stability data for one identical drug product formula for another market, you did not provide the supporting data for this assertion. Additionally, for other drug product formulas you failed to providedata to demonstrate that the chemical and (b)(4) properties of your drug products will remain acceptable throughout their labeled expiry period of up to 36 months.

你们的回复是不充分的。虽然你们在回复中声称你们同一药品配方在另一个市场有实时稳定性数据，但你们并未提交该声明的支持性数据。另外，对于另一药品配方，你们并未提交数据证明其化学和 XX 特性在标示的 36 个月有效期内保持在可接受水平。

In response to this letter, provide the following:

在回复本函时请提交以下：

- A comprehensive, independent assessment and corrective action and preventive action (CAPA) plan to ensure the adequacy ·of your stability program. Your remediated program should include, but not be limited to:
  一份全面独立的评估和 CAPA 计划，确保你们稳定性程序的充分性。你们的补救计划应包括但不仅限于：
  - Stability indicating methods
    稳定性指示性方法
  - Stability studies for each drug product in its marketed container-closure system before distribution is permitted
    对每种药品以其上市包装方式在允许销售前进行稳定性研究
  - An ongoing program in which representative batches of each product are added each year to the program to determine if the shelf-life claim remains valid
    每年将每种药品的代表性批次加入稳定性计划，确定货架期是否保持有效的持续计划
  - Detailed definition of the specific attributes to be tested at each station (time point)
    详细规定每个时间点要检测的具体属性
- All procedures that describe these and other elements of your remediated stability program.
  阐述你们补救之后的稳定性计划的这些和其它要素的程序

4. Your firm failed to establish adequate written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess (21 CFR 211.100(a)).

你公司未能建立充分的书面生产和工艺控制程序，以确保你们生产的药品具备其理当具备的鉴别、含量、质量和纯度（21 CFR 211.100(a)）。

Your firm failed to adequately validate the manufacturing processes for your drug products. You performed process validation for only one of your drug products; however, you manufacture numerous drug products with different formulations and with multiple active pharmaceutical ingredients. During the inspection you provided your rationalefor this practice, stating that each active ingredient was similar in its chemical properties and that during actual manufacturing you tested the formulation and the drug products had met specification. However, one of the active ingredients in your formulations is (b)(4), which you failed to test in finished product batches as detailed above.

你公司未对你们药品的生产工艺进行充分验证。你们仅对一个药品进行了工艺验证，但你们采用不同配方多个 API 生产了大量药品。在检查期间，你们提交了你们此种做法的合理性，声称每种活性成分的化学属性相近，并且在实际生产中你们检测了配方，且药品均满足标准要求。虽然如此，在你们配方中有一个活性成分是 XX，你们并未按上所述对该成品批次中的 XX 进行检测。

In your response, you committed to reperforming process validation for one drug product. Your response is inadequate. You did not provide sufficient process performance qualification (PPQ) protocols or studies for each formulation of your drug products.

在你们的回复中，你们承诺要对每种药品重新进行工艺验证。你们的回复是不充分的，你们并未提交足够的工艺性能确认（PPQ）方案或研究你们药品的每个配方。

Process validation evaluates the soundness ofdesign and state of control of a process throughout its lifecycle. Eachsignificant stage of a manufacturing process must be designed appropriately andassure the quality of raw material inputs, in-process materials, and finisheddrugs. Process qualification studies determine whether an initial state of controlhas been established.

工艺验证评估的是一个工艺在其生命周期中的设计合理性和受控状态。生产工艺的每个重要阶段均必须进行适当设计，确保原料输入、中间体和成品的质量。工艺确认研究能确定是否建立了初始的受控状态。

Successful process qualification studies arenecessary before commercial distribution. Thereafter, ongoing vigilant oversight of process performance and product quality is necessary to ensure you maintain a stable manufacturing operation throughout the product lifecycle. See FDA's guidance document Process Validation: General Principles and Practices for general principles and approaches that FDA considers appropriate elements of process validation at http://www.fda.gov/media/71021/download.

商业销售之前必须进行成功的工艺确认研究。之后要进行持续的严格工艺性能和产品质量监测，以确保你们在整个产品生命周期中维持稳定的生产操作。参见 FDA 指南文件“工艺验证一般原则和规范”。

In response to this letter, provide the following:

在回复本函时请提交以下：

- A detailed summary of your validation program for ensuring a state of control throughout the product lifecycle, along with associated procedures. Describe your program for process performance qualification, and ongoing monitoring of both intra-batch and inter-batch variation to ensure a continuing state of control. ·
  一份对你们确保产品在整个生命周期的受控状态的验证计划，以及相关程序的详细总结。说明你们的工艺性能确认程序，以及对批间和批内波动进行持续监测从而确保持续受控状态的程序。
- A timeline for performing appropriate PPQ for each of your marketed drug products.
  一份对你们所有已上市药品实施适当 PPQ 的时间表。
- Your process performance protocol(s) and written procedures for qualification of equipment and facilities.
  你们的工艺性能方案和设备设施确认书面程序。

5. Your firm failed to use equipment in the manufacture, processing, packing or holding of drug products that is of appropriate design, adequate size, and suitably located to facilitate operations for its intended used and for its cleaning and maintenance (21 CFR211.63).

你公司在生产、加工、包装或存贮药品过程未使用经过适当设计、具备足够尺寸，以及适当定位的设备，从而便于其既定用途操作及清洁和维护（21 CFR 211.63）。

You have not established that your (b)(4) is adequately designed, controlled, maintained, and monitored to ensure it consistently produces (b)(4) that is suitable for use in your drug products. For example, neither your (b)(4) qualification nor your routine monitoring of the (b)(4) includes testing the (b)(4) for (b)(4).

你们未建立程序对你们的 XX 进行适当设计、控制、维护和监测，从而确保其持续生产出 XX，适合你们药品用途。例如，你们的 XX 确认和日常监测均未包括 XX 检测。

In your response, you stated that you revised the monitoring and testing frequency of your (b)(4) for (b)(4) to twice a month, and you provided the test report from a third-party laboratory who performs these tests on your behalf.

在你们的回复中，你们声称你们已修订了你们 XX 监控和检测频次为每月 2 次，并且提交了代表你们执行这些检测的第三方实验室的检测报告。

Your response is inadequate. You failed to provide data to demonstrate that your (b)(4) system is capable of producing (b)(4) in a reproducible manner that consistently meets the (b)(4) USP monograph and appropriate microbial specifications. Further, you failed to conduct a risk assessment to determine the potential impacts of substandard (b)(4) on the drug products that you manufacture.

你们的回复是不充分的。你们未提交数据证明你们的 XX 能够以可重复方式生产出持续符合 XX USP 各论和适当微生物标准的 XX。另外，你们未进行风险评估，确定不合格 XX 对你们所生产的药品的潜在影响。

In response to this letter, provide the following:

在回复本函时请提交以下：

- A comprehensive, independent assessment of your (b)(4) design, control, and maintenance.
  一份对你们的 XX 设计、控制和维护的全面独立评估
- Then, a comprehensive remediation plan for the design, control, and maintenance of the (b)(4).
  一份对 XX 的设计、控制和维护的全面补救计划
  - Followed by a (b)(4) validation report to evaluate whether the remediated system design consistently produces (b)(4) adhering to (b)(4), USP monograph specifications and appropriate microbial limits. Also include the summary of any improvements made to system design and to the program for ongoing control and maintenance.
    然后是一份 XX 验证报告，评估经过补救的系统设计是否能够持续生产出符合 XX、USP 各论标准和适当微生物限度的 XX。还要包括一份对系统设计，和持续控制和维护计划所做的所有改进的汇总，
- A procedure governing your program for ongoing control, maintenance, and monitoring that ensures the remediated system consistently produces (b)(4) that meets (b)(4), USP monograph specifications and appropriate microbial limits.
  一份管理你们持续控制、维护和监测计划的程序，确保补救后的系统能持续生成符合 XX、USP 各论标准和适当微生物限度的 XX。
- A tabular summary of the chemical and microbial monitoring results that you have collected from testing your (b)(4) for the past two years. Also include within the table the following:
  一份你们过去 2 年检测中采集的化学和微生物监测结果汇总表，表格内还要包括以下内容：

- specifications for the tested attribute
  所检测属性的标准
- date of sampling
  取样日期
- point of use (POU) from which the sample was collected
  样品采集的使用点（POU）

In addition, provide a description of the location of each POU and how it is used in drug manufacturing, along with a description of the (b)(4) during (b)(4) testing.

此外，请提交一份每个 POU 位置的描述，以及其在药品生产中的使用情况，和 XX 检测中 XX 的描述。

- A detailed risk assessment addressing the potential effects of the observed (b)(4) failures on the quality of all drug product lots currently in U.S. distribution. Specify actions that you will takein response to the risk assessment, such as customer notifications and productrecalls.
  一份详细的风险评估，说明所发现的 XX 失败对所有目前仍在美国销售的药品批次的潜在影响。写明你们根据风险评估将采取的措施，如通知客户和召回产品。

Concerns Regarding Glycerin 关于丙三醇的担忧

The drug products you manufacture contain glycerinas an ingredient. The use of glycerin contaminated with diethylene glycol (DEG) has resulted in various lethal poisoning incidents in humans worldwide. See FDA's guidance document, Testing of Glycerin for Diethylene Glycol, to help you meet CGMP requirements when distributing glycerin for use in drug products, including testing for DEG and recommendations for supply chain integrity, at https://www.fda.gov/media/71029/download.

你们生产的药品含有丙三醇。使用受二甘醇（DEG）污染的丙三醇已导致全球多次人类因毒致死事件。参见 FDA 指南“丙三醇中 EG 检测”，有助于你们满足 CGMP 要求前提下销售使用了丙三醇的药品，以及对 DEG 的检测和供应链完整性的建议。

Responsibilities as a Contractor 作为合同商的义务

You are responsible for the quality of drugs you produce as a contract facility, regardless of agreements in place with product owners. You are required to ensure that drugs are made in accordance with section 501(a)(2)(B) of the FD&C Act for safety, identity, strength, quality, and purity. See FDA's guidance document Contract Manufacturing Arrangements for Drugs: Quality Agreements at https://www.fda.gov/media/86193/download.

作为合同场所，虽然你们与药品所有者订有协议，但你们仍对你们所生产的药品负有义务。你们应确保药品生产符合 FDCA 第 501(a)(2)(B)条款对安全性、鉴别、剂量、质量和纯度的要求。参见 FDA 指南文件“药品合同生产安排：质量协议”。

CGMP Consultant Recommended CGMP 顾问建议

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualifiedas set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements. We also recommend that the qualified consultant perform a comprehensive audit of your entire operation for CGMP compliance and that the consultant evaluates the completion and

efficacy of your corrective actions and preventive actions before you pursue resolution of your firm 's compliance status with FDA.

鉴于我们在你公司所发现的违规情况，我们强烈建议你们使用一位有 21 CFR 211.34 所述资质的顾问来协助你们公司符合 CGMP 要求。我们亦建议该具备资质的顾问对你们整体运营情况进行药品 CGMP 合规情况全面审计，并由其在你们寻求满足 FDA 合规要求之前对你们 CAPA 的完成情况和有效性进行评估。

Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm 's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

你们使用顾问并不能解除你们公司符合 CGMP 的义务。你们公司的高级管理层仍负有义务全面解决所有缺陷，确保持续 CGMP 符合性。

Conclusion 结论

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of other violations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

FDA placed your firm on Import Alert 66-40 on November 8, 2019.

FDA 已于 2019 年 11 月 8 日将你公司置于进口禁令 66-40 中。

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产的新申报和增补申报的批准。

Failure to correct these violations may also resultin the FDA continuing to refuse admission of articles manufactured at Huaian Zongheng Bio-Tech Co., Ltd., at No. 615 North Xiangyu Road, Huaian into theUnited States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Articles under this authority may be subject to refusal of admission, in thatthe methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

17. 320-20-17 2020-01-09 Cosmelab Co Ltd 韩国

Dear Mr. Park:

The U.S. Food and Drug Administration (FDA) inspected your facility, Cosmelab Co., Ltd., FEI 3009647084, at 4F CL Building,42, Teheran-ro 28-gil, Oangnam-gu, Seoul, from July 15 to 17, 2019.

美国 FDA 于 2019 年 7 月 15 日至 17 日检查了你们位于韩国的 Cosmelab Co.,Ltd.（FEI 3009647084）生产场所。

This warning letter summarizes significant violations of current good manufacturing practice (COMP) regulations for finished pharmaceuticals. See Title 21 Code of Federal Regulations (CFR), parts210 and 211 (21 CFR parts 210 and 211).

本警告信总结了制剂生产严重违反 CGMP 的行为。参见 21CFR 第 210 与 211 部分。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to COMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

由于你们的制剂生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的药品根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C. 351(a)(2)(B)被认为是掺假药品。

We reviewed your August 6, 2019, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

我们已详细审核了你公司 2019 年 8 月 6 日的回复，并此告知已收到后续通信。

During our inspection, our investigator observed specific violations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

1. Your firm failed to establish an adequate quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging materials, labeling, and drug products (21 CFR 211.22(a)).

你公司未建立具备足够职责和权力批准或拒收所有组份、药品容器、密闭器、中间体、包材、标签和药品成品的质量部门（21 CFR 211.22(a)）。

You failed to establish an adequate quality unit (QU) to carry out quality control duties. For example, you failed to ensure that assay tests were performed for your over-the-counter (OTC) drug products and that results were reviewed prior to release for distribution. At the time of the inspection you lacked a QU with appropriate oversight over the drug manufacturing and testing operations conducted by your contracted facilities.It is your responsibility to assure all manufacturing records and test results are adequately reviewed and approved, and that every drug product batch is released only when satisfactory product quality testing is completed.

你们未建立足以执行质量控制职责的质量部门（QU）。例如，你们未能确保对你们的 OTC 药品进行含量检测，并在放行销售之前对结果进行审核。在检查期间，你们没有对外包场所执行的药品生产和检测操作进行适当的监管的 QU。确保所有生产记录和检测结果经过足够的审核和批准，并对每批药品在圆满完成质量检测之后才进行放行是你们的义务。

Additionally, your supplier oversight is deficient. Your firm released OTC drug products to the United States produced by a contract manufacturer on FDA's Import Alert 66-40. During the inspection you stated you were unaware that your supplier, (b)(4), was on FDA import alert, until you were made aware during the inspection.

另外，你们的供应商监管有缺陷。你公司将已列入 FDA 进口禁令 66-40 的合同生产商生产的 OTC 药品销售至美国。在检查期间，你们声称你们不知道你们的供应商 XX 在 FDA 的进口禁令清单上，直到检查时才知道此事。

It is your responsibility to have appropriate resources and trained personnel to perform required CGMP operations. FDA is aware that many firms use independent contractors such as production facilities, testing laboratories, packagers, and labelers. FDA regards contractors as extensions of the manufacturer.

你们有义务提供适当的资源并培训员工执行所需的 CGMP 操作。FDA 了解许多公司会使用独立的合同商如生产场所、检测实验室、包装商和贴标商。FDA 认为合同商是生产商的延伸。

You are responsible for the quality of your drugs regardless of agreements in place with your contract facilities. You are required to ensure that drugs are made in accordance with section 501(a)(2)(B) of the FD&C Act to ensure safety, identity, strength, quality, and purity.See FDA's guidance document Contract Manufacturing Arrangements for Drugs: Quality Agreements at https://www.fda.gov/media/86193/download.

无论是你们与合同场所之间是否订有协议，你们均对你们的药品负有义务。你们必须确保药品生产符合 FDCA 第 501(a)(2)(B)条款要求，确保其安全性、鉴别、含量、质量和纯度。参见 FDA 的指南文件“药品合同生产安排：质量协议”。

In your response, you acknowledged that you have not tested the active ingredients for three of your four drug products prior to release, as required, and that you are planning to use a third-party laboratory to analyze the active ingredients in your drug products. In addition, you stated that a lack of understanding of FDA drug regulations contributed to your not establishing a dedicated quality unit. You committed to hire a consultant knowledgeable about FDA regulations.

在你们的回复中，你们承认你们在放行之前并未按要求对 4 种药品中的 3 种检测活性成分，并且你们计划使用第三方实验室分析你们药品中的活性成分。另外，你们声称不了解 FDA 药品法规，因此未建立专门的质量部门。你们承诺要聘请一位了解 FDA 法规要求的顾问。

You also committed to cease distribution for one of your drug products, (b)(4), to the United States market until your contract manufacturer addresses FDA findings that led to them being placed onFDA's Import Alert 66-40.

你们还承诺在你们合同生产商解决 FDA 发现的导致将其置于进口禁令 66-40 清单的问题之前会停止销售你们的一种药品，XX，至美国市场。

Your response is inadequate because you did notprovide a detailed interim plan of action to establish a comprehensive quality unit. Without an adequate QU, you are unable to ensure that your drug products meet required specifications and manufacturing standards for safety, identity, strength, purity, and quality.

你们的回复是不充分的，因为你们并未提交一份详细的临时计划，采取措施建立一个全面的质量部门。没有足够的 QU，你们无法确保你们的药品满足所需的安全、鉴别、含量、纯度和质量标准和生产标准。

See FDA's guidance document Quality Systems Approach to Pharmaceutical CGMP Regulations for help implementing quality systems and risk management approaches to meet the requirements of CGM Pregulations 21 CFR, parts 210 and 211 at https://www.fda.gov/media/71023/download.

参见 FDA 指南文件“药品 CGMP 法规质量体系方法”，它将有助于实施质量体系和风险管理方法，满足 CGMP 法规 21CFR 第 210 和 211 部分。

In response to this letter, provide:

在回复本函时请提交：

- A comprehensive independent assessment and remediation plan to ensure your QU is given the authority and resources to effectively function. The assessment should also include, but not be limited to:
  一份全面独立的评估和补救措施，确保你们的 QU 被赋予了权力和资源可有效运作。评估还应包括但不仅限于：
  - A determination of whether procedures used by your firm are robust and appropriate
    确定是否你公司所用的程序稳健恰当
  - Provisions for QU oversight throughout drug product distribution to evaluate adherence to appropriate practices
    QU 监管整个药品销售以评估遵守适当的规范的条款
  - A complete and final review of each batch and its related information before the QU disposition decision
    QA 作出处置决策之前对每个批次及其相关信息进行的最终完整审核
  - Oversight and approval of investigations and discharge of all other QU duties to ensure identity, strength, quality, and purity of all products
    监管和批准调查，履行所有其它 QU 职责，以确保所有药品的鉴别、含量、质量和纯度
- A retrospective evaluation of your drug products that remain on the U.S. market. You should address any drug product quality or patient safety risks including those potentially affected by your lack of adequate quality oversight, and assess the adequacy of investigations (if any) into any deviations, out-of-specification results, or other manufacturing quality issues. Include a full corrective and preventive action (CAP A) plan (e.g., notification to customers, recall) for any drug products that may have aquality or safety risk.
  一份对你们仍在美国市场的药品的回顾性评估。你们应解决所有药品质量或患者安全风险，包括因你们缺乏足够的质量监管而可能受到的影响，评估对所有偏差、OOS 结果或其它生产问题的调查（如有）的充分性。包括一份对可能有质量或安全风险的药品的 CAPA 计划（例如，通知客户，召回）
- A list of chemical specifications, including testmethods, used to analyze each lot of your drug products before a lot disposition decision. Specify the responsibilities of all contract manufactures that will perform these analyses.
  一份在批放行之前用于分析每批药品的化学标准清单，包括检测方法，说明所有将要执行这些分析的合同生产商的职责：

- An action plan and timelines for conducting full chemical testing of retain samples to determine the quality of all batches of drug product distributed to the United States within expiry as of the date of this letter
  一份对留样执行全面化学检测的行动计划和时间表，以确定所有销售至美国且本函签发时仍在效期内的所有药品批次的质量
- A summary of all results obtained from testing retain samples from each batch. If such testing reveals substandard quality drug products, take rapid corrective actions, such as notifying customers and product recalls
  一份对每批留样进行检测所得到的结果总结。如果该检测结果显示有药品质量不合格，则应采取快速纠正措施，如通知客户和召回产品

- A detailed plan for ongoing assessments of each lot of component used for production of finished drug product to meet appropriate standards of identity, strength, quality, and purity. Outline your plans to establish a robust supplier qualification program, including a detailed supplier qualification and audit program that specifies how you ensure that oversight of suppliers is commensurate with risk to finished product.
  一份对每批药品生产所用组份的持续评估使得其满足鉴别、含量、质量和纯度标准的详细计划。列出你们建立稳健的供应商确认程序的计划，包括详细的供应商确认和审计计划，说明你们要如何确保供应商监管水平与其对药品风险相称

Purchase and Distribution of Drugs From a Manufacturer on FDA Import Alert 66-40

从 FDA 进口禁令 66-40 清单中的生产商采购药品并销售

We reviewed a list of your suppliers, which includes (b)(4). (b)(4) is currently on FDA Import Alert 66-40 Detention Without Physical Examination of Drugs From Firms Which Have Not Met Drug GMPssince December 27, 2017. Import Alert 66-40 can be found on the FDA public website, https://www.accessdata.fda.gov/cmsia/importalert_189.html.

我们审核了你们的供应商清单，其中有 XX。XX 自 2017 年 12 月 27 日起即被列入 FDA 进口禁令 66-40“对来自不符合药品 GMP 的公司的药品无需实质性检查即行扣留”清单。

Import Alert 66-40 includes firms for which an FDA inspection has revealed that a firm is not operating in conformity with CGMP and their drugs appear to be adulterated. If your firm is being directly or indirectly supplied by establishments that lack adequate CGMP, your firm's drugs could be subject to import alert. FDA recommends that you ensure that you properly evaluate and qualify all your suppliers as required by CGMP, and change the source of your supply, where appropriate. Consequently, your use of this supplier on Import Alert 66-40 led to the appearance of adulteration of your drugs.

进口禁令 66-40 包括 FDA 检查发现未按 CGMP 运行的公司及其被认为掺假的药品。如果你公司由缺乏足够 CGMP 的场所直接或间接供应药品，则你公司的药品可能受制于进口禁令。FDA 建议你们确保你们对你们的供应商按 CGMP 要求进行评估和确认，并更改你们供应源（适当时）。相应地，你们使用进口禁令 66-40 中的该供应商导致你们药品被认为是掺假药品。

FDA placed your firm on Import Alert 66-40 on November 12, 2019.

FDA 已于 2019 年 11 月 12 日将你公司置于 66-40 清单中。

CGMP Consultant Recommended CGMP 顾问建议

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualified as set forth in 21 CFR 211.34 to assist your firm in meeting drug CGMPrequirements. We also recommend that the qualified consultant perform a comprehensive audit of your entire operation for drug CGMP compliance and that the consultant evaluates the completion and efficacy of your corrective actions and preventive actions before you pursue resolution of your firm's compliance status with FDA.

鉴于我们在你公司所发现的违规情况，我们强烈建议你们使用一位有 21 CFR 211.34 所述资质的顾问来协助你们公司符合 CGMP 要求。我们亦建议该具备资质的顾问对你们整体运营情况进行药品 CGMP 合规情况全面审计，并由其在你们寻求满足 FDA 合规要求之前对你们 CAPA 的完成情况和有效性进行评估。

Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm' s executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

你们使用顾问并不能解除你们公司符合 CGMP 的义务。你们公司的高级管理层仍负有义务全面解决所有缺陷，确保持续 CGMP 符合性。

Conclusion 结论

Violations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these violations,for determining the causes, for preventing their recurrence, and for preventing other violations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

FDA placed your firm on Import Alert 66-40 on November 12, 2019.

FDA 已于 2019 年 11 月 12 日将你公司置于进口禁令 66-40 中。

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产的新申报和增补申报的批准。

Failure to correct these violations may also result in FDA continuing to refuse admission of articles manufactured at Cosmelab Co.,Ltd. at 4F CL Building, 42, Teheran-ro 28-gil, Gangnan1-gu, Seoul, into theUnited States under section 801(a)(3) of the FD&C Act (21 U.S.C. 381(a)(3)). Under the same authority, articles may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 35 l (a)(2)(B)).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you

cannot complete corrective actions within l 5 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

18. 320-20-18 2020-01-09 Zhuhai Aofute Medical Technology Co., Ltd. 珠海澳福特医疗科技有限公司

Dear Mr. Wu:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Zhuhai Aofute Medical TechnologyCo., Ltd., FEI 3013761135, at Room 202, Building 2, No. 33, Yongnan Road, Zhuhai, from July 15 to 18, 2019.

美国 FDA 于 2019 年 7 月 15 日至 18 日检查了你们位于珠海市香洲区永南路 33 号 1 栋 2 楼 202 号的珠海澳福特医疗科技有限公司生产场所。

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See Title 21 Code of Federal Regulations (CFR), parts 210 and 211 (21 CFR parts 210 and 211).

本警告信总结了制剂生产严重违反 CGMP 的行为。参见 21CFR 第 210 与 211 部分。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug product is adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

由于你们的制剂生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的药品根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C. 351(a)(2)(B)被认为是掺假药品。

Your firm manufactures “Magic Spray for Pain Relief.” This product is an unapproved new drug in violation of section 505(a) of the FD&C Act, 21 U.S.C. 355(a), and is misbranded under sections 502(c) and (x) of the FD&C Act, 21 U.S.C.352(c) and (x). Introduction or delivery for introduction of such products into interstate commerce is prohibited under sections 301(d) and (a) of the FD&C Act, 21 U.S.C. 331(d) and (a). These violations are described in more detail below.

你公司生产“神奇止痛喷雾”。该产品是未经批准的新药，违反了 FDCA 第 505(a) 条款 21 U.S.C. 355(a)规定，并且根据 FDCA 第 502(c) 和 (x)条款 21 U.S.C. 352(c) 和(x)为错标药品。FDCA 第 301(d) 和(a)条款 21 U.S.C. 331(d) 和(a)禁止引入或运输此类产品至州际贸易。这些违规情况在以下进行详细说明。

We have not received a response from your firm detailing corrective actions to our Form FDA 483 observations identified during the inspection.

我们尚未收到你公司对我们在检查期间发现的 FDA483 表缺陷项的详细纠正措施回复。

During our inspection, our investigator observed specific violations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

1. Your firm failed to have, for each batch of drug product, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release (21 CFR 211.165(a)).

你公司未在放行之前对每批药品进行适当的实验室检测，确定其满足药品的最终标准，包括每种活性成分的鉴别和含量（21 CFR 211.165(a)）。

Your firm failed to perform critical quality control tests of finished drug products before a batch release decision. For example, our inspection found you lacked identity and strength testing for each batch of your over-the-counter (OTC) finished drug product, “Magic Spray for Pain Relief.”

你公司未在批放行决策之前对成品进行关键质量控制检测。例如，我们检查中发现你们对每批 OTC 成品“神奇止痛喷雾”缺少鉴别和含量检测。

Complete and appropriate testing of each batch is one of many essential elements necessary to ensure that the drug products you manufacture meet appropriate specifications.

对每个批次进行完整恰当的检测是确保你们所生产的药品符合适当标准所必需的要素之一。

Your staff also stated during the inspection thatyou did not evaluate the suitability of incoming component (e.g., ingredient) lots, as you lacked appropriate testing including but not limited to identification (21 CFR 211.84).

你们的员工在检查期间亦声称你们并未评估进厂组份（例如成分）的适当性，因为你们缺少适当的检测，包括但不仅限于鉴别（21 CFR 211.84）。

In response to this letter, provide the following:

在回复本函时，请提交以下：

- A comprehensive, independent assessment of your laboratory practices, procedures, methods, equipment, documentation, and analyst competencies. Based on this review, provide a detailed plan to remediate and evaluate corrective and preventive action plan (CAPA) effectiveness for your laboratory system.
  一份对你们实验室做法、程序、方法、设备、文件和化验员能力的全面独立评估。基于该审核，提交一份详细的计划补救你们实验室系统，并评估 CAPA 的有效性。
- A list of chemical and microbial specifications, including test methods, used to analyze each batch of your drug products before a batch disposition decision. Include:
  一份用于批放行之前分析每批药品的化学和微生物标准清单，包括检测方法。包括：
  - An action plan and timelines for conducting full chemical and microbiological testing of retain samples to determine the quality of all batches of drug product distributed to the United States within expiry as of the date of this letter.
  - 一份对留样执行全面化学和微生物检测的行动计划和时间表，以确定所有销售至美国且在本函签发日时尚在有效期内的药品批次质量。
  - A summary of all results obtained from testing retain samples from each batch. If such testing reveals substandard quality drug products, take rapid corrective actions, such as notifying customers and product recalls.
  - 一份对每批留样检测所得结果的总结。如果该检测显示药品质量不合格，则应采取快速纠正措施，如通知客户和召回产品。
- A complete assessment of documentation systems used throughout your manufacturing and laboratory operations to determine where documentation practices are insufficient. Include a detailed CAPA plan that comprehensively remediates your firm’s documentation practices to

ensure you retain attributable, legible, complete, original, accurate, contemporaneous records throughout your operation.

一份你们生产和实验室操作所用文件系统的完整评估，以确定文件记录规范是否充分。包括一份详细的 CAPA 计划，全面补救你们公司的文件规范，确保你们将保存所有操作中可追溯的、清晰的、完整的、原始的、准确的、同步记录。

- A comprehensive, independent review of your material system to determine whether all suppliers of components, containers, and closures, are each qualified and the materials are assigned appropriate expiration or retest dates. The review should also determine whether incoming material controls are adequate to prevent use of unsuitable components, containers, and closures.

  一份对你们物料体系的全面独立审核，以确定是否所有组份、容器和密闭器供应商均经过确认，并且物料被给定了适当的有效期或复验期。审核还应确定进厂物料控制是否足以防止使用不适当的组份、容器和密闭器。

- The chemical and microbiological quality control specifications you use to test and release each incoming lot of component for use in manufacturing.

  一份你们用于检测和放行用于生产的每批进厂组份的化学和微生物质量控制标准。

- A description of how you will test each component lot for conformity with all appropriate specifications for identity, strength, quality, and purity. If you intend to accept any results from your supplier's certificates of analysis (COA) instead of testing each component lot for strength, quality, and purity, specify how you will robustly establish the reliability of your supplier's results through initial validation as well as periodic re-validation. In addition, include a commitment to always conduct at least one specific identity test for each incoming component lot.

  一份说明阐述你们将如何检测每批组份，以确定其符合所有恰当的鉴别、含量、质量和纯度标准。如果你们准备接受你们供应商 COA 的所有结果，替代你们对每批组份的含量、质量和纯度检测，则请说明你们将如何通过初始验证和定期重新验证稳定建立你们供应商结果的可靠性。另外，要包括一份承诺声明你们会一直对每批进厂组份执行至少一项特定鉴别测试。

- A summary of results obtained from testing all components to evaluate the reliability of the COA from each component manufacturer. Include your SOP that describes this COA validation program.

  一份对所有组份检测所得结果的总结，以评估每个组份生产商 COA 的可靠性。包括阐述该 COA 验证程序的 SOP。

2. Your firm failed to establish an adequate quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging materials, labeling, and drug products (21 CFR 211.22(a)).

你公司未建立充分的质量部门，使其具备职责与权力可批准或拒收所有组份、药品容器、密闭器、中间体、包材、标签和成品（21 CFR 211.22(a)）。

You failed to establish an independent and effective quality unit. For example, you failed to adequately perform basic quality unit (QU) responsibilities, including but not limited to:

你们未建立独立有效的质量部门。例如，你们并未充分履行基本的质量部门（QU）职责，包括但不仅限于：

- Approval or rejection of all components and drug product containers, closures, in-process materials, packaging materials, labeling, and drug products.
  批准或拒收所有组份和药品容器、密闭器、中间体、包装材料、标签和药品成品
- Review of all production and control records.
  审核所有生产和检测记录
- Assure establishment of adequate batch records.
  确保建立充分的批记录
- Approval of procedures and specifications impacting on the identity, strength, purity and quality of all drug products.
  批准影响所有药品的鉴别、含量、纯度和质量的程序和标准

Notably, you lacked adequate production and laboratory records. Your firm did not demonstrate the appropriate controls to assure drug product batches were manufactured following appropriate written procedures. Because no meaningful production records were available, there is no assurance that, if errors occurred, they were fully investigated before batches were released. Furthermore, your laboratory technician stated that original raw data is routinely discarded.

值得注意的是，你们缺少足够的生产和实验室记录。你公司未能证明有适当的控制确保药品批次生产是遵守适当的书面程序的。因为无法获得实质性生产记录，所以无法确保在发生错误时能进行全面调查之后再放行批次。另外，你们实验室技术员声称原始数据通常是丢弃掉的。

Your QU was also not independent from the manufacturing unit. For example, during the inspection your Factory Director, responsible for manufacturing operations, was also acting as the Quality Director.

你们的 QU 亦未独立于生产部门。例如，在检查期间，你们负责生产运营的工厂总监亦是质量总监。

In response to this letter, provide the following:

在回复本函时请提交以下：

- a comprehensive assessment and remediation plan to ensure your QU is given the authority and resources to effectively function. The assessment should also include, but not be limited to:
  一份全面评估和补救计划，确保你们 QU 被授予权力和配置资源可有效运行。该评估亦应包括但不仅限于：
  - A determination of whether procedures used by your firm are robust and appropriate.
    确定你公司所用程序是否稳健和恰当
  - Provisions for QU oversight throughout your operations to evaluate adherence to appropriate practices.
    QU 监管你们整个运营以评估是否遵守适当规范的规定
  - A complete and final review of each batch and its related information before the QU disposition decision.
    对每批及其相关信息在 QU 处置决策之前进行完整的最终审核
  - Oversight and approval of investigations and discharging of all other QU duties to ensure identity, strength, quality, and purity of all products.
    监管和批准调查，履行所有其它 QU 职责，确保所有药品的鉴别、含量、质量和纯度

- Also describe how top management supports quality assurance and reliable operations, including but not limited to timely provision of resources to proactively address emerging manufacturing/quality issues and to assure a continuing state of control.
  亦请阐述高层管理人员要如何支持质量保证和可靠的运行，包括但不仅限于及时提供资源主动解决新发现的生产/质量问题，确保持续受控状态

3. Your firm failed to establish adequate written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess (21 CFR 211.100 (a)).

你公司未能建立充分的生产和工艺控制程序，用以确保你们生产的药品具备其显示具备的鉴别、含量、质量和纯度（21 CFR 211.100 (a)）。

Inadequate control of manufacturing processes 生产工艺控制不充分

Your firm lacks an ongoing program for monitoring process control to ensure stable manufacturing operations. You have not demonstrated that your manufacturing process is capable of consistently producing drugs of uniform character and quality. Specifically, you have not validated your manufacturing process for “Magic Spray” OTC topical liquid spray drug products.

你公司缺乏持续工艺控制监测计划，从而确保稳定的生产操作。你们并未证明你们的生产工艺能够持续生产出具备均匀特性和质量的药品。具体来说，你们并未验证你们的“神奇喷雾”OTC 局部液体喷雾药品的生产工艺。

During the inspection, you failed to provide validation protocol records and lacked adequate written production and process control procedures.

在检查期间，你们未能提供验证方案记录，缺少充分的书面程序和工艺控制程序。

See FDA’s guidance document Process Validation:General Principles and Practices for general principles and approaches that FDA considers appropriate elements of process validation at https://www.fda.gov/media/71021/download.

参见 FDA 指南文件“工艺验证：一般原则和规范”。

In response to this letter, provide a remediation plan that better assures ongoing management oversight throughout the manufacturing lifecycle of all drug products. Provide a data-driven and scientifically sound program that identifies sources of process variability and assures that manufacturing, including production operations, meets appropriate parameters and quality standards. This includes, but is not limited to,evaluating suitability of equipment for its intended use, ensuring quality ofinput materials, determining the capability and reliability of each manufacturing process step and its controls, and vigilant ongoing monitoring of process performance and product quality. Also provide:

在回复本函时，请提交一份补救计划，更好保证在所有药品生产生命周期中的持续管理监督。提交一份以数据为依据的科学合理计划，识别出工艺波动来源，确保生产（包括生产操作）符合适当的参数和质量标准。其中应包括但不仅限于评估设备是否适合于其既定用途、确保输入物料的质量、确定每个生产工艺步骤及其控制的能力和可靠性，以及持续严格监测工艺性能和产品质量。亦请提交：

- A detailed summary of your validation program for ensuring a state of control throughout the product lifecycle, along with associated procedures. Describe your program for process performance qualification, and ongoing monitoring of both intra-batch and inter-batch variation to ensure a continuing state of control.
  一份对你们验证计划的详细总结，确保在产品生命周期中的受控状态，连同相关程序。阐述你们的工艺性能确认程序，以及批间和批内波动持续监测，从而确保其持续受控状态。
- A timeline for performing appropriate process performance qualification for each of your marketed drug products.
  对所有已销售药品执行适当工艺性能确认的时间表。
- Include your process performance protocol(s), and written procedures for qualification of equipment and facilities.
  包括你们的工艺性能方案和书面设备和设施确认程序
- A detailed program for designing, validating, maintaining, controlling and monitoring each of your manufacturing processes that includes vigilant monitoring of intra-batch and inter-batch variation to ensure an ongoing state of control. Also include your program for qualification of your equipment and facility.
  一份设计、验证、维护、控制和监测每个生产工艺的详细计划，包括严格监测批间和批内波动，确保其持续受控状态。还要包括你们设备和设施确认计划。

Inadequate control of (b)(4) system XX 系统控制不充分

The (b)(4) used to clean your non-dedicated equipment comes from a system that you have not validated. You did not demonstrate your (b)(4) quality is suitable for pharmaceutical use. Specifically, you have not established that your (b)(4) system is adequately designed, controlled, maintained, and monitored to ensure that it consistently produces (b)(4) that meets the USP monograph for (b)(4) and appropriate microbial limits. Your firm also failed to perform (b)(4) system validation studies. Your firm stated that the (b)(4) system is turned off after each use and run only when (b)(4) is needed.

用于清洁你们非专用设备的 XX 来自于你们尚未验证的一个系统。你们并未证明你们的 XX 质量适合于制药用途。具体来说，你们并未证明你们的 XX 系统经过充分设计、控制、维护和监测，从而确保其能持续生产出符合 USP 各论和适当微生物限度的 XX。你们公司亦未能执行 XX 系统验证研究。你公司声称 XX 系统在每次使用之后会关机，只是在 XX 需要时才开机运行。

In response to this letter, provide the following:

在回复本函时请提交以下内容：

- A comprehensive remediation plan for the design, control, and maintenance of the (b)(4) system. Include a (b)(4) system validation report of the studies conducted only after system design and control has been fully remediated. Summarize any improvements made to system design and to the program for ongoing control and maintenance.
  一份 XX 系统设计、控制和维护的全面补救计划。包括在全面弥补系统设计和控制之后执行的 XX 系统验证报告。总结对系统设计和持续控制与维护计划所做的所有改进。
- A procedure governing your program for ongoing control, maintenance, and monitoring that ensures the remediated system consistently produces water that meets (b)(4), USP monograph specifications and appropriate microbial limits.

你们管理持续控制、维护和监测计划的程序，确保经过补救的系统能持续产出符合 XX、USP 各论标准和适当微生物限度的水。

UnapprovedNew Drug and Misbranding Charges 未批准的新药和错标指控（略）

Data Integrity Remediation 数据完整性补救措施

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. See FDA's guidance document Data Integrity and Compliance With Drug CGMP for guidance on establishing and following CGMP compliant data integrity practices at https://www.fda.gov/media/119267/download.

你们的质量体系不能充分确保数据的准确性和完整性，无法支持你们生产的药品的安全性、有效性和质量。参见 FDA 指南文件"数据完整性和药品 GMP 合格"指导建立和遵守 CGMP 合格数据完整性规范。

We strongly recommend that youretain a qualified consultant to assist in your remediation. In response to this letter, provide the following:

我们强烈建议你们聘请一位具备资质的顾问协助你们进行补救。在回复此函时请提交以下信息：

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting including results of the data review for drugs distributed to the United States. Include a detailed description of the scope and root causes of your data integrity lapses.

一份对数据记录和报告不准确性程度的全面调查，其中要包括销售至美国的药品的数据审核结果。

B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity and analyses of the risks posed by ongoing operations.

你们药品质量中所发现的不合格情况的潜在影响的当前风险评估。你们的评估应包括由于受到数据完整性问题影响的药品放行导致的患者风险的分析，以及持续运营所具有的风险。

C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. The detailed corrective action plan should describe how you intend to ensure the reliability and completeness of all data generated by your firm including microbiological and analytical data, manufacturing records, and all data submitted to FDA.

你们公司的管理策略，包括你们全球 CAPA 计划详细情况。详细的纠正措施计划应阐述你们准备如何确保你公司生成的所有数据的可靠性和完整性，包括微生物和分析数据、生产记录和所有提交给 FDA 的数据。

CGMP Consultant Recommended CGMP 顾问建议

Based on the nature of the violations we identified at your firm, if your firm intends to resume manufacturing drugs for the U.S.market, we strongly recommend engaging a consultant qualified as set forth in21 CFR 211.34 to assist your firm in meeting CGMP requirements.

基于我们在你们公司发现的违规情况，如果你公司准备继续生产美国市场的药品，我们强烈建议你们使用一位有 21 CFR 211.34 所述资质的顾问来协助你们公司符合 CGMP 要求。

We also recommend that the qualified consultant perform a comprehensive audit of your entire operation for CGMP compliance and that the consultant evaluates the completion and efficacy of your corrective actions and preventive actions before you pursue resolution of your firm's compliance status with FDA.

我们亦建议该有资质的顾问对你们整个运营情况进行 CGMP 合规全面审核，并且在你公司寻求符合 FDA 要求之前由该顾问评估你们 CAPA 的完成情况和有效性。

If you intend to resume manufacturing and shipping drugs to the United States, you should provide comprehensive corrective actions which include systemic remediation as well as a global assessment and remediation of all six systems of your manufacturing operations.

如果你们准备继续生产和发运药品至美国，你们应提交全面的纠正计划，其中包括系统性补救措施以及对你们生产操作所有 6 个体系的全球评估和补救。

Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

你们使用顾问并不能解除你们公司符合 CGMP 的义务。你们公司的高级管理层仍负有义务全面解决所有缺陷，确保持续 CGMP 符合性。

Conclusion 结论

The violations cited in this letter are notintended to be an all-inclusive list of violations that exist at your facility/in connection with your product. You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of other violations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

FDA placed your firm on Import Alert 66-40 on November 13, 2019.

FDA 已于 2019 年 11 月 13 日将你公司置于进口禁令 66-40 中。

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产的新申报和增补申报的批准。

Failure to correct these violations may also result in the FDA continuing to refuse admission of articles manufactured at Zhuhai Aofute Medical Technology Co., Ltd., at Room 202, Building 2, No. 33, Yongnan Road into the United States under section 801(a)(3) of the FD&C Act, 21U.S.C. 381(a)(3). Articles under this authority may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since ourinspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

19. 320-20-19 2020-01-16 Dental-Kosmetik GmbH & Co. KG 德国

Dear Ms. Schendekehl:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Dental-Kosmetik GmbH & Co., FEI3001623034, at Katharinenstr. 4, Dresden from July 15 to 19, 2019.

美国 FDA 于 2019 年 7 月 15 日至 19 日检查了你们位于德国的 Dental-Kosmetik GmbH & Co.，（FEI 3001623034）生产场所。

This warning letter summarizes significant violationsof current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See Title 21 Code of Federal Regulations (CFR), parts 210 and 211 (21 CFR parts 210 and 211).

本警告信总结了制剂生产严重违反 CGMP 的行为。参见 21CFR 第 210 与 211 部分。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

由于你们的制剂生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的药品根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C. 351(a)(2)(B)被认为是掺假药品。

We reviewed your August 2, 2019, response to our Form FDA 483 in detail. Your response is inadequate because it did not provide sufficient detail or evidence of corrective actions to bring your operations into compliance with CGMP.

我们已详细审核了你公司 2019 年 8 月 2 日的回复。你们的回复是不充分的，因为其中并未提供足够详细的内容或证据，证明纠正措施可使得你们的运营转入 CGMP 合规状态。

During our inspection, our investigator observed specific violations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

1. Your firm failed to establish written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess, and your firm's quality control unit did not review and approve those procedures, including any changes (21 CFR 211.100(a)).

你公司未能建立书面生产和工艺控制程序，用以确保你们生产的药品具备其理当具备的的鉴别、含量、质量和纯度，并且你公司的质量部门并未审核和批准这些程序及任何变更（21 CFR 211.100(a)）。

You failed to adequately validate the processes used to manufacture your drug products.

你公司未能充分验证你们药品生产所用工艺。

Inadequate Control of Manufacturing Processes 生产工艺的控制不充分

You have not performed process performance qualification studies, nor do you have an ongoing program for monitoring process control to ensure stable manufacturing operations and consistent

drug quality for products shipped to the U.S. market. Your firm's process validation consisted of testing the first production batch followed by a joint decision between your Research and Development (R&D) and Quality Assurance departments on whether or not to release the batch.

你们并未执行工艺性能确认研究，亦无持续工艺控制监测程序，从而确保发送至美国市场的稳定生产操作和一致的药品质量。你公司的工艺验证为对首个生产批次进行检测，然后由你们研发（R&D）部门和 QA 部门对是否可放行该批次做出联合决定。

In addition, your firm had to significantly deviate from your batch manufacturing instructions in order to achieve passing results. For example, an out-of-specification (OOS) result for a bulk batch of (b)(4) required (b)(4) to obtain passing results for viscosity and density. Your procedure "Nonconformity Management" is inadequate as it does not require an investigation and identification of root causes when products do not meet quality requirements, and allows for repeat testing and adjustments until you obtain passing results.

此外，你公司为达到合格结果必须严重偏离你们的批生产工艺规程。例如，为达到合格的粘度和密度必须让批次的 XX 出现 OOS 结果。你们的程序“不合格管理”是不充分的，因为该程序不要求对不符合质量要求的产品进行调查并识别出根本原因，并且允许进行重复检测和调整直到获得合格结果。

In your response, you stated, in part:

在你们的回复中，你们声称：

- "Due to the variability the production process cannot be validated in general, instead all relevant parameters are controlled by measurements."
  由于生产工艺的波动一般不能进行验证，因此只能对所有相关参数采用测量方式进行控制。
- " .. . small deviations are considered acceptable, as they do not influence the general usability of the product."
  ……我们认为较小的偏差是可接受的，因为它们并不会影响产品的一般可用性。

Your response is inadequate because you failed to commit to perform appropriate process validation for each of your products and to fully remediate your systems for investigations.

你们的回复是不充分的，因为你们并未承诺对你们每个产品执行适当的工艺验证，并且全面补救你们的调查体系。

Process validation evaluates the soundness of design and state of control of a process throughout its lifecycle. Each significant stage of a manufacturing process must be designed appropriately and assure the quality of raw material inputs, in-process materials, and finished drugs. Process qualification studies determine whether an initial state of control has been established.

工艺验证评估的是一个工艺在其生命周期中的设计合理性和受控状态。生产工艺的每个重要阶段均必须进行适当设计，确保原料输入、中间体和成品的质量。工艺确认研究将确定是否已建立了初始的受控状态。

Successful process qualification studies are necessary before commercial distribution. Thereafter, ongoing vigilant oversight of process performance and product quality is necessary to ensure you maintain a stable manufacturing operation throughout the product lifecycle.

成功的工艺确认研究必须在商业销售之前完成。因此，持续严格监管工艺性能和产品质量，是确保你们在产品生命周期中维持稳定的生产操作所必须的。

See FDA's guidance document Process Validation: General Principles and Practices for general principles and approaches that FDA considers appropriate elements of process validation at https://www.fda.gov/media/71021/download

参见 FDA 工艺验证指南。

For more information about handling failing, out-of-specification, out-of-trend, or other unexpected results and documentation of your investigations, see FDA's guidance document Investigating Out-of-Specification (00S) Test Results for Pharmaceutical Production at https://www.fda.gov/media/71001/download

更多失败、OOS、OOT 或其它非预期结果和调查文件信息，参见 FDA 的药品生产 OOS 检测结果调查指南文件。

In response to this letter, provide:

在回复此函时请提交：

- An assessment of drug product processes to ensure that there is a data-driven and scientifically sound program that identifies and controls all sources of variability, such that your production processes will consistently meet appropriate specifications and manufacturing standards. This includes, but is not limited to, evaluating suitability of equipment for its intended use, sufficiency of detectability in your monitoring and testing systems, quality of input materials, and reliability of each manufacturing process step and control.
  一份对药品工艺的评估，以确保具备由数据推动的科学合理程序可识别和控制所有变异来源，使得你们的生产工艺能持续符合适当的标准和生产标准。其中包括但不仅限于评估设备是否适合其既定用途、在你们监测和检测系统中的可检出度是否充分、输入物料的质量，以及每个生产工艺步骤和控制的可靠性。
- A detailed summary of your validation program for ensuring a state of control throughout the product lifecycle, along with associated procedures. Describe your program for process performance qualification, and ongoing monitoring of both intra-batch and inter-batch variation to ensure a continuing state of control. Also include your program for qualification of your equipment and facility.
  一份确保产品生命周期中受控状态的验证程序及相关程序的详细总结。阐述你们的工艺性能确认程序和批间与批内波动的持续监测从而确保持续受控状态的程序。亦要包括你们的设备和设施确认程序。

Include your process performance protocol(s), and written procedures for qualification of equipment and facilities.

包括你们的工艺性能方案，以及设备和设施确认书面程序。

- A timeline for performing process performance qualification for your drug products marketed to the U.S.
  一份对销售至美国的药品执行工艺性能确认的时间表。

- A comprehensive, independent assessment of your overall system for investigating deviations, discrepancies, complaints, OOS results, and failures. Provide a detailed action plan to remediate this system. Your action plan should include, but not be limited to, significant improvements in investigation competencies, scope determination, root cause evaluation, corrective and preventive action (CAPA) effectiveness, quality assurance unit oversight, and written procedures. Address how your firm will ensure all phases of investigations are appropriately conducted.
  一份对你们调查偏差、差异、投诉、OOS 结果和失败的全面系统的独立全面评估。提交一份详细的补救该系统的行动计划。你们的行动计划应包括但不仅限于大大改进调查能力、范围确定、根本原因评估、CAPA 有效性、质量部门监管和书面程序。说明你公司要如何确保所有调查阶段均得到恰当执行。

Inadequate Control of (b)(4) System XX 系统控制不充分

You use (b)(4) as a component in your drug product and to clean production equipment. You have not established that your (b)(4) system is adequately designed, controlled, maintained, and monitored to ensureit consistently produces (b)(4) that meets (b)(4) USP monograph specifications and appropriate microbial limits. Your (b)(4) system hasnot been validated to produce (b)(4) USP. You also lacked appropriate testing of (b)(4) from your system. For example, you also acknowledged that you do not perform conductivity testing on (b)(4) generated from your system.

你们使用了 XX 作为你们药品的组份，并且用其清洁生产设备。你们并未确定你们的 XX 系统经过充分设计、控制、维护和监测，以确保其能持续生产出符合 USP 各论标准和适当微生物限度的 XX。你们的 XX 系统并未经过验证证明其可以生产出 USP 规格的 XX。你们对你们系统制备的 XX 亦缺乏适当的检测。例如，你们承诺你们并未对你们系统制备的 XX 进行电导率检测。

Pharmaceutical (b)(4) must be suitable for its intended use and routinely tested to ensure ongoing conformance with appropriate chemical and microbiological attributes.

药用 XX 必须适合其既定用途，并经过日常检测以确保持续符合适当的化学和微生物属性。

In your response, you acknowledged that you do not currently have the means to produce (b)(4), and committed to check for possible alternatives. Your response is inadequate because you failed to describe how you will ensure that (b)(4) will be used in the manufacture of your drug products.

在你们的回复中，你们承诺你们目前并无方法生产 XX，并承诺会寻找可能的替代品。你们的回复是不充分的，因为你们并未说明你们将如何确保会在你们的药品生产中使用 XX。

In response to this letter, provide:

在回复本函时请提交：

- All microbial monitoring test results from your (b)(4) system for the past three years including sampling and sanitization dates.
  你们 XX 系统在过去三年中的所有微生物监测检测结果，包括取样和消毒日期。
- Interim measures that will be implemented to ensure (b)(4) with the appropriate quality attributes is used in the production of your drug products.
  将要执行以确保你们药品生产所用 XX 具备适当的质量属性的临时措施。

- A thorough remediation plan to install and operate a suitable (b)(4) system. Include a robust ongoing control, maintenance, and monitoring program to ensure the new system consistently produces (b)(4)adhering to (b)(4), USP monograph specifications and appropriate microbial limits.
  一份安装和运行适当的 XX 系统的彻底补救计划。包括持续稳健的、维护和监测计划，以确保新的系统能持续生产出符合 XX、USP 各论标准和适当微生物限度的 XX。
- A validation report for the (b)(4) system obtained after an appropriately designed system has been installed. Include the system validation protocol and complete test results.
  安装了经过适当设计的系统之后所生成的一份 XX 系统的验证报告。包括系统验证方案和完成的检测结果。
- Revised procedures governing the updated (b)(4) system, including provisions that require collection of (b)(4) samples from your (b)(4) system for microbiological counts and microbial identification testing.
  修订后的更新后 XX 系统管理程序，包括要求从你们的 XX 系统采集 XX 样品用于微生物计数和微生物鉴别测试的规定。
- An effective program for ongoing control, maintenance, and monitoring that ensures the remediated system that you install consistently produces (b)(4) that meets (b)(4), USP, monograph specifications and appropriate microbial limits (including both total count and objectionable microbes). Regarding the latter, ensure that your total microbial count limit for (b)(4) is appropriate in view of the intended use of the products produced by your firm.
  一份可确保经过补救的系统符合 XX、USP 各论标准和适当的微生物限度（包括总计数和致病菌）的持续控制、维护和监测的有效程序。关于后者，确保你们的 XX 总微生物计数限度适合于你公司生产的产品既定用途。
- A detailed risk assessment addressing the potential effects of the observed (b)(4) system failures on the quality of all drug product lots currently in U.S. distribution. Specify actions that you will take in response to the risk assessment, such as customer notifications and product recalls.
  一份详细的风险评估，说明发现的 XX 系统失败对当前在美国市场的所有药品批次质量的潜在影响。说明你们为应对风险将采取的措施，例如通知客户和召回产品。

2. Your firm failed to establish and follow an adequate written testing program designed to assess the stability characteristics of drug products and to use results of stability testing to determine appropriate storage conditions and expiration dates (21 CFR211.166(a)).

你公司未能建立和遵守足够的书面检测程序，以评估药品的稳定特性，以及使用稳定性测试结果确定适当的存贮条件和有效期（21 CFR 211.166(a)）。

Your firm does not have an adequate stability testing program to demonstrate that the chemical and microbiological characteristics of your over-the-counter drug products remain acceptable throughout their labeled expiry period.

你公司并无充分的稳定性检测程序，用以证明你们 OTC 药品在其标示的有效期内保持可接受的化学和微生物特性。

A. You did not have long-term stability test data to support the three-year expiration date assigned to your (b)(4) products.Your product expiration dates were based on only three months of accelerated stability testing. Your accelerated stability testing data is also inadequate, because you

tested the samples only at the (b)(4), and not at appropriate intervals. In addition, you released for distribution your commercial size pack of (b)(4) into U.S. markets before completing the three-month accelerated stability study.

你们并无长期稳定性数据用于支持给定你们 XX 药品的 3 年有效期。你们的药品有效期是基于仅有的 3 个月加速稳定性测试。你们的加速稳定性测试数据亦是不充分的，因为你们仅在 XX 时检测了样品，而不是在适当的时间间隔内。另外，你们放行销售了你们的商业批量包装至美国，此前未完成 3 个月加速稳定性研究。

B. Your stability program did not include an adequate number of batches of each drug product. For example, your stability program included only a research and development batch, and the (b)(4) commercial batch. No additional batches were placed on stability throughout the lifecycle of your products.

你们的稳定性程序并未包括每种药品足够数量的批次。例如，你们的稳定性程序仅包括一个研发批次，和 XX 商业批次。在你们产品生命周期中没有其它批次放入稳定性研究计划中。

In addition, retain samples of (b)(4) batch numbers (b)(4) tested approximately (b)(4) after manufacture showed significant reduction in the amount of (b)(4). You lacked other data to support the expiration date.

另外，生产后对约 XX 批留样检测显示 XX 数量大大降低。你们缺乏其它数据支持有效期。

In your response, you stated that you could not delay the delivery process due to (b)(4) of additional shipping time required for the U.S. market, therefore you have to perform stability tests parallel to the shipping process. Your response is unacceptable as you released the product for distribution without data to support the labeled three-year expiry period.

在你们的回复中，你们声称你们不能推迟发货，因为美国市场要求的其它发运时间 XX，因此你们不得不在发运过程中同步进行稳定性测试。你们的回复是不可接受的，因为你们在没有数据支持所标示的三年有效期时即放行了你们的产品用于销售。

You also stated that the stability program for U.S. products will be revised to include (b)(4) stability tests and additional measurements. However, you did not provide a CAPA plan with timelines to remediate this issue.

你们还声称将修订美国产品的稳定性程序，在其中包括 XX 稳定性测试和其它测量。但是你们并未提交补救该问题的 CAPA 计划及时间表。

In regard to your accelerated stability data, you determined the formulation was "sufficiently stable" because you found the (b)(4) concentration stable for (b)(4)," even though you identified a reduction in the (b)(4)." You added that you will reformulate the product due to this issue.

关于你们的加速稳定性数据，你们确定该配方是“足够稳定的”，因为你们发现“即使你们发现了 XX 降低”但 XX 浓度稳定。你们说你们将因为该问题而调整该药品配方。

Your response is inadequate because you did not provide an adequate explanation with data to address the observed reduction in the concentration of "(b)(4)" and its impact on the labeled three-year expiry period.

你们的回复是不充分的，因为你们并未提交一份对数据的充分解释，说明所发现的“XX”浓度降低问题，及其对所标示 3 年有效期的影响。

In response to this letter, provide your investigation into degradation of (b)(4) concentration and an assessment of the impact of this degradation on distributed drug product. Also provide:

在回复本函时，提交你们对 XX 浓度降解的调查，以及该降解对所销售药品的影响性评估。亦请提交：

- A comprehensive, independent, assessment and CAPA plan to ensure the adequacy of your stability program. Your remediated program should include, but not be limited to:
  一份全面独立的评估和 CAPA 计划，以确保你们稳定性程序的充分性。你们的补救计划应包括但不仅限于：
  - Stability indicating methods
    稳定性指示性方法
  - Stability studies for each drug product in its marketed container-closure system before distribution is permitted
    每个药品在允许销售之前以其上市包装方式进行的稳定性研究
  - An ongoing program in which representative batches of each product areadded each year to the program to determine if shelf-life claims remain valid
    一份每年将每个产品代表性批次加入计划确定货架周期声明保持有效的持续计划
  - Detailed definition of the specific attributes to be tested at each station (timepoint)
    对在每个时间点要检测的具体属性的详细定义
- All procedures that describe these and other elements of your remediated stability program.
  阐述你们补救后稳定性计划中这些和其它要素的所有程序

3. Your firm failed to test samples of each component for identity and conformity with all appropriate written specifications for purity, strength, and quality. Your firm also failed to validate and establish the reliability of your component supplier's test analyses at appropriate intervals (21 CFR 211.84(d)(1) and (2)).

你们公司未能对每种组份样品进行鉴定，并确定其符合所有适当的书面纯度、含量和质量标准。你公司亦未以适当时间间隔验证和建立你们组份供应商检测分析的可靠性（21 CFR 211.84(d)(1) and (2)）。

You lacked adequate testing of the incoming (b)(4) active pharmaceutical ingredient (API) to determine identity, purity, and other appropriate quality attributes. In addition, your firm had not established the reliability of your suppliers' analyses through appropriate validation.

你们缺乏对进厂 XX 原料药（API）的充分检测，从而确定其鉴别、纯度和其它适当质量属性。另外，你公司并未通过适当的验证建立你们供应商分析的可靠性。

You may not rely upon the supplier's Certificates of Analyses (COA) to verify the identity of your (b)(4) API.

你们不可依赖供应商的 COA 来验证你们 XX API 的鉴别。

In your response, you stated that all your raw materials are sourced from trusted long-standing suppliers. Your response is unacceptable because you failed to demonstrate that your (b)(4) API

supplieris qualified. In addition, you did not commit to conduct at least (b)(4) specific identity test for each incoming lot of (b)(4) API.

在你们的回复中，你们声称你们所有原料均来源来受信任的长期供应商。你们的回复是不可接受的，因为你们并未证明你们的 XX API 供应商经过确认。另外，你们并未承诺要对每批进厂 XX API 执行至少一项专属鉴别测试。

In response to this letter, provide:

在回复本函时，请提交：

- A comprehensive, independent review of your material system to determine whether all suppliers of components, containers, and closures are each qualified, and the materials are assigned appropriate expiration or retest dates. The review should also determine whether incoming material controls are adequate to prevent the use of unsuitable components, containers, and closures.
  一份对你们物料体系的全面独立审核，以确定是否所有组份、容器和密闭器供应商均经过确认，并且物料被给定了适当的效期或复验期。审核还应确定进厂物料的控制是否足以防止使用不当组份、容器和密闭器。
- A description of how you will test each component lot for conformity with all appropriate specifications for identity, strength, quality, and purity. If you intend to accept any results from your supplier's COA instead of testing each component lot for strength, quality, and purity, specify how you will robustly establish the reliability of your supplier's results through initial validation as well as periodic re-validation. In addition, include a commitment to always conduct at least (b)(4) specific identity test for (b)(4) incoming component lot.
  一份说明阐述你们要如何检测每批组份，确认其符合所有适当的鉴别、含量、质量和纯度标准。如果你们准备接受你们供应商 COA 的所有结果，用以取代你们对每批组份的含量、质量和纯度检测，说明你们要如何通过初始验证和定期重新验证稳定建立你们供应商结果的可靠性。另外，要包括一份承诺声明你们会一直对每批进厂组份执行至少一项特定鉴别测试。
- A summary of results obtained from testing all components to evaluate the reliability of the COA from each component manufacturer. Include your SOP that describes this COA validation program.
  一份对所有组份检测所得结果的总结，以评估每个组份生产商 COA 的可靠性。包括阐述该 COA 验证程序的 SOP。
- A description of how you test incoming glycerin raw material lots for the presence of diethylene glycol and ethylene glycol, prior to releasing lots for use in drug product manufacturing.
  一份说明阐述你们如何在放行用于药品生产之前对每批进厂丙三醇原料批次进行二甘醇和乙二醇检测。

Products Containing Glycerin 含丙三醇的药品

You manufacture drugs that contain glycerin. The use of glycerin contaminated with diethylene glycol has resulted in various lethal poisoning incidents in humans worldwide. See FDA's guidance document Testing of Glycerin for Diethylene Glycol to help you meet the COMP requirements when manufacturing drugs containing glycerin at: https://www.fda.gov/media/71029/download

你们生产的药品含有丙三醇。使用受二甘醇（DEG）污染的丙三醇已导致全球多次人类因毒致死事件。参见 FDA 指南“丙三醇中 EG 检测”，有助于你们在生产含丙三醇药品时满足 CGMP 要求。

Quality Systems 质量体系

Your firm's quality systems are inadequate. See FDA's guidance document Quality Systems Approach to Pharmaceutical CGMP Regulations for help implementing quality systems and risk management approaches to meet the requirements of CGMP regulations 21 CFR, parts 210 and211 at https://www.fda.gov/media/71023/download

你公司的质量体系是不充分的。参见 FDA 的药品 CGMP 法规的质量体系方法，有助于帮助实施质量体系和风险管理方法，符合 21CFR 第 210 和 211 部分的 CGMP 法规要求。

Consultant Recommended CGMP 顾问建议

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualified as set forth in 21 CFR 211.34 to evaluate your operations and to assist your firm in meeting CGMP requirements if your firm intends to resume manufacturing drugs for the U.S. market. We also recommend that the qualified consultant perform a comprehensive audit of your entire operation for CGMP compliance and that the consultant evaluates the completion and efficacy of your corrective actions and preventive actions before you pursue resolution of your firm's compliance status with FDA.

基于我们在你公司发现的违规情况，如果你公司有意继续为美国市场生产药品，我们强烈建议你们使用一位有 21 CFR 211.34 所述资质的顾问来评估你们的操作以及协助你们公司符合 CGMP 要求。我们还建议该具备资质的顾问对你们整个运作的 CGMP 合格情况执行全面审计，并在你们寻求你公司符合 FDA 要求解决方案之前由该顾问评估你们 CAPA 的完成情况和有效性。

Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

你们使用顾问并不能解除你们公司符合 CGMP 的义务。你们公司的高级管理层仍负有义务全面解决所有缺陷，确保持续 CGMP 符合性。

Conclusion 结论

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of other violations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

FDA placed your firm on Import Alert 66-40 onJanuary 10, 2020.

FDA 已于 2020 年 1 月 10 日将你公司置于进口禁令 66-40 中。

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产的新申报和增补申报的批准。

Failure to correct these violations may also result in the FDA continuing to refuse admission of articles manufactured at Dental-Kosmetik GmbH & Co., Dresden, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Articles under this authority may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

20. 320-20-20 2020-01-22 Sunstar Guangzhou Ltd 盛势达（广州）化工有限公司

Dear Mr. Xu:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Sunstar Guangzhou Ltd., FEI 3009449945, at Blk D, 5/F, 203 Conbo Avenue, Free Trade Zone, Guangzhou, Guangdong, from June 24 to 28, 2019.

美国 FDA 于 2019 年 6 月 24 日至 28 日检查了你们位于广州保税区广保大道 203 号首层、第五层的盛势达（广州）化工有限公司生产场所（FEI 号 3009449945）。

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See Title 21 Code of Federal Regulations (CFR), parts 210 and 211 (21 CFR parts 210 and 211).

本警告信总结了制剂生产严重违反 CGMP 的行为。参见 21CFR 第 210 与 211 部分。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351 (a)(2)(B).

由于你们的制剂生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的药品根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C. 351(a)(2)(B)被认为是掺假药品。

We reviewed your July 15, 2019, response to our Form FDA 483 in detail. Your response is inadequate because it did not provide sufficient detail or evidence of corrective actions to bring your operations into compliance with CGMP.

我们已详细审核了你公司 2019 年 7 月 15 日对我们 FDA483 表的回复。你们的回复是不充分的，因为其中并未提供足够详细的内容或证据，证明纠正措施可使得你们的运营转入 CGMP 合规状态。

During the inspection, our investigator observed specific violations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

1. Your firm failed to perform, for each batch of drug product, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release, and conduct appropriate laboratory testing for each batch of drug product required to be free of objectionable microorganisms (21 CFR 211.165(a)).

你公司未能在放行之前对每批药品执行适当的实验室检测，证明其符合最终的药品质量标准，包括每种活性成分的鉴别和含量，并对每批要求不得检出致病菌的药品执行适当的实验室检查（21 CFR 211.165(a)）。

Your firm manufactures over-the-counter (OTC) (b)(4) drug products, including those specifically marketed to children. You released certain drug products without conducting identity and strength testing. For example, you released your (b)(4) without testing for identity and strength of its labeled active ingredients: (b)(4).

你公司生产 OTC 药品，包括儿童用药。你们未执行鉴别和含量测试即放行了一些药品。例如，你们放行了你们的 XX，却没有检测其所标示的活性成分 XX 的鉴别和含量。

Complete testing of each batch before release is essential to determine if the drug products you manufacture meet appropriate specifications.

在放行前必须对每批药品进行完整的测试以确定你们所生产的药品是否符合适当的质量标准。

In your response, you stated that all batches of finished products with (b)(4) " ... will be subjected to lab analysis prior to distribution." Specifically, you plan to perform assay testing for (b)(4). However, you also stated you will evaluate the "feasibility" of performing assay testing for (b)(4).

在你们的回复中，你们声称所有含 XX 的成品批次均“……将在销售之前进行实验室分析”。具体来说，你们计划对 XX 进行含量检测。但是你们亦声称你们将评估执行 XX 含量检测的“可行性”。

Your response is inadequate. You failed to test all your reserve samples of drug products containing (b)(4) as active ingredients within expiry to determine whether they meet established specifications for identity and strength. You did not commit to perform the assay test for (b)(4) in your finished drug products.

你们的回复是不充分的。你们未能检测你们所有含有 XX 活性成分的效期内药品留样，以确定其是否符合既定的鉴别和含量标准。你们未承诺对你们成品中 XX 的含量进行检测。

Your response is also inadequate because you did not include information about your testing procedures, methods, timeline for implementation, or a detailed description of the tests you will conduct (e.g.,identity, strength, and purity).

你们的回复不充分还因为你们未在其中包括你们检测程序、方法、实施时间限的信息，或你们将要执行的检测的详细描述（例如，鉴别、含量和纯度）。

In your response to this letter, provide the following:

在回复本函时请提交以下内容：

- A list of chemical and microbial specifications, including test methods, used to analyze each lot of your drug products before a disposition decision. Also include method validation and/or method verification data and reports that evaluate these test methods.
  一份在做出处置决策之前用于分析每批药品的化学和微生物标准清单，包括检测方法。亦要包括评估这些检测方法的方法验证和/或方法确认数据和报告。
- An action plan and timelines for conducting full chemical and microbiological testing of retain samples to determine the qualityof all batches of drug product distributed to the United States within expiry as of the date of this letter. Summarize all results obtained from testing retain samples from each batch. If such testing reveals substandard quality drug products, take rapid corrective actions, such as notifying customers and product recalls.
  一份对留样执行全面化学和微生物检测的行动计划和时间表，以确定已销售至美国的仍在效期内的所有批次药品截至本函发出的质量。总结所有从留样检测中获得的结果。如果结果显示有不合格的药品，则采取快速纠正措施如通知客户和召回产品。
- A comprehensive, independent assessment of your laboratory practices, procedures, methods, equipment, documentation, and analyst competencies. Based on this review, provide a detailed plan to remediate and evaluate the effectiveness of your laboratory system.
  一份对你们实验室规范、程序、方法、设备、文件和化验员资格的全面独立评估。基于该审核，提交一份详细的补救计划，并评估你们实验室系统的有效性。

- Your procedure to ensure that any test methods performed by a contract testing laboratory on your behalf are properly validated before use.
  你们用于确保外包检测实验室在执行任何检测方法之前均会经过恰当验证的程序。

2. Your firm failed to test samples of each component for identity and conformity with all appropriate written specifications for purity, strength, and quality (21 CFR 211.84(d)(1)).

你公司未能检测每种成分的样品的鉴别，并且确定其符合所有适当的书面纯度、含量和纯度质量标准（21 CFR 211.84(d)(1)）。

Your firm failed to test incoming components used to manufacture your drug products to determine their identity. For example, your firm did not ensure that at least (b)(4) specific identity test was conducted for (b)(4) lot of components, including active ingredient identity testing for (b)(4) received from another site in your network.

你公司未检测你们药品生产所用进厂组份，以确定其鉴别。例如，你公司未能确保至少执行一项专属鉴别测试，包括从你们网络另一场所收到的 XX 活性成分鉴别。

It your responsibility to ensure that you performat least (b)(4) test to verify the identity of all of the components used in drug product manufacturing, including your active ingredient (b)(4).

你们有义务确保你们会执行至少一项鉴别测试来核查药品生产所用所有组份的鉴别，包括你们的活性成分 XX。

In response to this letter, provide the following:

在回复本函时请提交以下内容：

- A comprehensive, independent review of your material system to determine whether all suppliers of components, containers, and closures are each qualified, and the materials are assigned appropriate expiration or retest dates. The review should also determine whether incoming material controls are adequate to prevent use of unsuitable components, containers, and closures.
  一份对你们物料系统的全面独立审核，以确定是否所有组份、容器和密闭器供应商均经过确认，且物料均给定了适当的有效期或复验期。审核亦应确定进厂物料控制是否足以防止使用不当的组份、容器和密闭器。
- The chemical and microbiological quality control specifications you use to test and determine disposition of each incoming lot of components to evaluate whether they are suitable for use in manufacturing.
  你们用于检测和确定对每批进厂组份的处置，评估其是否适合用于生产的化学和微生物质量控制标准。
  - An action plan and timelines for conducting full chemical and microbiological testing of retain samples to determine the quality of all batches of active ingredients used in the manufacture of drug products distributed to the United States within expiry as of the date of this letter.
    一份对留样执行全面化学和微生物检测的行动计划和时间表，以确定用于销往美国的且在本函签发时仍在有效期内的药品生产所用所有批次活性成分的质量。

- A summary of all results obtained from testing retain samples from each batch. If such testing reveals substandard quality drug substances, take rapid corrective actions, such as notifying customers and product recalls.
  一份对每批留样进行检测所得结果的总结。如果检测结果显示原料药质量不合格，则采取快速纠正措施，如通知客户和召回产品。

- A description of how you will test each component lot for conformity with all appropriate specifications for identity, strength, quality, and purity. If you intend to accept any results from your supplier's certificate of analysis instead of testing each component lot for strength, quality, and purity, specify how you will robustly establish the reliability of your supplier's results through initial validation as well as periodic re-validation. In addition, include a commitment to always conduct at least one specific identity test for each incoming component lot.
  一份你们将如何检测每批组份确保其符合所有适当的鉴别、含量、质量和纯度标准的描述。如果你们准备接受来自你们供应商 COA 的所有结果，取代你们对每批组份的含量、质量和纯度检测，则说明你们将如何通过初次验证以及定期再评估牢固建立你们供应商结果的可靠性。另外，还要包括一份承诺书说明你们将对每批进厂组份一直执行至少一项专属鉴别测试。

3. Your firm failed to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that all components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength,quality, and purity (21 CFR 211.160(b)).

你公司未能建立实验室控制，包括设计用于确保所有组份、药品容器、密闭器、中间体、标准和药品符合适当鉴别、含量、质量和纯度标准的科学合理和适当的规格、标准、取样计划和检测方法（21 CFR 211.160(b)）。

You lack scientific data to demonstrate that your growth promotion procedures and practices are suitable and reliable for microbiological testing of your drug products.

你们缺乏科学数据来证明你们促生长程序和做法适用于你们药品的微生物测试并且具有可靠性。

Specifically, you do not consistently perform growth promotion testing on the in-house media used for microbiological testing of your finished drug products and for water testing to ensure the media supports growth and acceptable recovery. As such, each batch of media you use for microbiological testing has not been adequately verified for growth promotion. You cannot ensure that, upon release, your drug products meet acceptable microbiological specifications.

具体来说，你们并未对内部制作用于成品和水微生物测试的培养基持续执行促生长试验，以确保培养基能支持生长并获得可接受的回收率。因此，你们用于微生物测试的每批培养基均未经过充分的促生长验证。你们无法确保你们药品在放行时符合可接受的微生物标准。

In your response, you stated a new growthefficiency test will be performed on the (b)(4) plates. You also committed to purchase (b)(4) plates from third parties for water quality testing.

在你们的回复中，你们声称新的生长效率测试将在 XX 碟上执行。你们还承诺要从第三方购买 XX 碟用于水质量检测。

Your response was inadequate. Your response couldnot be fully evaluated because you did not provide sufficient details describing how growth promotion testing will be performed, or your interim

corrective actions until the testing is complete. Your finn also failed to give information on the (b)(4) to be used for water quality testing.

你们的回复是不充分的。我们无法对你们的回复进行全面评估，因为你们并未提交足够详细的信息，说明要如何进行促生长试验，亦未说明在试验完成之前你们的临时纠正措施是什么。你们公司亦未能提供水质量检测用 XX 的信息。

In response to this letter, provide the following:

在回复本函时请提交以下内容：

- A comprehensive review of your laboratory practices, procedures, methods, equipment, and analyst competencies. Based onthis review, provide a detailed corrective action and preventive action (CAPA) plan to remedy your laboratory system. Your plan should include the process you will use to evaluate the effectiveness of the implemented CAPA plan.
  一份对你们实验室规范、程序、方法、设备和化验员资格的全面审核。基于该审核，提交一份详细的实验室系统补救 CAPA 计划。你们的计划应包括你们将于评估所执行 CAPA 计划有效性的流程。
- Microbiological testing methods that conform to USP<61> and <62>, which are capable of recovering product bioburden and determining whether any microorganisms are objectionable relative to the product's intended use, route of administration, and patient (i.e., consumer) population.
  微生物检测方法应符合 USP<61>和<62>要求，能够回收到产品的生物负载，确定是否存在任何影响产品既定用途、给药途径和患者人群（即消费者）的微生物存在。
- A commitment to test each batch using qualified methods to ensure conformance to finished product specifications before final disposition decision.
  一份承诺将使用经过验证的方法检测每个批次的承诺书，确保做出最终处置决策之前符合成品标准。

4. Failure to establish an adequate quality control unit and the responsibilities and procedures applicable to the quality control unit are not in writing and fully followed. (21 CFR 211.22(a) and 211.22(d)).

未能建立足够的质量部门和职责，未全面遵守适用于质量部门的程序（21 CFR 211.22(a) and 211.22(d)）。

Your quality unit (QU) failed to ensure that you have adequate procedures and did not provide adequate oversight of your manufacturing activities. For example: ·

你们的质量部门（QU）未能确保你们具备足够的程序，未能对你们的生产活动进行充分的监管。例如：

- You lack adequate control over the issuance, use, and reconciliation of manufacturing batch records and equipment maintenance sheets. Uncontrolled copies of manufacturing batch records and in-processcontrol forms were pre-printed and kept in a room with unrestricted access.
  你们对发放、使用和平衡生产批记录和设备维护日志缺乏足够的控制。生产批记录和中控表格未受控，被重复印制并保存在无出入限制的房间内。

- Several test reports of your drug product assay were reviewed and the raw data for the standard curve could not be located. It was noted that scrap pieces of paper were used to record data which was later entered to calculate the (b)(4) concentration for the assay test.
  我们审核了你们药品含量的几份检测报告，你们找不到标准曲线的原始数据。我们注意到你们使用小纸片记录数据，然后再录入计算含量检测的 XX 浓度。
- Your firm failed to establish and follow procedures for calculating production yields.
  你们公司未能制订并遵守生产收率计算的程序。

In your response, you stated" ... starting July 2019, relevant personnel will be handed just enough blank forms on a (b)(4) basis and they must account for the whereabouts of all blank forms at the (b)(4). "You stated that all documents will be archived and procedures will be drafted and/or updated to meet CGMP requirements.

在你们的回复中，你们声称“……自 2019 年 7 月始，相关人员将按 XX 发放仅够使用的空白表格，他们在 XX 时必须说明所有空白表格的去向”。你们声称所有文件将归档，并将起草和/或更新程序以符合 CGMP 要求。

Your response is inadequate. You did not adequately address the impact of the lack of QU oversight on your distributed drug products. You failed to describe procedures to issue and maintain controlled documents and whether your QU will have control of the pre-printed documents prior to distribution. Your response did not give sufficient details of the new documentation archival system and if it will be proceduralized. There was no explanation how analysts will be trained to use laboratory notebooks and adhere to good documentation practices.

你们的回复是不充分的。你们并未充分说明缺乏 QU 对你们已销售药品监管的影响。你们未能说明发放和维护受控文件的程序，以及你们 QU 是否会在发放前对再次印制文件进行控制。你们的回复并未提供足够详细内容说明新的文件归档系统，以及是否会将其订为程序。你们未解释你们将如何培训化验员使用实验室笔记本，以及遵守优良文件规范。

In response to this letter, provide a comprehensive assessment with your planned CAPA(s) to ensure yow· QU is given the authorityand resources to independently and effectively function. The assessment should also include, but not be limited to:

在回复本函时，请提交一份对你们计划 CAPA 的全面评估，以确保你们的 QU 被授予了权力和资源，可独立有效工作。评估亦应包括但不仅限于：

- A determination of whether procedures used by yourfirm are robust and appropriate.
  确定你们所用程序是否可靠恰当。
- Provisions for QU oversight throughout your operations to evaluate adherence to appropriate practices.
  QU 监管你们所有操作以评估是否遵守了适当规范的条款。
- A complete and final review of each batch and its related information before the QU disposition decision.
  QU 在做出处置决策之前对每个批次及其相关信息进行完整最终审核。
- Oversight and approval of investigations and discharging all other QU duties to ensure the identity, strength, quality, andpurity of all products.
  监管和批准调查，履行所有其它 QU 职责，以确保所有产品的鉴别、含量、质量和纯度。

- A complete assessment of documentation systems used throughout your manufacturing and laboratory operations to determine where documentation practices are inadequate. Include a detailed CAPA plan that remedies documentation practices and ensures you retain complete and accurate records.
  一份对整个生产和实验室操作文件系统的完整评估，确定文件规范是否不够。包括一份详细的 CAPA 计划，弥补文件规范，并确保你们保存了完整准确的记录。
- Provide a detailed description of the quantifiable standard of production. Provide evidence of a theoretical yield in batch record with defined upper and lower limits for production yields.
  提交一份可量化的生产标准详细说明。提交批记录中规定有上下限的理论收率证据。

Concerns Regarding Glycerin 关于丙三醇的担忧

The drug products you manufacture contain glycerinas an ingredient. The use of glycerin contaminated with diethylene glycol (DEG) has resulted in various lethal poisoning incidents in humans worldwide.

你们生产的药品含有丙三醇。使用受二甘醇（DEG）污染的丙三醇已导致全球多次人类因毒致死事件。

See FDA's guidance document, Testing of Glycerinfor Diethylene Glycol, to help you meet CGMP requirements when distributing glycerin for use in drug products. including testing for DEG and recommendations for supply chain integrity, at https://www.fda.gov/media/71029/download.

参见 FDA 指南“丙三醇中 EG 检测”，有助于你们满足 CGMP 要求前提下销售使用了丙三醇的药品，以及对 DEG 的检测和供应链完整性的建议。

CGMP Consultant Recommended CGMP 顾问建议

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualifiedas set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements.

鉴于我们在你们公司发现的违规情况，我们强烈建议你们使用一位有 21 CFR 211.34 所述资质的顾问来协助你们公司符合 CGMP 要求。

Your use of a consultant does not relieve your firm' s obligation to comply with CGMP. Your firm's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

你们使用顾问并不能解除你们公司符合 CGMP 的义务。你们公司的高级管理层仍负有义务全面解决所有缺陷，确保持续 CGMP 符合性。

Conclusion 结论

The violations cited in this letter are not intendedto be an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of other violations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

FDA may withhold approval of requests for export certificates and approval of pending new drug applications or supplements listing your facility as a supplier or manufacturer until the above violations are corrected. We may re-inspect to verify that you have completed your corrective actions.

FDA 可能会暂停批准出口证书申请，暂停批准所有将你公司列为供应商或生产商的在审新药申报或增补，直到上述违规情况得到改正。我们可能会重新进行现场检查，以核实你们是否已完成了纠正措施。

FDA placed your firm on Import Alert 66-40 on January 21, 2020.

FDA 已于 2020 年 1 月 21 日将你公司置于进口禁令 66-40 中。

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产商的新药申报和增补申报的批准。

Failure to correct these violations may also resultin the FDA continuing to refuse admission of articles manufactured at Sunstar Guangzhou Ltd., Blk D, 5/F, 203 Conbo Avenue, Free Trade Zone, Guangzhou, Guangdong, into the United States under section 801(a)(3) of the FD&C Act,21 U.S.C. 381 (a)(3). Articles under this authority may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351 (a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days. state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

21. 320-20-21 2020-01-23 Guangzhou Tinci Materials Technology Co., Ltd.广州天赐高新材料股份有限公司

Dear Mr. Xu:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Guangzhou Tinci Materials Technology Co., Ltd., FEI 3007544618, at 8th Kangda Road, Yunpu Industrial Zone, Huangpu District, Guangzhou, from July 29 to August 2, 2019.

美国 FDA 于 2019 年 7 月 29 日至 8 月 2 日检查了你们位于中国广州市黄埔区云埔工业区东诚片康达路 8 号的广州天赐高新材料股份有限公司生产场所。

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See Title 21 Code of Federal Regulations (CFR), parts210 and 211 (21 CFR parts 210 and 211).

本警告信总结了制剂生产严重违反 CGMP 的行为。参见 21CFR 第 210 与 211 部分。

Our inspection noted that your firm produces the active pharmaceutical ingredient (API) (b)(4). The API is then mixed into a (b)(4). The (b)(4) is by definition an in-process material for a finished drug product under Title 21, Code of Federal Regulations section 210.3(b)(9), and therefore subject to the CGMP regulationsat 21 CFR 211.

我们检查中注意到你公司生产 API XX。该 API 然后混合进 XX。根据定义，XX 为 CFR 210.3(b)(9)部分定义的制剂的中间体，因此受 21CFR211 CGMP 的监管。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug product adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351 (a)(2)(B).

由于你们的制剂生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的药品根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C. 351(a)(2)(B)被认为是掺假药品。

We received your response to our Form FDA 483 on August 22, 2019 and reviewed it in detail. Your response is inadequate because it did not provide sufficient detail or evidence of corrective actions to bring your operations into compliance with CGMP.

我们已详细审核了你公司 2019 年 8 月 22 日对我们 FDA483 表的回复。你们的回复是不充分的，因为其中并未提供足够详细的内容或证据，证明纠正措施可使得你们的运营转入 CGMP 合规状态。

During our inspection, our investigator observed specific violations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

1. Your firm failed to use equipment in the manufacture, processing, packing, or holding of drug products that is of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance (21 CFR211.63).

你公司在生产、加工、包装或保存药品时未使用经过适当设计、具备足够尺寸并适当定位安装的设备，便于其既定用途和清洁与维护（21 CFR 211.63）。

Inadequate (b)(4) System Monitoring XX 系统监测不充分

Your procedures for testing (b)(4) requires (b)(4) sampling for total aerobic microbial count (TAMC) and total yeast and molds count (TYMC). On (b)(4), you manufactured drug product batch (b)(4):you did not test your (b)(4) for TAMC and TYMC at the time. In fact, you did not test your (b)(4) system until (b)(4), more than a (b)(4) later, when your (b)(4) testing yielded an out-of-limit result of 255 colony forming units per mL (cfu/mL) for TAMC.

你们检测 XX 的程序要求 XX 取样检测 TAMC 和 TYMC。XX 日你们生产了药品批号 XX，你们在当时并未检测你们 XX 的 TAMC 和 TYCM。事实上，你们直到 XX 时长之后你们 XX 的 TAMC 检测结果为 OOS 225CFU/ML 时才检测你们的 XX 系统。

In your response, you stated "(b)(4)." However, batch (b)(4) was manufactured on (b)(4). You did not have adequate data to justify the use of (b)(4) from your system as a component in that batch. Without routine (b)(4) monitoring, you lack assurance that your (b)(4) meets minimum microbiological and chemical standards suitable for the manufacture of your drug product.

在你们的回复中，你们声称“XX”。但是 XX 批次是在 XX 时间生产的。你们并没有足够的数据支持你们使用你们系统的 XX 作为该批次的组份。没有日常的 XX 监测，你们无法确保你们的 XX 符合你们药品生产所需的最低微生物和化学标准。

Inadequate (b)(4) system design and maintenance XX 系统设计和维护不充分

Your firm manufactures an over-the-counter (b)(4) drug product intended to treat (b)(4). You use (b)(4) as acomponent in manufacturing this drug product. Your (b)(4) system is not adequately designed, controlled, maintained, and monitored to ensure it consistently produces (b)(4) suitable for its intended use.

你公司生产 OTC 药品 XX，用于治疗 XX。你们使用 XX 作为该产品的一种组份。你们的 XX 系统未经过充分设计、控制、维护和监测，以确保其持续产生适合其既定用途的 XX。

Your (b)(4) and distribution systems appear to have multiple dead-legs, which can foster the development of biofilms. The piping and installation diagrams for your (b)(4) system in your response lack adequate information regarding the slope of the piping.

你们的 XX 和分配系统看起来有多个死管，其中可能会生长生物膜。你们回复中的你们 XX 系统管道和安装图缺少足够的管道坡度信息。

Moreover, your (b)(4) system lacks proper maintenance. For example, there were visible corrosion on pipes, brackets, fittings, valves, and tanks in the utilities area, which is covered but not completely enclosed from outside elements. During the inspection, you stated that some poorly maintained equipment and piping in the (b)(4) utility area is not currently in use. However, during the inspection it appeared that the poorly maintained equipment and piping was still connected to the (b)(4) system you use to make components of drugs.

还有，你们的 XX 系统缺少适当的维护。例如，公用工程区域的管道、支架、配件、阀门和储罐上有可见腐蚀，上面有遮盖但没有完全封闭，与外界隔开。在检查期间，你们声称在 XX 公用系统区域有些维护不良的设备和管道现在你们未再使用。但在检查期间，维护不良的设备和管道仍连接至你们用于产出药品组份的 XX 系统。

In response to this letter provide the following: 在回复本函时请提交：

- A comprehensive remediation plan for the design, control, and maintenance of the (b)(4) system.
  一份对 XX 系统的设计、控制和维护的全面补救计划
- A (b)(4) system validation report. Also summarize any improvements made to system design and to the program for ongoing control and maintenance.
  XX 系统的验证报告。还要总结对系统设计所做的所有改进，和连续控制和维护的程序
- Your total microbial count limits to monitor whether this system is producing (b)(4) suitable for the intended uses for each of your products.
  你们监测该系统是否产生出适合用于每种产品的 XX 的总微生物计数限度
- A detailed risk assessment addressing the potential effects of the observed (b)(4) system failures on the quality of all drug product lots currently in U.S. distribution. Specify actions that you will take in response to the risk assessment, such as customer notifications and product recalls.
  一份详细的风险评估，解决所发现的 XX 系统失败对所有当前在美国销售的药品批次的潜在影响。写明你们针对风险评估结果将要采取的具体措施，例如通知客户和召回产品
- A procedure governing your program for ongoing control, maintenance, and monitoring that ensures your (b)(4) system consistently produces (b)(4) that meets (b)(4), USP monograph specifications and appropriate microbial limits.
  你们持续控制、维护和监测管理程序，确保你们的 XX 系统持续产出符合 XX、USP 各论标准和适当微生物限度的 XX

2. Your firm failed to conduct, for each batch ofdrug product, appropriate laboratory testing, as necessary, required to be free of objectionable microorganisms (21 CFR 211.165(b)).

你公司未能在必要时对每批药品进行适当的致病菌实验室检测（21 CFR 211.165(b)）。

Your firm released drug product without adequate testing to ensure it is free of objectionable microorganisms and meets appropriate microbial limits. For example, you manufactured batch (b)(4) on (b)(4), without performing adequate microbial limit tests. It is unclear if you have addressed the lack of microbial testing of your drug product.

你公司放行了未经足够检测的药品，无法确保其无致病菌及符合适当的微生物限度。例如，你们于 XX 日期生产的 XX 批次未进行足够的微生物限度检测。尚不清楚你们是否解决了你们药品缺少微生物检测的问题。

In response to this letter provide the following: 在回复本函时请提交以下：

- A list of chemical and microbial specifications, including test methods, used to analyze each lot of your drug products before a lot disposition decision.
  一份批处置之前对你们每批药品进行分析所用化学和微生物标准清单，包括检测方法
- An action plan and timelines for conducting full chemical and microbiological testing of retain samples to determine the quality of all batches of drug product distributed to the United States within expiry as of the date of this letter.
  一份对留样进行化学和微生物全检的行动计划和时间表，以确定所有销售至美国且仍在效期内的药品批次的质量

- A summary of all results obtained from testing retain samples from each batch. If such testing reveals substandard quality drug products, take rapid corrective actions, such as notifying customers and product recalls.
  一份对每批留样检测所得所有结果的总结。如果检测显示有药品质量不合格，则快速采取纠正措施如通知客户和召回产品
- A comprehensive, independent assessment of your laboratory practices, procedures, methods, equipment, documentation, and analyst competencies. Based on this review, provide a detailed plan to remediate and evaluate the effectiveness of your laboratory system.
  一份对你们实验室规范、程序、方法、设备、文件和化验员能力的全面独立评估。根据该审核结果，提交一份详细的计划补救和评估你们实验室系统的有效性

3.Failure to establish an adequate quality control unit and the responsibilities and procedures applicable to the quality control unit are not in writing and fully followed (21 CFR 211.22(a) and (d)).

未能建立足够的质量部门，未书面制订并完全遵守质量部门适用职责与程序（21 CFR 211.22(a) and (d)）。

Your quality unit (QU) did not have adequate procedures describing the appropriate oversight of your manufacturing operation. For example, you lacked written procedures describing the review of test records, raw electronic data, and batch production records prior to approval and release.

你们的质量部门（QU）没有足够的程序阐明对你们生产操作的适当监管。例如，你们缺少书面程序说明在批准和放行之前对检测记录、原始电子数据和批生产记录的审核。

Additionally, your QU released and distributed batches despite deviations from the batch record. The deviations were not investigated or reviewed by the QU prior to the release of the batch. For example, although the batch record for (b)(4) states a standard (b)(4), the operator recorded a stir time of one hour and forty minutes.

另外，你们的 QU 未理会批记录偏差就放行并销售了一些批次。这些偏差在批放行之前未经 QU 调查或审核。例如，虽然 XX 批记录写明了标准 XX，但操作员记录的搅拌时间为 1 小时 40 分钟。

Your response is inadequate. You did not explain why you distributed drug product despite deviations from the batch record. Furthermore, you did not sufficiently address the need for improvements in the disposition of lots and other quality-related functions of your quality system.

你们的回复是不充分的。你们并未解释你们为何不顾批记录中的偏差就将药品销售。另外，你们并未充分解决对批处置的改进需求，以及其它你们质量体系的质量相关职能。

Multiple deviations noted in your manufacturing process cause concern about the quality of your drug product. It is essential that executive management supports and implements effective actions to address the source(s) of the variations and ensure a continued state of control.

在你们的生产工艺中标注的多起偏差引起了对你们药品质量的关切。高级管理层支持并实施有效措施解决波动源并确保持续受控状态是基本要求。

Your firm's quality systems are inadequate. See FDA's guidance document Quality Systems Approach to Pharmaceutical CGMP Regulations for help implementing quality systems and risk

management approaches to meet the requirements of CGMP regulations 21 CFR, parts 210 and211 at https://www.fda.gov/media/71023/download

你公司的质量体系不充分。参见 FDA 指南文件"药品 CGMP 法规的质量体系方法"。

In response to this letter provide the following:

在回复本函时请提交:

- A comprehensive assessment and remediation plan to ensure your QU is given the authority and resources to effectively function. The assessment should also include, but not be limited to:
  一份全面评估和补救计划，确保你们的 QU 被赋予权力和资源可有效运转。评估还应包括但不仅限于:
  - A determination of whether procedures used by your firm are robust and appropriate
    你们公司所用程序是否稳健和恰当的判定
  - Provisions for QU oversight throughout your operations to evaluate adherence to appropriate practices
    QU 监管你们整个操作以评估是否遵守适当的规范的条款
  - A complete and final review of each batch and its related information before the QU disposition decision
    QU 在批处置决策前对每个批次及其相关信息进行全面最终审核
  - Oversight and approval of investigations and discharging of all other QU duties to ensure identity, strength, quality, and purity of all products
    监管和批准调查，履行所有其它 QU 义务以确保所有产品的鉴别、含量、质量和纯度
- A detailed summary of your validation program for ensuring a state of control throughout the product lifecycle, along with associated procedures.
  一份你们确保产品生命周期中受控状态的验证程序及相关程序的详细总结
- A description of your program for process performance qualification and ongoing monitoring of both intra-batch and inter-batch variation to ensure a continuing state of control.
  对你们工艺性能确认和持续监测批间与批内波动从而确保持续受控状态的程序说明

CGMP Consultant Recommended CGMP 顾问建议

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualified as set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements if your firm intends to resume manufacturing drugs for the U.S. market. We also recommend that the qualified consultant perform a comprehensive audit of your entire operation for CGMP compliance and that the consultant evaluates the completion and efficacy of your corrective actions and preventive actions before you pursue resolution of your firm's compliance status with FDA.

鉴于我们在你公司所发现的违规情况，我们强烈建议你们使用一位有 21 CFR 211.34 所述资质的顾问来协助你们公司符合 CGMP 要求。我们亦建议该具备资质的顾问对你们整体运营情况进行药品 CGMP 合规情况全面审计，并由其在你们寻求满足 FDA 合规要求之前对你们 CAPA 的完成情况和有效性进行评估。

Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

你们使用顾问并不能解除你们公司符合 CGMP 的义务。你们公司的高级管理层仍负有义务全面解决所有缺陷，确保持续 CGMP 符合性。

Conclusion 结论

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of other violations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

FDA placed your firm on Import Alert 66-40 on November 27, 2019.

FDA 已于 2019 年 11 月 27 日将你公司置于进口禁令 66-40 中。

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产的新申报和增补申报的批准。

Failure to correct these violations may also result in the FDA continuing to refuse admission of articles manufactured at Guangzhou Tinci Materials Technology Co., Ltd. 8th Kangda Road, Yunpu Industrial Zone, Huangpu District, Guangzhou, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Articles under this authority may besubject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to COMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351 (a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

22. 320-20-22 2020-02-11 Chemland Co., Ltd 韩国

Dear Mr. Lee:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Chemland Co., Ltd, FEI 3010165627,at 77 Gaejeongsaneopdanji-ro, Miyang-myeon, Anseong-si, Gyeonggi-do, from August 19 to 22, 2019.

美国 FDA 于 2019 年 8 月 19 日至 22 日检查了你们位于韩国的 Chemland Co.,Ltd 生产场所。

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. Sec Title 21 Code of Federal Regulations (CFR). parts 210 and 211 (21 CFR parts 210 and 211).

本警告信总结了制剂生产严重违反 CGMP 的行为。参见 21CFR 第 210 与 211 部分。

Because your methods, facilities, or controls for manufacturing. processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501 (a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C.351 (a)(2)(B).

由于你们的制剂生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的药品根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C. 351(a)(2)(B)被认为是掺假药品。

We reviewed your September 11, 2019, response to our Form FDA 483 in detail. Your response is inadequate because it did not provide sufficient detail or evidence of corrective actions to bring your operations into compliance with CGMP.

我们已详细审核了你公司 2019 年 9 月 11 日对我们 FDA483 表的回复。你们的回复是不充分的，因为其中并未提供足够详细的内容或证据，证明纠正措施可使得你们的运营转入 CGMP 合规状态。

During our inspection. our investigator observed specific violations including, but not limited to the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

1. Your firm failed to establish an adequate quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging materials, labeling, and drug products (21 CFR 211.22(a)).

你公司未能建立足够的质量部门，使其具备职责和权力可批准或拒收所有组份、药品容器、密闭器、中间体、包材、标签和成品（21 CFR 211.22(a)）。

Your quality unit (QU) lacked adequate responsibilities and authorities to assure reliable operations. For example:

你们的质量部门（QU）缺乏足够的职责和权力，无法确保可靠运作。例如：

A. You failed to ensure the audit trail feature was enabled on your Inductively Coupled Plasma - Optical Emission Spectrometry(ICP-OES) instrument to track creation, modification, or deletion of data. This instrument was used to obtain assay results for your drug products.

你们未能确保激活你们的 CIP-OES 仪器上的审计追踪功能以追踪数据的创建、修改或删除。该仪器用于你们药品的含量检测。

B. You stored your master batch records as unlocked Excel files which were open to alteration, duplication, and deletion by unauthorized personnel.

你们将主批记录保存为未锁定的 EXCEL 文件，可被未经授权的人员打开进行修改、复制和删除。

C. Your analysts used open Excel files for documenting sample preparation information and final calculations. These records were not retained. For example, your personnel admitted during the inspection that records and data, such as volume of test solution, sample weight, and final calculations, are not retained.

你们的化验员使用了开放式 EXCEL 文件用于记录样品制备信息和最后的计算。这些记录未保存。例如，你们的人员在检查中承认记录和数据如检测溶液的体积、样品重量和最后计算均未保存。

Manufacturing data must be retained to support CGM Pactivities including but not limited to your batch disposition decisions, stability studies, and investigations.

必须保存生产数据用于支持 CGMP 活动，包括但不仅限于你们的批处置决策、稳定性研究和调查。

In your response, you stated your plan to purchase compliant software for your ICP-OES and to begin using Ecount, your Enterprise Resource Planning program, to issue batch records. You also indicated that you will revise your test record form to capture test information and calculations. Your response is inadequate because it did not include interim control measures to prevent alteration and deletion of data. You also did not assess the impact of releasing products without complete CGMP data.

在你们的回复中，你们声称你们计划为你们的 ICP-OES 采购合规软件，并开始使用 Ecount，即你们的 ERP 程序用于签发批记录。你们还说你们会修订你们的检验记录表，以采集检测信息和计算信息。你们的回复是不充分的，因为其中并未包括为防止修改和删除数据而采取的临时控制措施。你们亦未评估没有完整的 CGMP 数据就放行产品的影响。

In response to this letter, provide: 在回复本函时请提交：

- Your interim controls to prevent deletion and modification of data for all computerized systems used in COMP-related operations at your facility.
  你们为防止删除和修改你们工厂 CGMP 相关操作中所用的所有计算机化系统数据而制订的临时控制措施
- Timelines for the implementation and qualification of your updated software for the ICP-OES. Include procedural updates and associated training for user role assignments, review of audit trail data, and other appropriate controls.
  实施和确认你们更新后的 ICP-OES 软件的时间表。包括程序更新和用户身份分配的相关培训、审计追踪数据的审核以及其它相关控制
- A complete assessment of documentation systems used throughout your manufacturing and laboratory operations to determine where documentation practices are insufficient. Include a detailed corrective action and preventive action (CAPA) plan that comprehensively remediates your firm's documentation practices to ensure you retain attributable, legible, complete, original, accurate, and contemporaneous records throughout your operation.

在你们整个生产和实验室操作中所用的文件记录的完整评估，以确定哪些文件规范不充分。包括详细的 CAPA 计划，全面补救你公司的文件规范，以确保你们在整个操作中能保存可追溯的、清楚的、完整的、原始的、准确的和同步记录。

- A comprehensive, independent assessment of your laboratory practices, procedures, methods, equipment, documentation, and analyst competencies. Based on this review, provide a detailed CAPA plan to remediate the effectiveness of your laboratory system.
  一份对你们实验室规范、程序、方法、仪器、文件和化验员能力的全面独立评估。根据这些审核，提交一份详细的 CAPA 计划用于补救你们实验室系统的有效性。
- A comprehensive, independent assessment of your overall system for investigating deviations, discrepancies, complaints, out-of-specification results, and failures. Provide a detailed action plan to remediate this system. Your action plan should include, but not be limited to, significant improvements in investigation competencies, scope determination,root cause evaluation, CAPA effectiveness, quality unit oversight, and written procedures. Address how your firm will ensure all phases of investigations are appropriately conducted.
  一份对你们偏差、差异、投诉、OOS 结果和失败调查的全面系统的全面独立评估。提交一份详细的行动计划以补救该系统。你们的行动计划应包括但不仅限于对调查能力、范围界定、根本原因评估、CAPA 有效性、质量部门监管和书面程序的重大改进。说明你们公司要如何确保恰当地执行了所有调查阶段。
- A comprehensive assessment and remediation plan to ensure your QU is given the authority and resources to effectively function.The assessment should also include, but not be limited to:
  一份全面评估和补救计划，以确保你们的 QU 被赋予权力和资源可有效运转。评估还应包括但不仅限于：
  - A determination of whether procedures used by your firm are robust and appropriate
    你们公司所用程序是否稳健和恰当的判定
  - Provisions for QU oversight throughout your operations to evaluate adherence to appropriate practices
    QU 监管你们整个操作以评估是否遵守适当的规范的条款
  - A complete and final review of each batch and its related information before the QU disposition decision
    QU 在批处置决策前对每个批次及其相关信息进行全面最终审核
  - Oversight and approval of investigations and discharging of all other QU duties to ensure identity, strength, quality, and purity of all products
    监管和批准调查，履行所有其它 QU 义务以确保所有产品的鉴别、含量、质量和纯度

Also describe how top management supports quality assurance and reliable operations, including but not limited to timely provision of resources to proactively address emerging manufacturing/quality issues and to assure a continuing state of control.

还要阐明高级管理层如何支持质量保证和可靠的操作，包括但不仅限于及时提供资源以主动解决新发生的生产/质量问题和确保持续受控状态。

2. Your firm failed to establish written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess (21 CFR 211.100(a)).

你公司未能建立书面生产和工艺控制程序，设计用以确保你们生产的药品具备其理当具备或显示具备的鉴别、含量、质量和纯度（21 CFR 211.100(a)）。

Your firm failed to validate the manufacturing processes for your (b)(4) over-the-counter (OTC) drug products. In addition, the inspection found that (b)(4) of a batch of (b)(4) was (b)(4) of a different batch of (b)(4). This operation was not included in your master batch record and there is no assurance that the quality of the product was not adversely affected.

你公司未验证你们 OTC 药品 XX 的生产工艺。另外，检查发现一批 XX 不同于批次 XX。该操作并未包括在你们的主批记录中，不能确保产品质量未受到不良影响。

You also lacked qualification for your (b)(4) and your ICP-OES instrument. This equipment was used to manufacture your products and for release testing.

你们对你们的 XX 和你们的 ICP-OES 仪器亦未进行确认。该设备和仪器分别被用于生产你们的产品及放行检测。

Furthermore, you lacked appropriate written cleaning procedures and cleaning validation for the (b)(4). Your personnel stated that this equipment was not disassembled after use and instead was cleaned as a single unit. During the inspection, a cleaning procedure was verbally described to the investigator. This equipment was used in the manufacture of (b)(4) OTC drug products and was non-dedicated until June 2019.

另外，你们对 XX 缺少适当的书面清洁程序和清洁验证。你们的人员声称该设备在使用之后未拆卸，而是作为整个单元进行清洁。在检查期间，有人向检查员口头讲解了一套清洁程序。该设备被用于生产 XX OTC 药品，截止 2019 年 6 月时并非专用。

In your response, you stated that you will retain a CGMP consulting firm to qualify your equipment used to manufacture these drugs and that you will also conduct process validation studies. You also committed to revise your cleaning procedures for the (b)(4). Your response is inadequate because you did not provide a detailed validation plan for your products or equipment. You also failed to provide interim controls until your CAPA are fully implemented.

在你们的回复中，你们声称你们会聘请 CGMP 顾问公司确认你们用于生产这些药品的设备，你们还会执行工艺验证研究。你们还承诺要修订你们的 XX 清洁程序。你们的回复不充分，因为你们并未提供你们产品或设备的详细验证计划。你们未提供全面实施 CAPA 前的临时控制。

Process validation evaluates the soundness of design and state of control of a process throughout its lifecycle. Each significant stage of a manufacturing process must be designed appropriately and assure the quality of raw material inputs, in-process materials, and finished drugs. Process qualification studies determine whether an initial state of control has been established.

工艺验证评估的是工艺生命周期中其设计合理性和受控状态。每个生产工艺的重大阶段均必须进行恰当设计，确保原料输入、中间体和成品的质量。工艺确认研究会确定是否建立初始的受控状态。

Successful process qualification studies are necessary before commercial distribution. Thereafter, ongoing vigilant oversight of process performance and product quality is necessary to ensure you maintain a stable manufacturing operation throughout the product lifecycle.

在商业化销售之前必须完成成功的工艺确认研究。因此，持续严格监测工艺性能和产品质量是确保你们在产品生命周期中维护稳定的生产操作所必须的。

See FDA's guidance for industry, Process Validation: General Principles and Practices, at: https://www.fda.gov/downloads/drugs/guidances/ucm070336.pdf

参见 FDA 行业指南"工艺验证通则和规范"。

In response to this letter, provide: 在回复本函时请提交：

- A detailed summary of your validation program for ensuring a state of control throughout the product lifecycle, along with associated procedures. Describe how your program ensures appropriate design, process performance qualification, and vigilant monitoring of both intra-batch and inter-batch variation to ensure an ongoing state of control. Also include your program for qualification of your equipment and facility.
  一份你们验证程序的详细总结，确保整个产品生命周期中的受控状态，以及相关程序。阐述你们程序如何确保适当设计、工艺性能确信和严格监测批间与批内波动，以确保持续受控状态。还要包括你们的设备与设施确认程序。
- A timeline for performing process performance qualification (PPQ) for each of your marketed drug products.
  一份对你们所有已上市药品执行工艺性能确认（PPQ）的时间表
- Your process performance protocol(s), and written procedures for qualification or equipment and facilities.
  你们的工艺性能方案和书面设备与设施确认程序
- Appropriate improvements to your cleaning validation program, with special emphasis on incorporating conditions identified as worst case in your drug manufacturing operation. This should include but not be limited to identification and evaluation of all worst-case:
  你们清洁验证程序的适当改进，特别要强调结合识别为你们药品生产操作中最差情况的条件。其中应包括但不仅限于识别并评估所有最差情形：
  - drugs with higher toxicities
    毒性高的药品
  - drugs with higher drug potencies
    药物效价高的药品
  - drugs or lower solubility in their cleaning solvents
    在其清洁溶剂中溶解度较低的药品
  - drugs with characteristics that make them difficult to clean
    具有难以清洁特性的药品
  - swabbing locations for areas that are most difficult to clean
    最难清洁部位的擦拭取样点
  - maximum hold times before cleaning
    清洁前的最长放置时长

In addition. describe the steps that must be taken in your change management system before introduction of new manufacturing equipment or a new product.

另外要说明引入新生产设备或新产品之前在你们变更管理系统中必须采取的措施

- A summary of updated SOPs that ensure an appropriate program is in place for verification and validation of cleaning procedures for products, processes, and equipment.
  更新后的 SOP 总结，确保具备适当程序对产品、工艺和设备清洁程序进行核查和验证

3. Your firm failed to establish and follow an adequate written testing program designed to assess the stability characteristics of drug products and to use results of stability testing to determine appropriate storage conditions and expiration dates (21 CFR211.166(a)).

你公司未建立和遵守足够的书面检测程序，设计用以评估药品的稳定性特性，以及使用稳定性测试结果确定适当的存贮条件和有效期（21 CFR 211.166(a)）。

You lacked an adequate stability program for your OTC drug products. You initially established a (b)(4) shelf life based on insufficient accelerated and long-term stability data. Only one batch of each OTC product was included in these studies. The accelerated stability studies consisted of only (b)(4) at (b)(4) with no relative humidity controls. Your long-term stability studies were conducted at "(b)(4)" in your quality control laboratory, which was not controlled or monitored for temperature or humidity.

你们 OTC 药品缺少足够的稳定性程序。你们最初基于不充分的加速和长期稳定性数据制订了 XX 货架期。在该研究中每种 OTC 产品只放了一个批次。加速稳定性研究只包括了 XX 但没有相对湿度控制。你们的长期稳定性研究是在你们 QC 实验室“XX”下做的，对温湿度没有控制和监测。

In addition, your stability timepoints did not include assay tests to demonstrate the active ingredients, (b)(4), remain within specification. Furthermore, your stability and retain samples were packaged in (b)(4) containers while the finished drug product was packaged in (b)(4) containers. Stability samples should be stored in containers that simulate the market container.

另外，你们的稳定性时间点并未包括含量检测，以证明活性成分 XX 仍保持在标准内。另外你们的稳定性和留样包装在 XX 容器中，而成品是包装在 XX 容器中。稳定性样品应存贮在模拟市售包装的容器中。

In your response, you committed to verify the (b)(4) shelf life of your OTC products, purchase stability chambers, and start using (b)(4) containers for retain and stability samples. Your response is inadequate because you failed to provide stability protocols, including all relevant quality attributes and acceptance criteria, and to provide assurance that your test methods (e.g., assay) will be adequate to assess drug stability. Further, your response did not provide interim plans to assure that the shelf-lives of your products in distribution are supported by adequate stability studies.

在你们的回复中，你们承诺要核查你们 OTC 药品的 XX 货架期，采购稳定性考察箱，并开始使用 XX 容器用于留样和稳定性样品。你们的回复不充分，因为你们未提交稳定性方案，包括所有相关质量属性和可接受标准，亦未能保证你们的检测方法（例如含量）能充分评价药品稳定性。还有，你们的回复并未提交保证你们药品货架期有足够的稳定性研究支持的临时计划。

In response to this letter. provide: 在回复本函时请提交：

- A comprehensive, independent assessment and CAPA plan to ensure the adequacy of your stability program. Your remediated program should include. but not be limited to:

一份全面独立的评估和 CAPA 计划，以确保你们的稳定性程序的充分性。你们的补救程序应包括但不仅限于：

- Stability indicating methods
  稳定性指示性方法
- Stability studies for each drug product in its marketed container-closure system before distribution is permitted
  批准销售之前每种药品在其市售包装中的稳定性研究
- An ongoing program in which representative batches of each product are added each year to the program to determine if the shelf-life claim remains valid
  每年将每种药品代表批次加入程序以确定货架期声明是否保持有效的持续计划
- Detailed definition of the specific attributes to be tested at each station (timepoint)
  在每个时间点要检测的具体属性的详细规定

• All procedures that describe these and other elements of your remediated stability program
  阐述你们经过补救的稳定性计划中这些和其它要素的所有程序

Data Integrity Remediation 数据完整性补救措施

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. See FDA's guidance document Data integrity and Compliance With Drug CGMP for guidance on establishing and following CGMP compliant data integrity practices at https://www.fda.gov/media/119267/download.

你们的质量体系不能充分确保数据的准确性和完整性，无法支持你们生产的药品的安全性、有效性和质量。参见 FDA 指南文件“数据完整性和药品 GMP 合格”指导建立和遵守 CGMP 合格数据完整性规范。

We acknowledge that you are using a consultant to audit your operation and assist in meeting FDA requirements.

我们知悉你们正聘用顾问对你们的操作进行审计并协助你们符合 FDA 要求。

In response to this letter, provide the following: 在回复此函时请提交以下信息：

A. A comprehensive investigation into the extent ofthe inaccuracies in data records and reporting including results of the data review for drugs distributed to the United States. Include a detailed description of the scope and root causes of your data integrity lapses.

一份对销售至美国的药品数据记录和报告不准确性程度包括数据审核结果的全面调查。要包括一份对你们数据完整性问题范围和根本原因的说明。

B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity and analyses of the risks posed by ongoing operations.

你们药品质量中所发现的不合格情况的潜在影响的当前风险评估。你们的评估应包括由于受到数据完整性问题影响的药品放行导致的患者风险的分析，以及持续运营所具有的风险。

C. A management strategy for your firm that includes the details of your global CAPA plan. The detailed corrective action plan should describe how you intend to ensure the reliability and

completeness of all data generated by your firm including microbiological and analytical data, manufacturing records, and all data submitted to FDA.

你们公司的管理策略，包括你们全球 CAPA 计划详细情况。详细的 CA 计划，描述你们准备如何确保你们生成的所有数据的可靠性和完整性，包括包括微生物和分析数据、生产记录和所有提交给 FDA 的数据。

CGMP Consultant Recommended CGMP 顾问建议

Based upon the nature of the violations we identified at your firm, if your firm intends to resume manufacturing drugs for the U.S. market, we strongly recommend engaging a consultant qualified as set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements. We also recommend that the qualified consultant perform a comprehensive audit of your entire operation for CGMP compliance and that the consultant evaluates the completion and efficacy of your corrective actions and preventive actions before you pursue resolution of your firm's compliance status with FDA.

鉴于我们在你公司所发现的违规情况，我们强烈建议你们使用一位有 21 CFR 211.34 所述资质的顾问来协助你们公司符合 CGMP 要求。我们亦建议该具备资质的顾问对你们整体运营情况进行药品 CGMP 合规情况全面审计，并由其在你们寻求满足 FDA 合规要求之前对你们 CAPA 的完成情况和有效性进行评估。

Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

你们使用顾问并不能解除你们公司符合 CGMP 的义务。你们公司的高级管理层仍负有义务全面解决所有缺陷，确保持续 CGMP 符合性。

Conclusion 结论

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of other violations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

FDA placed your firm on Import Alert 66-40 on December 17, 2019.

FDA 已于 2019 年 12 月 17 日将你公司置于进口禁令 66-40 中。

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产的新申报和增补申报的批准。

Failure to correct these violations may also result in the FDA continuing to refuse admission of articles manufactured at Chemland Co., Ltd, 77 Gaejeongsaneopdanji-ro, Miyang-myeon,

Anseong-si, Gyeonggi-do into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C.381(a)(3). Articles under this authority may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&CAct, 21 U.S.C. 351(a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

23. 320-20-23 2020-02-13 JHS Svendgaard Hygiene Products Ltd. 印度

Dear. Mr. Nanda:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, JHS Svendgaard Hygiene ProductsLtd., FEI 3009223273, at Trilokpur Road, Kheri, Kala-Amb, Sirmour, Hirnachal Pradesh, from August 19 to 22, 2019.

美国 FDA 于 2019 年 8 月 19 日至 22 日检查了你们位于印度的 JHS Svendgaard Hygiene Products Ltd.（FEI3009223273）生产场所。

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See Title 21 Code of Federal Regulations (CFR), parts 210 and 2 11 (21 CFR parts 210 and 211).

本警告信总结了制剂生产严重违反 CGMP 的行为。参见 21CFR 第 210 与 211 部分。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug product is adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

由于你们的制剂生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的药品根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C. 351(a)(2)(B)被认为是掺假药品。

We reviewed your September 9, 2019, response to our Form FDA 483 in detail.

我们已详细审核了你公司 2019 年 9 月 9 日对我们 FDA483 表的回复。

During our inspection, our investigator observed specific violations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

1. Your firm failed to validate and establish the reliability of your component supplier's test analyses at appropriate intervals (21 CFR 211.84(d)(2)).

你公司未验证和并以适当时间间隔建立你们组份供应商的分析结果可靠性（21 CFR 211.84(d)(2)）。

You lacked adequate testing of the incoming (b)(4) active pharmaceutical ingredient (API) to determine assay and other appropriate quality attributes. Instead, your firm relied on your suppliers' certificates of analyses (COA) without establishing the reliability of the suppliers' analyses through appropriate validation.

你们未对进厂 XX API 进行足够检测以确定其含量和其它适当的质量属性。相反，你公司依赖于你们供应商的 COA，却没有通过适当验证建立起供应商分析的可靠性。

You must test each component for conformity with appropriate written specifications for purity, strength, and quality unless and until you have appropriately qualified the suppliers and validated their test results at appropriate intervals.

你们必须对每种组分进行检测，确定其符合适当的书面纯度、含量和质量标准，直到你们对供应商进行适当的确认，并以适当时间间隔验证其检验结果。

In your response, you stated that you have developed a standard operating procedure (SOP) to qualify your suppliers. However, your response is inadequate in that it lacks specificity regarding your validation program. Additionally, your response did not address retrospective assessment of your over-the-counter (OTC) drug products such as (b)(4) which have been manufactured with components that have not been adequately tested to ensure adherence to quality attribute specifications.

在你们的回复中，你们声称你们已制订 SOP 对你们的供应商进行确认。但是你们的回复是不充分的，其中没有具体说明你们的验证计划。另外，你们的回复并未说明你们对 OTC 药品的回顾性评估，如 XX 生产所用组份未经充分检测以确保其符合质量属性标准。

In response to this letter, provide the following:

在回复本函时请提交以下内容：

- A comprehensive, independent review of your material system to determine whether all suppliers of components, containers, and closures are each qualified and the materials are assigned appropriate expiration or retest dates. The review should also determine whether incoming material controls are adequate to prevent use of unsuitable components, containers, and closures.
  一份对你们物料系统的全面独立审核，确定是否所有组份、容器和密闭器的供应商均一一确认，且物料被给定了适当的效期或复验期。审核还应确定对进厂物料的控制是否足以防止使用不适当的组份、容器和密闭器。
- The chemical and microbiological quality control specifications you use to test and release each incoming lot of component for use in manufacturing.
  你们用于检测和放行每批组份用于生产的化学和微生物质量控制标准。
- A description of how you will test each component lot for conformity with all appropriate specifications for identity, strength, quality, and purity. If you intend to accept any results from your suppliers' COA instead of testing each component lot for strength, quality, and purity, specify how you will robustly establish the reliability of your suppliers' results through initial validation as well as periodic re-validation. In addition, include a commitment to always conduct at least one specific identity test for each incoming component lot.
  说明你们准备如何检测每批组份，确定其符合所有适当的鉴别、含量、质量和纯度标准。如果你们准备接受你们供应商的 COA 中的任何结果，取代你们对每批组份的含量、质量和纯度检测，则请说明你们准备如何通过初始验证和定期重新验证稳定地建立你们供应商结果的可靠性。另外，要包括一份承诺保证会一直对每批进厂组份执行至少一项专属鉴别。
- A summary of results obtained from testing all components to evaluate the reliability of the COA from each component manufacturer. Include your SOP that describes this COA validation program.
  一份对所有组份进行检测所得结果的总结，以评估每个组份生产商 COA 的可靠性。要包括一份你们的 SOP 说明该 COA 验证程序。

2. Your firm failed to establish and document the accuracy, sensitivity, specificity, and reproducibility of its test methods (21CFR 211.165(e)).

你公司未建立和记录其检测方法的准确性、灵敏度、专属性和重复性（21 CFR 211.165(e)）。

Your firm lacked appropriate validation (or verification, for United States Pharmacopeia (USP) compendial methods) of your analytical test methods used to determine acceptability of your drug product before release for distribution.

你们公司对你们用于在放行销售之前确认你们药品可接受度的分析方法缺乏适当的验证（或确认，对于 USP 药典方法而言为确认）。

Analytical methods must be validated to show they are suitable for their intended use, and equivalent or better than applicableUSP compendial methods. Verifying the accuracy, sensitivity, specificity,and reproducibility of your test methods is essential to determine if the drug products you manufacture meet established specification for chemical and microbial attributes.

分析方法必须进行验证，证明其适合于其既定用途，并且等同或优于适用的 USP 药典方法。确认你们检验方法的准确性、灵敏度、专属性和重复性是确定你们生产的药品是否符合既定化学和微生物属性标准的基础。

During the inspection, our investigator also noted that your firm lacked identity testing for your finished drug product. Without this testing, you do not have scientific evidence that the drug product batches you manufactured met their established specifications prior to release.

在检查期间，我们的检查员还注意到你公司对你们的成品缺乏鉴别测试。没有此项测试，你们就没有科学证据证明你们所生产的药品批次在放行之前符合其既定标准。

In your response, you stated that all the required methods have been prepared and documented. Your response is inadequate becauseyou did not provide sufficient information regarding the validation or verification of your test methods for (b)(4) concentration and identity, including a timeframe to complete method validation or verification.

在你们的回复中，你们声称所有要求的方法均已起草成为书面文件。你们的回复是不充分的，因为你们并未提交你们 XX 浓度和鉴定的方法验证或确认方面足够的信息，包括完成方法验证或确认的时间表。

In response to this letter, provide the following:

在回复本函时请提交以下内容：

- A comprehensive independent assessment of your laboratory practices, procedures, methods, equipment, documentation, andanalyst competencies. Based on this review, provide a detailed plan to remediate and evaluate the effectiveness of your laboratory system.
  一份你们实验室做法、程序、方法、设备、文件和化验员能力的全面独立评估。根据此回顾，提交一份详细的补救计划，并评估你们实验室系统的有效性。
- A list of chemical and microbial specifications, including test methods, used to analyze each batch of your drug products before batch disposition decisions.
  一份用于批处置决策之前分析你们每批药品的化学和微生物质量标准清单，包括检验方法。
  - An action plan and timelines for conducting full chemical and microbiological testing of retain samples to determine the quality of all batches of drug product distributed to the United States within expiry.
    一份对留样执行全面化学和微生物检测的行动计划和时间表，以确定所有销售至美国且仍在效期内的药品批次的质量。

- A summary of all results obtained from testing retain samples from each batch. If such testing reveals substandard quality drug products, take rapid corrective actions, such as notifying customers and product recalls.
  对每批留样检测所得所有结果的总结。如果检测结果显示有药品质量不合格，则采取快速纠正措施，如通知客户和召回产品。

3.Your firm failed to establish adequate written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess, and to follow all of its written production and process control procedures (21 CFR 211.100 (a) and (b)).

你公司未建立足够的生产和工艺控制书面程序，以确保你们生产的药品具备其理当具备或标示具备的鉴别、含量、质量和纯度，并遵守所有书面生产和工艺控制程序（21 CFR 211.100 (a) and (b)）。

Your firm lacks an adequate process validation program. You failed to follow your written procedure for process validation and implement a program that ensures an ongoing state of control throughout the lifecycle of your drug product. Your firm also failed to validate your current cleaning procedures.

你公司缺少足够的工艺验证程序。你们未遵守你们的书面工艺验证程序，未执行某个程序以确保你们的药品在其生命周期中处于持续受控状态。你公司亦未验证你们当前的清洁程序。

In your response, you stated that the manufacturing processes and cleaning validation will be "revalidated." However, your response is unclear because, at the time of inspection, your management indicated that process validation and cleaning validation had not been conducted. Please explain this discrepancy. Your response is inadequate because it lacked sufficient information on your planned validation activities, including timelines for completion and draft protocols. Furthermore, you did not address the effects of your lack of process validation on the products in the market within expiry.

在你们的回复中，你们声称生产工艺和清洁验证将进行“再验证”。但是你们的回复并不明确，因为在检查期间，你们的管理人员说并未执行工艺验证和清洁验证。请解释为何有不同说法。你们的回复是不充分的，因为其中缺少你们所计划的验证活动的详细信息，包括完成和起草方案的时间表。另外，你们并未说明你们缺少工艺验证对已销售但仍在效期内药品的影响。

Process validation evaluates the soundness of design and state of control of a process throughout its lifecycle. Each significant stage of a manufacturing process must be designed appropriately and assure the quality of raw material inputs, in-process materials, and finished drugs. Process qualification studies determine whether an initial state of control has been established.

工艺验证评估的是工艺在其生命周期中的设计合理性和受控状态。每个生产工艺重要阶段均必须恰当设计，确保原料输入、中间体和成品的质量。工艺验证研究确定是否建立了初始的受控状态。

Successful process qualification studies are necessary before commercial distribution. Thereafter, ongoing vigilant oversight of process performance and product quality is necessary to ensure you maintain a stable manufacturing operation throughout the product lifecycle. See FDA's guidance document, Process Validation: General Principles and Practices, for general principles and approaches that FDA considers appropriate elements of process validation at http://www.fda.gov/media/71021/download.

在商业化销售之前需要完成成功的工艺确认研究。之后，需要对工艺性能和产品质量进行连续严格的监控，以确保你们在产品生命周期中维护稳定的生产操作。参见 FDA 指南文件“工艺验证通则和规范”。

In response to this letter, provide the following:

在回复本函时请提交以下内容：

- A remediation plan that assures ongoing management oversight throughout the manufacturing lifecycle of all drug products. Provide a more data-driven and scientifically sound program that identifies sources of process variability and assures that manufacturing, including production operations, meets appropriate parameters and quality standards. This includes, but is not limited to, evaluating suitability of equipment for its intended use, ensuring quality of input materials, determining the capability and reliability of each manufacturing process step and its controls, and vigilant ongoing monitoring of process performance and product quality.
  一份补救计划，确保在所有药品的生产生命周期中持续的管理监管。提交一份有数据支持的科学合理程序，识别工艺波动的来源，确保生产包括生产操作符合适当的参数和质量标准。其中包括但不仅限于评估设备适合于其既定用途、确保输入物料的质量、确定每个生产工艺步骤及其控制的能力和可靠性，以及连续严格监测工艺性和产品质量。
- A detailed summary of your validation program for ensuring a state of control throughout the product lifecycle, along with associated procedures. Describe your program for process performance qualification, and ongoing monitoring of both intra-batch and inter-batch variation to ensure a continuing state of control.
  一份对你们确保整个产品生命周期中其处于受控状态的验证程序的详细总结，以及相关程序。阐述你们的工艺性能确认程序，以及对批间和批内波动的连续监测，从而确定工艺的持续受控状态。
- A timeline for performing appropriate process performance qualification for each of your marketed drug products.
  一份对你们所有已上市药品执行适当工艺性能确认的时间表。
- Your process performance protocol(s) and written procedures for qualification of equipment and facilities.
  你们设备和设施确认方案和书面程序。
- Appropriate improvements to your cleaning validation program, with special emphasis on incorporating conditions identified as worst case in your drug manufacturing operation. This should include but not be limited to identification and evaluation of all worst-case:
  对你们的清洁验证程序进行的适当改进，特别要强调包括你们药品生产中识别为最差情形的条件。其中应包括但不仅限于识别和评估所有最差情形：
  - drugs with higher toxicities
    高毒性药品
  - drugs with higher drug potencies
    高药物效价药品
  - drugs of lower solubility in their cleaning solvents
    在其清洁溶剂中溶解度低的药品
  - drugs with characteristics that make them difficult to clean
    具有难以清洁特性的药品

- swabbing locations for areas that are most difficult to clean
  最难清洁区域的擦拭点
- maximum hold times before cleaning
  清洁前的最长放置时间

In addition, describe the steps that must be taken in your change management system before introduction of new manufacturing equipment or a new product.

另外，要说明引入新的生产设备或新产品之前你们变更管理系统中必须采取的措施。

- A summary of updated SOPs that ensure an appropriate program is in place for verification and validation of cleaning procedures for products, processes, and equipment.
  一份更新后 SOP 的总结，确保具备适当的产品清洁、工艺和设备确认和验证程序。

4. Your firm's quality control unit failed to exercise its responsibility to ensure drug products manufactured are incompliance with CGMP, and meet established specifications for identity, strength, quality, and purity (21 CFR 211.22).

你公司的质量控制部门未履行其职责，确保药品生产符合 CGMP 要求，并符合既定的鉴别、含量、质量和纯度标准（21 CFR 211.22）。

Your quality unit's oversight of your drug manufacturing operations was inadequate.

你们的质量部门对你们药品生产操作的监管是不充分的。

Your quality unit (QU) failed to report and investigate deviations that could compromise your finished drug products. For example, process parameters recorded by operators in the batch production records were outside the established limits for speed and temperature in several different steps. In one instance, operators changed the predefined (b)(4) setting specified in your batch production record from (b)(4) (unit of (b)(4) not specified). Based on findings such as these, there is a lack of assurance that your firm performs production activities within appropriate parameters that can assure consistent product quality.

你们的质量部门（QU）未报告和调查可能影响你们药品的偏差。例如，操作工在批生产记录中在几个不同步骤中记录的工艺参数超出了既定的速度和温度限度。有一例是操作员修改了你们批生产记录中规定的 XX 设置（XX 单元未写明）。基于此类发现，我们认为你们公司不能保证在可保证持续产品质量的适当参数范围内实施生产活动。

Your QU also failed to ensure that representative batches of (b)(4) were placed on your stability testing program. For example, although numerous batches were manufactured in 2018 and 2019, no batches were placed on your stability testing program.

你们的 QU 亦未能确保将代表性批次放入你们的稳定性测试计划。例如，虽然在 2018 年和 2019 年生产了大量批次，但一批都没有放入你们的稳定性测试计划。

In your response, you provided revised proceduresfor some of the QU functions. Your response lacks a commitment to test batches currently in market to ensure the product meets the quality attributes throughout its expiry.

在你们的回复中，你们提交了一份修订后的一些 QU 职能的程序。你们的回复缺少了一份承诺，保证对当前在售批准的进行检测，以确保这些药品在其有效期内符合其质量属性。

In response to this letter, provide the following:

在回复本函时请提交以下内容：

- A comprehensive assessment and remediation plan to ensure your QU is given the authority and resources to effectively function. The assessment should also include, but not be limited to:
  一份确保你们 QU 被赋予权力和资源有效运作的全面评估和补救计划。评估还应包括但不仅限于：
  - A determination of whether procedures used by your firm are robust and appropriate.
    一份确定你公司所用程序是否稳健恰当的说明
  - Provisions for QU oversight throughout your operations to evaluate adherence to appropriate practices.
    QU 对你们整个操作进行监管以评估其遵守适当规范的条款
  - A complete and final review of each batch and its related information before the QU disposition decision.
    一份在 QU 进行批处置决策之前对每个批次及其相关信息的完整最终审核
  - Oversight and approval of investigations and discharging of all other QU duties to ensure identity, strength, quality, and purity of all products.
    监管和批准调查，履行所有其它 QU 职责，以确保所有药品的鉴别、含量、质量和纯度
  - Retrospective review of all batches released to the market and within expiry.
    对所有已放行销售且在效期内的批次的回顾性审核
  - Your plan to test, with timelines, retain samples of batches currently in the market. This plan should include an assessment of the stability by testing retain samples of your drug product currently on the U.S. market within expiry. Indicate the corrective actions that you will take, including notifying customers, if your testing of any previously released batches yields an out-of-specification result.
    你们对当前在售批次留样的检测计划和时间表。该计划应包括通过对你们当前在美国销售且仍在效期内的药品的留样进行检测而得出的稳定性评估。说明你们要采取的纠正措施，包括如果你们对之前已放行批次得到 OOS 结果时对客户的通知。
- A comprehensive assessment of your overall system for investigating deviations, discrepancies, complaints, OOS results, and failures. Provide a detailed action plan to remediate this system. Your action plan should include, but not be limited to, significant improvements in investigation competencies, scope determination, root cause evaluation, CAPA effectiveness, quality unit oversight, and written procedures. Address how your firm will ensure all phases of investigations are appropriately conducted.
  一份对你们偏差、差异、投诉、OOS 结果和失败调查的整个系统的全面评估。提交一份详细的行动计划补救该系统。你们的行动计划应包括但不仅限于对调查能力、范围确定、根本原因评估、CAPA 有效性、质量部门监管和书面程序的显著改进。说明你们公司要如何确保适当执行了所有调查阶段。

CGMP Consultant Recommended CGMP 顾问建议

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualifiedas set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements.

鉴于我们在你公司所发现的违规情况，我们强烈建议你们使用一位有 21 CFR 211.34 所述资质的顾问来协助你们公司符合 CGMP 要求。

We also recommend that the qualified consultant perform a comprehensive audit of your entire operation for CGMP compliance and that the consultant evaluates the completion and efficacy of your corrective actions and preventive actions before you pursue resolution of your firm's compliance status with FDA.

我们亦建议该具备资质的顾问对你们整体运营情况进行药品 CGMP 合规情况全面审计，并由其在你们寻求满足 FDA 合规要求之前对你们 CAPA 的完成情况和有效性进行评估。

Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoingCGMP compliance.

你们使用顾问并不能解除你们公司符合 CGMP 的义务。你们公司的高级管理层仍负有义务全面解决所有缺陷，确保持续 CGMP 符合性。

Conclusion 结论

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of other violations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

FDA placed your firm on Import Alert 66-40 on January 2, 2020.

FDA 已于 2020 年 1 月 2 日将你公司置于进口禁令 66-40 中。

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产的新申报和增补申报的批准。

Failure to correct these violations may also resultin the FDA continuing to refuse admission of articles manufactured at JHS Svendgaard Hygiene Products Ltd., at Trilokpur Road, Kheri, KalaAmb, Sirmourinto the United States under section 80l(a)(3) of the FD&C Act, 21 U.S.C.381(a)(3). Articles under this authority may be subject to refusal of admission, in that the methods and controls used in their manufacture do notappear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasonsfor delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

24. 320-20-24 2020-02-13 Yibin Lihao Biotechnical Co., Ltd 宜宾市利豪生物科技有限公司

Dear Mr. Tuo:

The U.S. Food and Drug Administration (FDA) conducted an inspection at Yibin Lihao Biotechnical Co., Ltd, FET 3008846564, at Number 5 Binjiang Road, Luolong Industrial Central Park. Yibin, Sichuan, from July 31 to August 6, 2019.

美国 FDA 于 2019 年 7 月 31 日至 8 月 6 日检查了你们位于中国四川宜宾市南溪区罗龙工业园区滨江西路 5 号的宜宾市利豪生物科技有限公司生产场所。

This warning letter summarizes significant deviations from current good manufacturing practice (CGMP) for active pharmaceutical ingredients (API).

本警告信总结了原料药生产严重违反 CGMP 的行为。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your API are adulterated within the meaning of section 501 (a)(2)(B) of the Federal food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351 (a)(2)(B).

由于你们的原料药生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的原料药根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C.351(a)(2)(B)被认为是掺假药品。

We reviewed your August 26, 2019, response to our Form FDA 483 in detail.

我们已详细审核了你公司 2019 年 8 月 26 日对 FDA483 表的回复。

During our inspection, our investigator observed specific deviations including. but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

1. Failure to prepare and use production and control records for each intermediate and APT batch.

未制订和使用各中间体和 APT 批次的生产和检验报告。

Your site produces crude heparin for purification into finished API. During a pre-inspectional call on July 10, 2019, your firm stated to FDA that you had not manufactured any materials for months. At the start of the FDA inspection on July 31, 2019, your firm stated to the investigator that you were not manufacturing crude heparin and were only performing equipment testing.

你们的工厂生产肝素粗品用于最终 API 的精制。在检查之前 2019 年 7 月 10 日的电话里，你公司向 FDA 声称你们有多月未进行生产了。在 FDA 于 2019 年 7 月 31 日检查开始时，你公司向检查员说你们没在生产肝素粗品，只是在进行设备测试。

During a walkthrough of your warehouse, the investigator observed a warehouse employee leaving the warehouse with a fiber drum and inquired about the contents of the drum. Your firm stated that the drum contained (b)(4) bags. However. inspection of the drum revealed two batches of crude heparin manufactured just a few days before the FDA inspection (CU190726, (b)(4), manufacturing date July 26, 2019, and CU 190727, (b)(4), manufacturing date July 27, 2019). When asked about manufacturing and testing records pertaining to these two crude heparin batches, your firm told us that you do not have records for the two crude heparin batches.

在仓库检查时，检查员发现有个仓库员工拿着一只纤维桶离开仓库，于是询问桶里装了什么。你公司说桶里装的 XX 袋。但是对桶进行检查时发现有 2 批肝素粗品是 FDA 检查之前几天刚刚生产的（CU190726，XX，生产日期 2019 年 7 月 26 日，以及 CU190727，XX，生产日期 2019 年 7 月 27 日）。在索取这 2 批肝素粗品的生产和检测记录时，你公司告诉我们你们没有这 2 批肝素粗品的记录。

In your response, you acknowledged the failure to provide timely and complete records for crude heparin batches CU190726 and CU190727 due to deficiencies in your record keeping practices. Additionally, your response indicated that your firm is providing training to warehouse employees and your firm would not sell to European or U.S. markets before "official approval". However, you did not adequately address how you would remediate your documentation practices, nor did you assess the impact of poor documentation practices for distributed drugs.

在你们的回复中，你们承认因你们记录保存规范的缺陷，所以未能及时提供肝素粗品 CU190726 和 CU190727 的完整记录。另外，你们的回复说你公司正在给仓库员工进行培训，你公司在“官方批准”之前不会再向欧洲或美国市场销售产品了。但是，你们并未充分说明你们要如何弥补你们的文件规范，你们亦未评估不良文件规范对已销售药品的影响。

In response to this letter, you should provide:

在回复本函时请提交以下内容：

- A complete reconciliation of all drugs, including crude heparin, distributed from your facility. Include in the reconciliation:
  你们公司销售的所有药品的全部数量平衡，包括肝素粗品。包括以下数据：
  - Batch number
    批号
  - Batch quantity
    批数量
  - Name of drug
    药品名称
  - Date of release
    放行日期
  - Date of shipment
    发货日期
  - Destination of shipment
    发货目的地
  - Destination market
    目的市场
- A complete assessment of documentation systems used throughout your manufacturing and laboratory operations to determine where documentation practices are insufficient. Include a detailed corrective action and preventive action (CAP A) plan that comprehensively remediates your firm's documentation practices to ensure you retain attributable, legible, complete, original, accurate, contemporaneous records throughout your operation.

对你们生产和实验室操作所用文件系统的全面评估，以确定有哪些做法是有缺陷的。要包括一份详细的 CAPA 计划，全面补救你们公司的文件规范，确保你们会保存你们整个操作可追溯、清晰的、完整的、原始的、准确的同步记录。

2. Failure to establish, document, and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel.

未建立、记录和实施有效的质量管理系统，包括管理人员主动参与和适当的生产人员配置。

During the inspection, the investigator observed your firm did not adequately control critical documentation pertinent to the traceability of crude heparin manufactured at your facility. During the walkthrough on July 31, 2019, our investigator observed numerous records on the floor, desks, and cabinets of the Quality Assurance (QA) Office on the third floor of the office building. Some of these records included batch production records for heparin.

在检查期间，检查员发现你公司并未充分控制你工厂所生产的肝素粗品追溯性有关的关键文件。在 2019 年 7 月 31 日检查现场时，我们检查员在行政楼 3 楼的 QA 办公室的地板上、桌子上和柜子里发现大量记录。其中一些记录是肝素批生产记录。

During the inspection, one of your employees stated that these records were generated to support an application for govern mentfunding, but the crude heparin batches specified in the records had not actually been manufactured. However, later during the inspection, on August 2, 2019, your firm stated that all the records in the QA Office were in fact associated with genuine crude heparin batches.

在检查期间，你们一个员工说这些记录是制作来支持政府基金申报的，但记录中所写的肝素粗品批准并未实际生产过。后来在 2019 年 8 月 2 日的检查期间，你公司又说 QA 办公室的所有记录实际上是真实的肝素粗品批次的。

Additionally, even though your Crude Heparin Sodium Inventory and Distribution Record indicated your firm manufactured (b)(4) batches of crude heparin (CU190601 to CU190730) fromJune 1, 2019, to July 30, 2019, your firm was only able to provide complete batch records for two batches, CU190728 and CU190730.

另外，虽然你们的肝素钠粗品库存和销售记录显示你公司在 2019 年 6 月 1 日至 2019 年 7 月 30 日期间生产了 XX 批次肝素粗品（CU190601 至 CU190730），但你公司只能提供 2 批（CU190728 和 CU190730）的完整批记录。

Traceability of crude heparin is a critical part of managing quality. You must ensure that a complete contemporaneous record of each batch of drug manufactured is retained for CGMP purposes. Your system for managing quality is inadequate and calls into question the traceability of all drugs, including crude heparin. manufactured at your facility.

肝素粗品的可追溯性是质量管理的一个关键部分。你们必须确保所生产的每批药品的完整同步记录均得到保存，以符合 GMP 要求。你们的质量管理体系是不充分的，导致在你工厂所生产的所有药品，包括肝素粗品有追溯问题。

For further reference regarding heparin. see the guidance for industry Heparin for Drug and Medical Device Use: Monitoring Crude Heparin for Quality available online at

http://www.fda.gov/downloads/Drugs/GuidanceComplianccRegulatoryInformation/Guidances/UCM291390.pdf.

关于肝素的更多参考资料，参见行业指南“药品和医疗器械用肝素：监测肝素粗品的质量”。

Your response is inadequate because it does not holistically address systemic Quality Unit (QU) deficiencies.

你们的回复是不充分的，因为它并未全面解决 QU 的系统性缺陷。

In response to this letter, you should provide a comprehensive assessment and remediation plan to ensure your firm will establish, document, implement, and maintain a robust system for managing quality involving the active participation of management and appropriate manufacturing personnel. The assessment should also include, but not be limitedto:

在回复本函时，你们应提交一份全面评估和补救计划，以确保你公司会制订、记录、实施和保存稳健的质量管理系统，包括管理人员主动参与和适当的生产人员配置。评估还应包括但不仅限于：

- A determination of whether procedures used by your firm are robust and appropriate.
  确定你公司所用程序是否稳健和恰当
- Provisions for oversight throughout your operations to evaluate adherence to appropriate practices.
  对你们整个操作进行监管以评估是否遵守恰当规范的条款
- A complete and final review of each batch and its related information before the QU disposition decision.
  在 QU 批处理决策之前对每个批次及其信息的完整和最终审核
- Oversight and approval of investigations and discharging of all other QU duties to ensure identity, strength, quality, andpurity of all products.
  监管和批准调查，履行所有其它 QU 职责以确保所有药品的鉴定、含量、质量和纯度

Data Integrity Remediation 数据完整性补救措施

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. See FDA's guidance document Data Integrily and Compliance with Drug CGMP for guidance on establishing and following CGMP compliant data integrity practices at https://www.fda.gov/media/97005/download.

你们的质量体系不能充分确保数据的准确性和完整性，无法支持你们生产的药品的安全性、有效性和质量。参见 FDA 指南文件“数据完整性和药品 GMP 合格”指导建立和遵守 CGMP 合格数据完整性规范。

We strongly recommend that you retain a qualified consultant to assist in your remediation.

我们强烈建议你们聘请一位具备资质的顾问协助你们进行补救。

In response to this letter, you should provide the following:

在回复此函时请提交以下信息：

- A comprehensive investigation into the extent of inaccuracies in data records and reporting, including results of the data review for drugs distributed to the United States. Describe the scope and root causes of your data integrity lapses in detail.
  一份对数据记录和报告不准确性程度的全面调查。在其中详细写明你们数据完整性问题的范围和根本原因。
- A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity and analyses of the risks posed by ongoing operations.
  你们药品质量中所发现的不合格情况的潜在影响的当前风险评估。你们的评估应包括由于受到数据完整性问题影响的药品放行导致的患者风险的分析，以及持续运营所具有的风险。
- A management strategy for your firm that includes the details of your global CAPA plan. The detailed corrective action plan should describe how you intend to ensure the reliability and completeness of all data generated by your firm, including microbiological and analytical data, manufacturing records, and all data submitted to FDA.
  你们公司的管理策略，包括你们全球 CAPA 计划详细情况。详细的纠正计划应写明你们准备如何确保你公司生成的所有数据的可靠性和完整性，包括微生物和分析数据、生产记录和提交给 FDA 的所有数据。

Conclusion 结论

The deviations cited in this letter are not intended to be an all-inclusive list of deviations that exist at your facility/in connection with your products. You are responsible for investigating and determining the causes of these deviations and for preventing their recurrence or the occurrence of other deviations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

FDA placed your firm on Import Alert 66-40 and 55-03 on January 15, 2020.

FDA 已于 2020 年 1 月 15 日将你公司置于进口禁令 66-40 和 55-03 中。

Until you correct all deviations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产的新申报和增补申报的批准。

Failure to correct these deviations may also result in the FDA continuing to refuse admission of articles manufactured at Yibin Lihao Bio-technical Co., Ltd at Number 5 Binjiang Road, Luolong Industrial Central Park, Yibin, Sichuan, into the United States under section 801 (a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Under this authority, articles may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your deviations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

25. 320-20-25 2020-02-16 Essnd Global 印度

Dear Mr. Chilakalpudi:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Essnd Global, FEI 3014466792, atC-176 Maharashtra Industrial Development Corp. (MDIC), Sinnare, Nashik, Maharashtra, India, from September 9 to September 13, 2019.

美国 FDA 于 2019 年 9 月 9 日至 13 日检查了你们位于印度的 Essnd Global（FEI 3014466792）生产场所。

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See Title 21 Code of Federal Regulations (CFR), parts 210 and 211 (21 CFR parts 210 and 211).

本警告信总结了制剂生产严重违反 CGMP 的行为。参见 21CFR 第 210 与 211 部分。

Because your methods, facilities, or controls for manufacturing, processing. packing, or holding do not conform to CGMP, your drug product is adulterated within the meaning of section 501 (a)(2)(B) of the Federal Food. Drug, and Cosmetic Act (FD&C Act). 21 U.S.C. 351 (a)(2)(B).

由于你们的制剂生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的药品根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C. 351(a)(2)(B)被认为是掺假药品。

We have not received a response from your firm regarding corrective actions to the observations identified during the inspection.

我们尚未收到你公司对检查期间所发现缺陷的任何纠正措施回复。

During our inspection, our investigator observed specific violations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

1. Your firm failed to perform, for each batch ofdrug product, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release, and for each batch ofdrug product required to be free of objectionable microorganisms, appropriate laboratory testing, as necessary (21 CFR 211.165(a) and (b)).

你公司未在放行前对每批药品进行适当的实验室检测，保证其满足药品的最终质量标准，包括每种活性成分的鉴别和含量，以及对每批需要不检出致病菌的药品批次在必要时执行适当的实验室检测（21 CFR 211.165(a) and (b)）。

Your firm contract manufactures an over-the-counter (b)(4) drug product. You released your drug product without adequate testing, including identity and strength testing of the active ingredient. In addition, you released your drug product without appropriate testing for total aerobic microbial count and objectionable microorganisms.Testing is essential to ensure that the drug product you manufacture meets established specifications for the chemical and microbial attributes they purport to possess.

你公司受托生产一种 OTC 药品。你们没有进行足够的检测即放行了你们的药品，包括活性物质的鉴别和含量。另外，你们没有对总需氧菌和致病菌进行检测即放行了药品。为确保你们生产的药品符合其理当具备的既定化学和微生物属性就必须进行检测。

In response to this letter, provide the following:

在回复本函时请提交以下内容：

- A list of chemical and microbial specifications, including test methods, used to analyze each lot of your drug products before a lot disposition decision.
  一份用于批处置决策之前分析你们每批药品的化学和微生物质量标准，包括检测方法。
- An action plan and timelines for conducting full chemical and microbiological testing of retain samples to determine the quality of all batches of drug product distributed to the United States that are within expiry.
  一份对留样进行全面化学和微生物检测的行动计划和时间表，以确定销售至美国且仍在效期内的所有药品批次的质量。
- A summary of all results obtained from testing retain samples from each batch. If such testing reveals substandard quality drug products, take rapid corrective actions, such as notifying customers and product recalls.
  一份对每批药品留样进行检测所得所有结果的汇总。如果检测结果显示有药品质量不合格，则快速采取纠正措施，如通知客户和召回产品。
- The method to be used for assay testing of your active ingredients.
  用于检测你们活性物质含量的方法。
- Your timeline for implementation of finished product assay testing of your active ingredients.
  你们对产品中活性物质进行含量检测的时间表。

2. Your firm failed to test samples of each component for identity and conformity with all appropriate written specifications for purity, strength, and quality. Your firm also failed to validate and establish the reliability of your component supplier's test analyses at appropriate intervals (21 CFR 211.84(d)(1) and (2)).

你公司未对每种组份样品进行鉴别检测，确定其符合所有适当的书面纯度、含量和质量标准。你公司亦未以适当时间间隔验证和建立你们组份供应商的分析结果的可靠性（21 CFR 211.84(d)(1) and (2)）。

Inadequate Component Testing 对组份检测不够

Your firm failed to adequately test incoming components, including the active ingredient (b)(4), for their identity, purity, strength, and other appropriate quality attributes. Furthermore, you informed our investigator that your clients can send the raw materials, the labeling, and packaging materials without the Certificates of Analysis (COA) to your facility. Identity testing is required for each component lot used in drug product manufacturing, and you can only rely on a COA for other component attributes by validating the supplier's test results at appropriate intervals.

你公司未对进厂组分进行足够的检测，包括活性成分 XX 的鉴别、纯度、含量和其它适当的质量属性。还有，你们告诉我们检查员说你们的客户可能会把没有 COA 的原料、标准和包材发到你们工厂。药

品生产所用的每批组份均需要进行鉴别测试，你们只能在适当时间间隔验证供应商的检测结果后依赖 COA 上组份其它属性结果。

In response to this letter, provide the following:

在回复本函时请提交以下内容：

- The chemical and microbiological quality control specifications you use to test and release each incoming lot of component for use in manufacturing.
  你们用于放行生产所用每批进厂组份的化学和微生物质量控制标准。
- A description of how you will test each component lot for conformity with all appropriate specifications for identity, strength,quality, and purity. If you intend to accept any results from your supplier's COA instead of testing each component lot for strength, quality, and purity, specify how you will robustly establish the reliability of your supplier's results through initial validation as well as periodic re-validation. Inaddition, include a commitment to always conduct at least one specific identity test for each incoming component lot.
  一份关于你们将如何检测每批组份确认其是否符合所有恰当的鉴别、含量、质量和纯度标准的说明。如果你们准备接受你们供应商 COA 中的结果，取代你们自己对每批组份的含量、质量和纯度检测，则请说明你们准备如何通过初始验证和定期再验证稳定建立你们供应商结果的可靠性。另外，要提交一份承诺表明你们会一直对每批进厂组份执行至少一项专属性鉴别测试。
- A summary of results obtained from testing all components to evaluate the reliability of the COA from each component manufacturer. Include your SOP that describes this COA validation program.
  对所有组份检测所得结果的汇总，以评估每个组份生产商的 COA 的可靠性。在其中要包括解释 COA 验证程序的 SOP。
- A comprehensive assessment of your laboratory practices, procedures, methods, equipment, documentation, and analyst competencies. Based on this review, provide a detailed plan to remediate and evaluate the effectiveness of your laboratory system.
  一份对你们实验室规范、程序、方法、设备、文件和化验员能力的全面评估。根据该回顾，提交一份详细的补救计划，并评估你们实验室系统的有效性。

Inadequate (b)(4) System Monitoring XX 系统监测不够

Your firm failed to routinely monitor your (b)(4) system for all required quality attributes. (b)(4) from this system is used as a component in your drug product. Your firm lacked microbiological testing of your (b)(4). Without routine (b)(4) monitoring, you cannot ensure that your (b)(4) meets minimum microbiological standards suitable for the manufacture of your drug product.

你公司未对你们的 XX 系统的所有所需质量属性进行日常监测。来自该系统的 XX 被用作你们药品的一种组份。你公司未对你们的 XX 进行微生物检测。没有日常的 XX 监测，你们无法确保你们的 XX 符合最低微生物标准，适合用于你们的药品生产。

In response to this letter, provide following:

在回复本函时请提交以下内容：

- A procedure for your (b)(4) system monitoring that specifies routine microbial testing of (b)(4) to ensure its acceptability for use in each batch of drug products produced by your firm.
  你们 XX 系统监测的程序，说明对 XX 的日常微生物检测，以确保其可用于你公司生产的每批药品中。
- The current action/alert limits for total counts and objectionable organisms used for your (b)(4) system. Ensure that the total count limits for your (b)(4) are appropriately stringent in view of the intended use of each of the antiseptic drug product produced by your firm.
  目前你们 XX 系统所用的总计数和致病菌行动限/警戒限。确保你们 XX 的总微生物计数限度对于你们公司所生产的所有消毒用药品来说都足够严格。
- A procedure governing your program for ongoing control, maintenance, and monitoring that ensures the system consistently produces water that meets (b)(4), USP monograph specifications and appropriate microbial limits
  你们的持续控制、维护和监测管理程序，确保系统持续产出符合 XX、USP 各论标准和适当微生物限度的水。
- A summary of your program for qualifying and overseeing contract facilities that test your raw materials, (b)(4), or the drug products you manufacture.
  对你们确认和监管检测你们原料 XX 和你们所生产药品的合同场所的程序总结。

3. Failure to establish an adequate quality unit and the responsibilities and procedures applicable to the quality control unit are not in writing and fully followed. (21 CFR 211.22(a) and (d)).

未采用书面方式建立足够的质量部门，制订适用于质量控制部门的职责与程序并全面遵守之（21 CFR 211.22(a) 和 (d)）。

Your firm lacks an adequate quality unit (QU). You informed our investigator that you had not fully established your QU. In addition, you lacked adequate written procedures for numerous quality functions. For example, you could not provide procedures for stability studies, out-of-specification investigations, product release, and deviation investigations. An adequate QU overseeing all manufacturing operations is necessary to consistently ensure drug quality.

你公司缺乏足够的质量部门（QU）。你们告诉我们检查员说你们没有全面建立 QU。另外，你们有许多质量职能缺少足够的书面程序。例如，你们无法提供稳定性研究、OOS 调查、产品放行和偏差调查程序。为持续确保药品质量，有必要由 QU 对所有生产操作进行全面监管。

Your firm's quality systems are inadequate. See FDA's guidance document Quality Systems Approach to Pharmaceutical CGMP Regulations for help implementing quality systems and risk management approaches to meet the requirements of CGMP regulations 21 CFR, parts 210 and 211 at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/quality-systems-approach-pharmaceutical-current-good-manufacturing-practice-regulations.

你公司的质量体系是不充分的。参见 FDA 指南文件“药物 CGMP 法规的质量体系方法”。

In response to this letter, provide a comprehensive assessment and remediation plan to ensure your QU is given the authority and resources to effectively function . The assessment should also include, but not be limited to:

在回复本函时，请提交一份全面评估和补救计划，以确保你们的 QU 被赋予了权力和资源可以有效运作。评估还应包括但不仅限于：

- A determination of whether procedures used by your firm are robust and appropriate.
  确定你公司所用程序是否稳健恰当
- Provisions for QU oversight throughout your operations to evaluate adherence to appropriate practices.
  QU 监管你们整个操作以评估是否遵守适当规范的条款
- A complete and final review of each batch and its related information before the QU disposition decision.
  对每批产品及其相关信息在 QU 批处置决策之前进行的完整最终审校
- Oversight and approval of investigations and discharging of all other QU duties to ensure identity, strength, quality, and purity of all products.
  监管和批准调查，履行所有其它 QU 职责，以确保所有产品的鉴别、剂量、含量和纯度

Responsibilities as a Contractor 作为合同商的义务

Drugs must be manufactured in conformance with COMP. FDA is aware that many drug manufacturers use independent contractors such as production facilities, testing laboratories, packagers, and labelers. FDA regards contractors as extensions of the manufacturer.

药品生产必须符合 CGMP 要求。FDA 了解许多药品生产商使用独立合同方如生产场所、检测实验室、包装商和贴标商。FDA 将合同商作为生产商的外延部分来对待。

You and your customer, (b)(4), have an agreement regarding your manufacture of drug products destined for the United States. You are responsible for the quality of drugs you produce as a contract facility regardless of agreements in place with product owners. You are required to ensure that drugs are made in accordance with section 501 (a)(2)(B) of the FD&C Act for safety, identity, strength, quality,and purity. See FDA's guidance document Contract Manufacturing Arrangements.for Drugs: Quality Agreements at https://www.fda.gov/media/86193/download.

你们和你们的客户 XX 之间订有药品生产的质量协议。作为合同场所，虽然你们与药品所有者订有协议，但你们仍对你们所生产的药品负有义务。你们应确保药品生产符合 FDCA 第 501(a)(2)(B)条款对安全性、鉴别、剂量、质量和纯度的要求。参见 FDA 指南文件“药品合同生产安排：质量协议”。

CGMP Consultant Recommended CGMP 顾问建议

Based upon the nature of the violations we identified at your firm. we strongly recommend engaging a consultant qualifiedas set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements if your firm intends to resume manufacturing drugs for the U.S. market. We also recommend that the qualified consultant perform a comprehensive audit of your entire operation for CGMP compliance and that the consultant evaluates the completion and efficacy of your corrective actions and preventive actions before you pursue resolution of your firm's compliance status with FDA.

鉴于我们在你公司所发现的违规情况，我们强烈建议你们使用一位有 21 CFR 211.34 所述资质的顾问来协助你们公司符合 CGMP 要求。我们亦建议该具备资质的顾问对你们整体运营情况进行药品

CGMP 合规情况全面审计，并由其在你们寻求满足 FDA 合规要求之前对你们 CAPA 的完成情况和有效性进行评估。

Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

你们使用顾问并不能解除你们公司符合 CGMP 的义务。你们公司的高级管理层仍负有义务全面解决所有缺陷，确保持续 CGMP 符合性。

Conclusion 结论

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility.You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of other violations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

FDA placed your firm on Import Alert 66-40 on January 31, 2020.

FDA 已于 2020 年 1 月 31 日将你公司置于进口禁令 66-40 中。

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产的新申报和增补申报的批准。

Failure to correct these violations may also result in the FDA continuing to refuse admission of articles manufactured at Essnd Global, C- 176 Maharashtra Industrial Development Corp. (MDIC), Sinnare, Nashik, Maharashtra, India, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381 (a)(3). Articles under this authority may besubject to refusal of admission. in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act. 21 U.S.C. 351 (a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

26. 320-20-26 2020-02-25 Cipla Limited 印度

Dear Mr. Vohra:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Cipla Limited, FEI 3004081307,at L138; Ll39 - 146; L147/A; L147/1 - 147/3; S103 - 105; S107 - 112; M61 - 63,Verna, Goa, from September 16 to 27, 2019.

美国 FDA 于 2019 年 9 月 16 日至 27 日检查了你们位于印度的 Cipla Limited（FEI 3004081307）生产场所。

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See Title 21 Code of Federal Regulations (CFR), parts 210 and 211 (21 CFR parts 210 and 211).

本警告信总结了制剂生产严重违反 CGMP 的行为。参见 21CFR 第 210 与 211 部分。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

由于你们的制剂生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的药品根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C. 351(a)(2)(B)被认为是掺假药品。

We reviewed your October 21, 2019, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

我们已详细审核了你公司 2019 年 10 月 21 日的回复，并此告知已收到后续通信。

During our inspection, our investigators observed specific violations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

1. Your firm failed to clean, maintain, and, as appropriate for the nature of the drug, sanitize and/or sterilize equipment and utensils at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or established requirements (21 CFR 211.67(a)).

你公司未能以适当时间间隔对设备和工器具进行清洁、维护，以及根据药品特性进行适当消毒和/或灭菌，以防止可能改变药品的安全性、鉴别、含量、质量或纯度使得超出正式或既定要求的故障或污染（21 CFR 211.67(a)）。

Your cleaning procedure for non-dedicated equipment, including your (b)(4) and tablet (b)(4) equipment ((b)(4)), is inadequate. Our investigators observed multiple (b)(4) and (b)(4) containing residues of what appeared to be different products inside the exhaust ducts. Analytical testing conducted by your firm onthe residues collected from this manufacturing equipment confirmed the presence of multiple active ingredients.

你们的非专用设备包括你们的 XX 和压片机设备 XX 的清洁程序不充分。我们检查员发现排风管内有多个 XX 和 XX 残留，看起来是不同产品。你公司对该生产设备上采集的残留进行了分析测试，确认是多种活性成分。

After our inspection, your firm also tested reserve samples of selected batches to assess the potential for cross contamination.Your testing confirmed the presence of active ingredients from a previous product in batches of the next product, including but not limited to:

在我们检查之后，你公司亦检测了所选批次的留样，对潜在交叉污染进行评估。你们检测确认了下一产品的批次中存在前一产品的活性成分残留，包括但不仅限于：

- Residues of (b)(4) active ingredient in (b)(4) tablets
  在 XX 片剂中有 XX 活性成分残留
- Residues of (b)(4) active ingredient in (b)(4)((b)(4)) tablets
  在 XX 片剂中有 XX 活性成分残留

Your response stated that 261 out of 268 batches tested did not show traces of previous product manufactured. You also indicated your belief that the layer of (b)(4) drug product residue seen in the exhaust duct did not pose a risk of contamination to your drug products.

你们的回复声称所测 268 批中有 261 批未发现前一生产产品的痕迹。你们还说你们相信在排风管中看到的 XX 药品残留层对你们的药品没有污染风险。

Your response is inadequate. Retain samples from several batches were found to be contaminated with another drug. However, your response continues to be equivocal about the source of the contamination. This lack of a clear root cause casts doubt on whether you have fully resolved aserious cross-contamination problem.

你们的回复是不充分的。有几批留样已发现被另一药品所污染。但你们的回复仍对污染来源含糊其辞。如此缺乏根本原因说明使得我们严重怀疑你们是否已全面解决严重的交叉污染问题。

In addition, reserve sample testing alone is insufficient to determine the scope of the cross-contamination issue and mitigate risks associated with it. Your response also failed to address that, in about 10 percent of the batches tested, your firm detected unknown peaks eluting at the retention time of a previous product. Your firm indicated that the carryover was not confirmed because the peak did not match the (photo-diode array) peak spectra of the standard solution from the previous product. However, your firm did not provide an adequate investigation that addressed the identity of each unknown peak and its source. Your response also acknowledged challenges with the analytical methodology due to interference of product matrix and poor peak response, but it lacked supporting documentation demonstrating that these challenges were adequately resolved.

另外，仅对留样进行检测并不足以确定交叉污染问题的范围并降低其所带来的风险。你们的回复亦未说明在所检测的批次中有约 10%在前一产品的保留时间检出未知峰的问题。你公司说无法对残留进行确认，因为该峰并不匹配前一产品标准溶液中的峰（二极管阵列 PDA）。但你们公司并未提交充分调查，说明每个未知峰鉴定及其来源。你们的回复亦承认由于产品基质干扰和峰响应不良，因此分析方法颇受挑战，但并没有支持性文件证明已充分解决了这些挑战。

There is no assurance that the scope of your evaluation was comprehensive. Your rationale for testing reserve samples consisted solely in selecting products with the largest amount of potential carryover, as represented by the longest campaign prior to a product changeover. Your selection also did not seem to include a toxicological hazard assessment to identify active ingredients that may represent a higher risk to patients due to low permitted exposure levels. ·

你们无法确保评估的全面性。你们对留样检测合理性仅是在选择有残留数量可能最大的产品，选择的是更换产品之前生产周期最长的批次。你们的选择貌似亦未包括毒性危害评估，识别出因允许暴露水平较低而可能对患者有更高风险的活性成分。

In response to this letter, provide the following:

在回复本函时请提交：

- A comprehensive, independent retrospective assessment of your cleaning effectiveness to evaluate the scope of cross-contamination hazards. Include the identity of residues, other manufacturing equipment that may have been improperly cleaned, and an expanded assessment to determine whether cross-contaminated product batches may have been released for distribution. The assessment should identify any inadequacies of cleaning procedures and practices, and encompass each piece of manufacturing equipment used to manufacture more than one product.
  一份对你们清洁效果的全面独立回顾性评估，评价交叉污染的范围。包括残留的成分，其它可能不当清洁的生产设备，并将评估扩展至确定是否有受到交叉污染的药品被放行销售。该评估应找出清洁程序和做法的所有不足处，并包括生产多个产品的每台生产设备。
- A corrective action and preventive action (CAP A) plan, based on the retrospective assessment, that includes appropriate remediations to your cleaning processes and practices, and timelines for completion. Provide a detailed summary of vulnerabilities in your process for lifecycle management of equipment cleaning. Describe improvements to your cleaning program, including enhancements to cleaning effectiveness; improved ongoing verification of proper cleaning execution for all products and equipment; and all other needed remediations.
  根据回顾性评估制订的 CAPA 计划，其中包括对你们清洁工艺和做法的适当补救措施，以及完成的时间表。提交一份对你们产品清洁生命周期管理中清洁工艺薄弱点的详细总结，阐述对你们清洁程序的改进，包括提高清洁有效性、改进对所有产品和设备清洁执行适当性的核查，以及所有其它必须改进措施。
- In addition to this holistic remediation, provide specific CAPA activities that are being undertaken to effectively remediate the conditions that caused the specific cross-contamination incidents discussed above. Provide an independent review by your consultant that determines the effectiveness of your CAPA, including but not limited to:
  除了这份全面补救措施外，还要提交一份正在有效补救导致上面所讨论的特定交叉污染的情形的特定 CAPA 行动。提交一份你们顾问的独立审核，确定你们 CAPA 的有效性，包括但不仅限于：
  - a list of all enhancements to cleaning and maintenance procedures including specific frequencies and locations to be cleaned in all relevant equipment (e.g., (b)(4), (b)(4), ductwork)
    一份清洁和维护程序的所有改进措施清单，包括具体频次和所有相关设备要清洁的位置（例如 XX、风管）
  - identify any other sources of cross contamination other than (b)(4) equipment, (b)(4) and ductwork
    找出 XX 设备、XX 和风管以外的所有其它交叉污染来源
  - determine the adequacy of your analytical methodology to identify residual carryover
    确定你们鉴定残留物的分析方法的充分性

- your investigations into the unknown (unidentified) peaks detected in your reserve samples
  你们对留样检测中发现的未知（未鉴定）峰的调查
- supporting evidence to demonstrate that the challenges identified during your study, such as interference of product matrix and co-eluting peaks, were adequately resolved
  证明你们研究中所发现的挑战，如产品基质干扰，和重叠峰已得到充分解决的支持性证据
- adequacy of scope of the investigation and its related CAPA
  调查及其相关 CAPA 范围的充分性
- We also understand that you are performing a study to determine cleanliness of ducts and assessing them (b)(4). Explain your interim plan for preventing any cross-contamination from the ducts before the given (b)(4) cleaning interval elapses.
  我们亦了解你们正在进行研究，以确定风管的清洁度，评估 XX。解释你们在指定的 XX 清洁时间间隔之前，防止风管交叉污染的临时计划

- The latest update on your improvements to your cleaning validation program, with special emphasis on incorporating conditions identified as worst case in your drug manufacturing operation. This should include but not be limited to identification and evaluation of all worst-case:
  对你们清洁验证程序改进的最新情况，特别注意结合你们药品生产操作中识别为最差情形的条件。其中包括但不仅限于对所有最差情形的识别和评估：
  - drugs with higher toxicities
    毒性高的药品
  - drugs with higher drug potencies
    药物效价高的药品
  - drugs of lower solubility in their cleaning solvents
    在其清洁溶剂中溶解度较低的药品
  - drug~ with characteristics that make them difficult to clean
    具有难以清洁特性的药品
  - swabbing locations for areas that are most difficult to clean
    最难清洁部位的擦拭取样点
  - maximum hold times before cleaning
    清洁前的最长放置时长

In addition, describe the steps that must be taken in your change management system before introduction of new manufacturing equipment or a new product.

另外要说明引入新生产设备或新产品之前在你们变更管理系统中必须采取的措施

- A full description of the correction factor for recovery that your firm applied in the reserve sample study. Include examples of the calculations and their applications for all seven batches in which you confirmed carryover. Describe whether any lot that appeared to have cross-contamination was discounted from your risk assessment due to the application of your correction factor.
  完整说明你公司在留样研究中所用的回收校正因子。包括计算例子及其在所有 7 个你们确认有残留批次中的应用情况。说明在你们风险评估中是否有因为你们使用了校正因子而低估了交叉污染的批次。

- For the seven products that were found contaminated with traces of other actives, provide details of at least the 30 prior batches manufactured in all non-dedicated equipment. Include the name of the product, stage of processing, all equipment identifications, and dates of manufacture. Also highlight any correlation between these preceding batches, residues present in the ductwork, and finished product batches found to be contaminated.
  对于发现有其它活性成分痕迹的 7 个批次，提交所有非专用设备中生产的之前至少 30 个批准的详细信息，包括产品名称、工艺步骤、所有识别编号和生产日期。亦要突出显示这些之前批次之间的相互关系、网管中的残留以及发现被污染的成品批次。

2. Your firm failed to thoroughly investigate any discrepancy or failure of a batch or any of its components· to meet any of its specifications, whether or not the batch has already been distributed (21CFR 211.192)

你公司未对已放行或未放行批次或其成分不符合其标准的情况进行彻底调查（21 CFR 211.192）。

In late 2018, your firm experienced excessive and atypical High Efficiency Particulate Air (HEPA) filters failures in a short period. More than 45 filters failed due to side leakages and media failures. The filters were often adjacent in the same room. You failed to adequately investigate these filter integrity test failures:

在 2018 下半年，你公司 HEPA 过滤器有短时异常。45 余过滤器因侧面泄漏和介质失败而失效。这些过滤器通常在相同房间里相互接近。你们未能对这些过滤器完整性检测失败进行充分调查。

- DEV-1011-2018-00322, December 2018, Line (b)(4) (Unit (b)(4)), 11 filter failures discovered during routine integrity testing of laminar air flow (LAFs) units IE/153, IE/154, IE/155 and IE/156, in Room (b)(4) (sterile (b)(4) area).
  DEV-1011-2018-00322，2018 年 12 月，产线 XX，在房间 XX（无菌 XX 区）LAF 单元 IE/153、IE/154、IE/155 和 IE/156 日常完整性测试中发现 11 个过滤器失效
- DEV-1011-2018-00246, September 2018, Line (b)(4) (Unit (b)(4)), filter media leakage observed in 14 filters and side leakages observed in 22 filters in sterile corridor, sterile vial filling and plugging, and (b)(4) loading & unloading room area (Room (b)(4)).
  DEV-1011-2018-00246，2018 年 9 月，产线 XX，在无菌走廊、无菌西林瓶灌装间和加塞间，以及 XX 进料&卸料间（房间 XX）发现 14 个过滤器介质泄漏，22 个过滤器侧面泄漏
- DEV-1011-2018-00261, October 2018, filter failure discovered major visible damage during routine cleaning in sterile injectable filling line (b)(4) (Unit (b)(4)), Room (b)(4).
  DEV-1011-2018-00261，2018 年 10 月，在无菌注射剂灌装线日常清洁中发现严重可见破损，过滤器失效

According to your investigations, the most probable causes were gasket deterioration and lack of timely filter replacement. Notably, some filters were installed more than (b)(4) years ago, exceeding the already permissive limit of (b)(4) years in your procedure. Approximately 80 batches intended for the U.S. market (commercial and/or registration) were compromised.

根据你们的调查，最可能的原因是垫圈老化，未及时更换过滤器。特别是有些过滤器是 XX 年前安装的，已经超出了你们程序规定的 XX 年限度。约有 80 批次准备销售至美国的药品（商业化和/或注册批次）受到影响。

HEPA filter integrity is essential to ensure aseptic conditions. Your firm's investigation did not substantially evaluate environmental data and other manufacturing information to sufficiently determine whether the HEPA filter failures compromised the aseptic conditions of your sterile processing line and product quality.

HEPA 过滤器完整性是确保无菌条件的基本要求。你公司的调查并未深入评估环境数据和其它生产信息，以充分确定 HEPA 过滤器失效对你们无菌工艺产线的无菌条件和产品质量的影响。

We acknowledge your commitment to conduct an independent retrospective review of the deviations related to the HEP A filter integrity failures. However, your response is insufficient. Your response lacked sufficient data to support that there was no impact on marketed batches. For example:

我们知晓你们承诺会对 HEPA 过滤器完整性失败有效的偏差进行独立的回顾性审核。但是你们的回复是不充分的，回复中缺少足够的数据来支持已上市批次不受影响。例如：

- Your response' documented missing and/or unclear information in your assessments for products potentially impacted by the filter failures. Unclear elements include but are not limited to correlations of viable excursions with breached filters; inconsistencies in the exposure time of settle plates; and lack of assurance that the cleaning and (b)(4) activities were performed as per the procedures. It is not clear if these and other weaknesses in the investigation have been addressed and CAPA identified.
  你们的回复记录缺失和/或未写明你们对可能受过滤器失效影响的产品的评估信息。不明要素包括但不仅限于：过滤器受损与微生物超标的关联性，沉降碟暴露时长的不一致情况，以及未按程序执行清洁和 XX 活动。不清楚调查中的薄弱点是否已解决，并已制订 CAPA。
- Your response acknowledged a trend increase in environmental monitoring excursions from May 2018 to August 2018 in Room (b)(4), but you lacked sufficient evidence to indicate that these excursions were unrelated to the HEPA filter failures. Your response acknowledged that the environmental trend warranted a review of the existing controls.
  你们的回复承认 2018 年 5 月至 2018 年 8 月 XX 房间内环境监测超标有增长趋势，但你们并没有足够的证据证明这些超标与 HEPA 过滤器失效没有关系。你们的回复承认根据环境趋势分析需要对现有控制进行审核。
- We acknowledge that you rejected certain batches during this period due to microbiological environmental excursions in critical (ISO 5) areas. Your response indicated that approximately 18 batches processed in Unit (b)(4) were rejected from April 2018 to September 2018. Your response failed to include information about what type of failure occurred, the root causes, the impact on other products manufactured under the same conditions, and all CAPA implemented regardless of whether the specific rejected batches were intended for the U.S. market.
  我们知晓你们在此期间因关键（ISO 5）区域微生物环境超标而拒收了一些批次。你们的回复说自 2018 年 4 月至 2018 年 9 月在 XX 单元生产的产品约有 18 批被拒收。你们的回复未包括所发生失败类型的信息、根本原因、对相同条件下所生产其它产品的影响，以及无论所拒批次是否准备销售至美国市场，对其所执行的所有 CAPA。

There is no assurance that all batches produced under inadequate conditions have been thoroughly evaluated, and that your firm has identified all contamination hazards associated with your sterile process.

你们未能确保在不充分条件下生产的所有批次均进行彻底评估，未能确保你公司识别出你们无菌工艺所有污染危害。

In response to this letter, provide the following:

在回复本函时请提交以下内容：

- A comprehensive, independent assessment of your overall system for investigating deviations, discrepancies, complaints, out-of-specification (OOS) results, and failures. Provide a detailed action plan to remediate this system. Your action plan should include, but not be limited to, significant improvements in investigation competencies, scope determination, root cause evaluation, CAPA effectiveness, quality assurance unit oversight, and written procedures. Address how your firm will ensure that all phases of investigations are conducted appropriately.
  一份对你们偏差、差异、投诉、OOS 结果和失败调查的全面系统的全面独立评估。提交一份详细的行动计划以补救该系统。你们的行动计划应包括但不仅限于对调查能力、范围界定、根本原因评估、CAPA 有效性、质量部门监管和书面程序的重大改进。说明你们公司要如何确保恰当地执行了所有调查阶段。
- An independent assessment and remediation plan for your CAPA program. Provide a report that evaluates whether staff possesses proper investigation competencies, effectively conducts root cause analysis, and assures CAPA effectiveness. Also determine whether your quality system ensures you regularly review investigation trends, implement improvements to the CAPA program when needed, ensure appropriate quality unit decision rights, and receive full executive management that promotes timely lifecycle manufacturing improvements.
  一份对你们 CAPA 程序的独立评估和补救计划。提交一份评估员工是否拥有适当调查能力、有效执行根本原因分析，以及确保 CAPA 有效性的报告。亦要评估你们质量体系是否能确保你们对调查趋势的定期审核，必要时对 CAPA 程序进行改进，确保适当的质量部门决策权，并得到全面的高级管理层促进及时生命周期生产改进。
- For all batches produced from February to December 2018 intended for the U.S. market, submit full environmental data for all ISO 5 air and contact surfaces (including operator gloves) in rooms (b)(4) and (b)(4). Submit individual results, action/alert limits for each of theselocations, batch manufactured that day, microbial identification, and whetherthe batch was supplied to the U.S. Include potential correlations between the HEPA filter failures and these micro excursions.
  对于 2018 年 2-12 月生产的准备销售至美国市场的所有批次，提交房间 XX 和 XX 内所有 ISO 5 级空气和接触表面（包括操作员手套）的全面环境数据。提交每个位置的单个结果、行动/警戒限、该天生产的批次、微生物鉴别，以及该批次是否销售至美国。包括 HEPA 过滤器失效与这些微生物超标之间的潜在关联。
- Your action plan to address any potential product quality or safety risks for any drug products in U.S. distribution.
  你们解决销售至美国的所有药品的所有潜在产品质量或安全风险的行动计划
- A detailed root cause analysis that explains why numerous and clustered HEPA filter failures occurred in such a very short period.
  一份详细的根本原因分析，解释为何在如此短的时间内有大量聚集性 HEPA 过滤器失效

3. Your firm failed to follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

你公司未遵守适当的书面程序，设计用于防止既定无菌的药品微生物污染，并包括所有无菌和灭菌工艺的验证（21 CFR 211.113(b)）。

You failed to perform adequate smoke studies to evaluate whether unidirectional flow exists in your aseptic operations. For example:

你们未执行足够的发烟试验，评估你们的无菌操作是否存在单向流。例如：

- You did not adequately document airflow patterns during aseptic interventions in units (b)(4) and (b)(4). In many instances, airflow patterns were not visible and could not be evaluated due to insufficient smoke, obstructions, and poor camera angles.
  你们并未充分记录 XX 和 XX 单元无菌干预过程中的气流模型。在许多情形下，气流模型并不可见，由于烟雾不够、受阻和摄像机角度不好无法评估。
- You failed to perform an air flow pattern evaluation of the mobile trolley during dynamic conditions in unit (b)(4).The mobile trolley is used to transfer equipment parts and utensils during the setup of the aseptic fill line and for the routine transfer of primary packaging components (e.g., sterilized stoppers) into the cleanroom.
  你们未在 XX 单元动态条件下对移动小车进行气流模型评估。移动小车在无菌灌装线组装中被用于转移设备部件和工器具，日常用于转移内包材部件（例如，灭菌后的塞子）至洁净间。

Thorough smoke studies are essential to evaluate the effects of interventions on unidirectional airflow and to ensure design modifications are made whenever necessary.

全面的发烟试验是评估单向流干预效果以及在必要时确保设计改造所必须的。

We acknowledge your commitment to conduct new smoke studies. We also acknowledge your commitment to complete facility upgrades of your sterile units including changes to your Heating, Ventilating and Air Conditioning system, and installation of additional non-viable particle counters.

我们知晓你们承诺要执行新的发烟试验。我们亦知晓你们承诺要完成无菌单元的设施升级，包括更换你们的 HVAC 系统，并安装另外的空气悬浮粒子计数器。

In response to this letter, provide the following:

在回复本函时，请提交以下内容：

- Comprehensive risk assessment of all contamination hazards with respect to your aseptic processes, equipment, and facilities, including an independent assessment that includes, but is not limited to:
  对你们无菌工艺、设备和设施所有污染危害的全面风险评估，包括独立评估，包括但不仅限于
  - All human interactions within the ISO 5 area
    ISO 5 级区域内的所有人为干预
  - Equipment placement and ergonomics
    设备更换和工效学
  - Air quality in the ISO 5 area and surrounding room
    ISO 5 级区和周围房间的空气质量

- Facility layout
  设施平面布局
- Personnel Flows and Material Flows (throughout all rooms used to conductand support sterile operations)
  人流和物流（穿过用于执行和支持无菌操作的所有房间）

- A detailed remediation plan with timelines to address the findings of the contamination hazards risk assessment. Describe specific tangible improvements to be made to aseptic processing operation design and control.
  一份解决污染危害风险评估发现问题的详细补救计划和时间表。阐述要对无菌加工操作设计和控制所做的具体真实改进。

Drug Production Suspended 暂停药品生产

We acknowledge your decision to suspend production in sterile units (b)(4) and (b)(4) (line (b)(4)). Note that remediating these CGMP violations will be necessary before resuming drug manufacturing operations intended for the U.S. market. Notify this office in writing when all corrections have been implemented and before resuming manufacturing and distribution of your drug products for the U.S. market.

我们知晓你们决定暂停无菌单元 XX 和 XX（产线 XX）的生产。注意在恢复美国市场药品生产操作之前要补救这些 CGMP 违规行为。在执行了所有纠正措施之后恢复生产和向美国市场销售你们药品之前请书面通知本办公室。

Conclusion 结论

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of other violations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov,so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b). This also allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

如果你们在考虑要采取的措施可能会导致你们工厂所生产的药品供应中断，FDA 要求你立即联系 CDER 药品短缺负责人员，这样 FDA 可以与你们一起采用最为高效的方式引导你们的操作符合法规要求。联系药品短缺负责人员还能让你满足依据 21 U.S.C. 356C(b)你可能必须报告你们药品中止或中断的义务，让 FDA 尽快考虑是否需要采取何种措施来避免短缺，保护依赖于你们药品的患者健康。

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产的新申报和增补申报的批准。

Failure to correct these violations may also result in the FDA refusing admission of articles manufactured at Cipla Limited into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Articles under this authority may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act,21 U.S.C. 351(a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

27. 320-20-27 2020-02-28 FICOSOTA LTD 保加利亚

Dear Mr. Kyurkchiev:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, FICOSOTA LTD., FEI 3014115921, at Madara Boulevard 48, Shumen, Shumen, from September 2 to 5, 2019.

美国 FDA 于 2019 年 9 月 2 日至 5 日检查了你们位于保加利亚的 FICOSOTA LTD.生产场所。

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations forf inished pharmaceuticals. See Title 21 Code of Federal Regulations (CFR), parts 210 and 211 (21 CFR parts 210 and 211).

本警告信总结了制剂生产严重违反 CGMP 的行为。参见 21CFR 第 210 与 211 部分。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug product is adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

由于你们的制剂生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的药品根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C. 351(a)(2)(B)被认为是掺假药品。

We reviewed in detail your September 25, 2019, response to om Form FDA 483.

我们已详细审核了你公司 XXXX 年 XX 月 XX 日的回复，并此告知已收到后续通信。

During our inspection, our investigator observed specific violations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

1. Your firm failed to have, for each batch.of drug product, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release (21 CFR 211.165(a))

你公司未在放行之前对每批药品进行适当的实验室检测，确定其满足药品的最终质量标准，包括每种活性成分的鉴别和含量（21 CFR 211.165(a)）。

Your firm failed to perform critical quality control tests of finished drug products prior to shipment to the U.S. market. For example, our inspection found you lacked identity and strength testing for each batch of your over-the-counter (OTC) finished drug product "(b)(4)"for its labeled active pharmaceutical ingredient (API) (b)(4).

你公司未对成品在运输至美国市场之前进行关键质量控制检测。例如，你们检查发现你们 OTC 药品 XX 每个批次均缺少对其所标示 API 的鉴别和含量检测。

Testing of each batch for identity and strength,and all other appropriate quality attributes prior to release, is the final ina series of essential CGMP controls that ensure a drug product meets appropriate specifications.

放行前对每个批次检测其鉴别和含量，以及其它所有适当的质量属性是为确保药品符合适当的标准而执行的一系列基本 CGMP 控制的最终步骤。

In response to this letter, provide:

在回复本函时请提交：

- A comprehensive assessment of your laboratory practices, procedures, methods, equipment, documentation, and analyst competencies. Based on this review, provide a detailed plan to remediate and evaluate the effectiveness of your laboratory system.
  一份对你们实验室规范、程序、方法、设备、文件和化验员能力的全面独立评估。根据该审核结果，提交一份详细的计划补救和评估你们实验室系统的有效性
- A list of chemical and microbial specifications, including test methods, used to analyze each batch of your drug products beforea batch disposition decision.
  一份批处置之前对你们每批药品进行分析所用已更新化学和微生物标准清单，包括检测方法
  - An action plan and timelines for conducting full chemical and microbiological testing of retain samples to determine the quality of all batches of drug product distributed to the United States that are within expiry.as of the date of this letter.
    一份对留样进行化学和微生物全检的行动计划和时间表，以确定所有销售至美国且本函签发时仍在效期内的药品批次的质量
  - A summary of all results obtained from testing retain samples from each batch. If such testing reveals substandard quality drug products, the rapid corrective actions, such as notifying customers and product recalls.
    一份对每批留样检测所得所有结果的总结。如果检测显示有药品质量不合格，则快速采取纠正措施如通知客户和召回产品

2.Your firm failed to conduct at least one test to verify the identity of each component of a drug product. Your firm also failed to validate and establish the reliability of your component supplier's test analyses at appropriate intervals (21 CFR 211.84(d)(1) & (2)).

你公司未检测每种组份样品的鉴别和相关项目，确保其符合所有书面的纯度、含量和质量标准。你公司亦未以适当时间间隔验证和建立你们组份供应商的检测分析可靠性(21 CFR 211.84(d)(1) and (2))。

Your firm failed to adequately test your incoming raw materials, including API and other components, for identity, purity, strength, and quality. You relied on your supplier's certificate of analysis (COA) in lieu of testing each component lot for purity, strength, and quality. However, you did not establish a supplier qualification program to assess (i.e., initially and periodically) the reliability of your suppliers' test results for these attributes.

你公司未对进厂原料包括 API 和其它组份进行充分的鉴别、纯度、含量和质量检测。你们依赖你们供应商的 COA，取代了你们自己对每批组份的纯度、含量和质量检测。但是你们并未建议供应商确认程序来评估（即初次和定期）你们供应商对这些属性检测结果的可靠性。

In response to this letter, provide:

在回复本函时请提交：

- A comprehensive review of your material system to determine whether all containers, closures, and ingredients from each supplier are adequately qualified; whether they are assigned appropriate expiration or retest dates; and whether incoming material lot controls are adequate to prevent the use of unsuitable containers, closures, and components.

一份对你们物料系统的全面审核，以确定是否来自每个供应商的所有容器、密闭器和组份均经过充分确认，是否给定了适当的有效期或复验期，以及进厂物料的批次控制是否足以防止使用不当的容器、密闭器和组份

- The chemical and microbiological quality control specifications you use to test each incoming lot of component to determine suitability for manufacturing.
  你们用于检测和放行每批生产所用进厂组份的化学和微生物质量控制标准
- A description of how you will test each component lot for conformity with all appropriate specifications for identity, strength, quality, and purity. If you intend to accept any results from your supplier's COA instead of testing each component lot for strength, quality, and purity, specify how you will robustly establish the reliability of your supplier's results through initial validation as well as periodic re-validation. In addition, include a commitment to always conduct at least (b)(4) specific identity test for each incoming component lot.
  说明你们准备如何检测每种组份的每个批准，确保其符合所有适当的鉴别、含量、质量和纯度标准。如果你们准备接受你们供应商的所有 COA 结果，取代你们对每批进厂物料的含量、质量和纯度检测，则需说明你们准确如何通过初始验证和定期再验证稳固地建立你们供应商结果的可靠性。另外，在其中包括一份承诺，保证会一直对每批进厂物料执行至少一项特定鉴别项目。
- A summary of results obtained from testing all components to evaluate the reliability of the COA from each component manufacturer.
  一份所有组份检测所得结果的汇总，以评估来自每个组份生产商的 COA 的可靠性。

3. Your firm's quality control unit failed to exercise its responsibility to ensure drug products manufactured are incompliance with CGMP, and meet established specifications for identity, strength, quality, and purity (21 CFR 211.22).

你公司的质量控制部门未履行其确保药品生产符合 CGMP 并满足既定鉴别、含量、质量和纯度标准的职责（21 CFR 211.22）。

During the inspection, our investigator observed that your quality unit (QU) did not provide adequate oversight for the manufacture of your OTC drug product. For example, your QU failed to ensure that:

在检查期间，我们的检查人员发现你们 QU 并未对你们的 OTC 药品生产进行充分的监管。例如，你们的 QU 未能确保：

- QU responsibilities to approve and reject API and drug products were defined.
  规定 QU 批准和拒收 API 和药品的职责
- All testing was performed and reviewed by the QU prior to batch release.
  在批放行之前由 QU 执行并审核所有检测
- An ongoing program for monitoring process control was established to ensure stable manufacturing operations and consistent drug quality.
  建立对工艺控制的持续监测程序，以确保稳定的生产操作和稳定的药品质量
- Master production records and batch production records with detailed manufacturing steps and parameters were adequate and approved.
  主生产记录和批生产记录有详细的生产步骤，参数足够详细并经过批准
- An annual ptoduct review program was established.

建立年度产品回顾程序

- Adequate procedures for out-of-specification (OOS) were established, and any unexplained discrepancies or failures of a batch or any of its components to meet any of its specifications, were thoroughly investigated.
  建立足够的 OOS 程序，成品或组份与其质量标准所有未经解释的差异或不合格均经过彻底调查

In addition, your QU was not independent from production. For example, your written procedure allows your production manager to make final batch release decisions.

另外，你们的 QU 未与生产相互独立。例如，你们的书面程序允许你们生产经理作出最终批放行决定。

In response to this letter, provide:

在回复本函时请提交以下内容：

- A comprehensive assessment and remediation plan to ensure your QU is given the authority and resources to effectively function. The assessment should also include, but not be limited to:
  一份全面的评估和补救计划，确保你们 QU 被授予权力和资源能有效运转。评估还应包括但不仅限于：
  - A determination of whether procedures used by your firm are robust and appropriate
    确定你公司所用程序是否稳健和恰当
  - Provisions for QU oversight throughout your operations to evaluate adherence to appropriate practices
    QU 监管你们整个操作以评估是否遵守适当的规范的条款
  - A complete and final review of each ·batch and its related information before the QU disposition decision .
    QU 监管你们整个操作以评估是否遵守适当的规范的条款
  - Oversight and approval of investigations and discharging of all other QU duties to ensure identity, strength, quality, and purity of all products
    监管和批准调查，履行所有其它 QU 义务以确保所有产品的鉴别、含量、质量和纯度
- A validation plan for ensuring a state of control throughout the product lifecycle, including a timeline for performing appropriate process performance qualification, description of your program for monitoring lot-to-lot variation to ensure an ongoing state of control, and process performance and equipment qualification protocols.
  一份验证计划，确保在产品生命周期中保持受控状态，包括执行适当工艺性能确认的时间表，你们监测批间波动以确保持续受控状态的计划、产品性能和设备确认方案
- A comprehensive review and remediation plan for your OOS result investigation systems. Provide a corrective action and preventive action (CAPA) plan to improve OOS handling. Your CAPA plan should include but not be limited to the following:
  一份对你们 OOS 结果调查系统的全面审核和补救计划。提交一份改进 OOS 处理的 CAPA 计划。你们的 CAPA 计划应包括但不仅限于：
  - Quality unit oversight of laboratory investigations
    QU 对实验室调查的监管
  - Identification of adverse laboratory control trends

发现不良实验室控制趋势

- Resolution of causes or laboratory variations
  原因或实验室波动解决方案
- Initiation of thorough investigations of potential manufacturing causes when a laboratory cause cannot be conclusively identified
  当未发现可得出结论的实验室原因时，对潜在生产原因启动彻底调查
- Adequately scoping of each investigation and its CAPA
  每起调查及其 CAPA 的范围界定
- OOS investigation procedures with these and other remediations
  OOS 调查程序及其它补救措施

- A risk assessment for any drug products in the U.S.market within expiration date for which an OOS result was obtained. Take appropriate actions, including customer notifications or recalls, if drug quality may be compromised.
  一份有 OOS 结果尚在美国市场且仍在效期内的所有药品的风险评估。采取适当措施，包括当药品质量有问题时通知客户和召回药品。

4. Your firm failed to establish an adequate written testing program designed to assess the stability characteristics of drug products and to use results of stability testing to determine appropriate storage conditions and expiration dates (21 CFR 211.166(a)).

你公司未建立和遵守足够的书面检测程序，设计用以评估药品的稳定性特性，以及使用稳定性测试结果确定适当的存贮条件和有效期（21 CFR 211.166(a)）。

Your stability program is inadequate because your procedure does not require a long-term stability study for your OTC drug product "(b)(4)." Although you informed our investigator that your product has a three-year expiration date, your stability program lacked chemical and microbial testing of your stability samples. During the inspection, you provided minimal data to support long-term stability of your OTC product.

你们的稳定性程序是不充分的，因为你们的程序并未要求对你们的 OTC 药品 XX 进行长期稳定性研究。虽然你们告诉我们检查员说你们的药品有 3 年有效期，但你们的稳定性计划中并没有稳定性样品的化学和微生物检测。在检查期间，你们提交了很少的数据来支持你们 OTC 药品的长期稳定性。

In response to this letter, provide:

在回复本函时请提交：

- A comprehensive assessment and CAPA plan.to ensure the adequacy of your stability program. Your CAPA plan should include, but not be limited to:
  一份全面独立的评估和 CAPA 计划，以确保你们的稳定性程序的充分性。你们的补救程序应包括但不仅限于：
  - Stability indicating method
    稳定性指示性方法
  - Stability studies for each drug product in its marketed container-closure system before distribution is permitted
    批准销售之前每种药品在其市售包装中的稳定性研究
  - An ongoing program in which representative batches of each product are added each year to the program to determine if the shelf-life claim remains valid

每年将每种药品代表批次加入程序以确定货架期声明是否保持有效的持续计划

- Detailed definition of the specific attributes to be tested at each station (timepoint)
  在每个时间点要检测的具体属性的详细规定

- All procedures that describe these and other elements of your remediated stability program.
  阐述你们经过补救的稳定性计划中这些和其它要素的所有程序
- Provide stability data to support that your product will meet the quality attributes for a period of (b)(4) after containers are opened, as claimed on your product label.
  提交稳定性数据支持你们药品标签所声明的在容器打开之后 XX 时间内药品仍满足质量属性要求。
- A retrospective risk assessment of the stability of all batches of your drug product on the U.S. market within expiry.
  一份对你们销售至美国且仍在效期内的所有药品批次的稳定性回顾风险评估
- A retrospective, independent review of the impact of all OOS results for all products currently in the U.S. market and within expiry as of the date of this letter.
  一份所有 OOS 结果对当前在美国市场且本函签发时仍在效期内的所有药品的影响的独立回顾审核

Inadequate Response 回复不充分

In your response, you stated that you did not intend to respond to each Form FDA 483 observation since you had ceased production for the U.S. market.

在你们的回复中，你们声称无意回复 FDA483 表中所有缺陷，因为你们已停止生产美国产品。

Your response is inadequate because it did not provide any detail or evidence of corrective actions to bring your operations into compliance with CGMP. Specifically, your response did not address the effect these violations may have on your OTC drug product within expiry and currently in the U.S. market.

你们的回复是不充分的，因为你们并未提交任何可令你公司回复 CGMP 合规状态的整改措施的详细信息或证据。具体来说，你们的回复并未解决这些违规行为对你们当前仍在美国市场且在效期内的 OTC 药品的影响。

Remediating these CGMP violations will be necessaryif you plan to resume drug manufacturing operations for the U.S. market. We acknowledge your commitment to notify this office if you propose to resume U.S.supply. We also acknowledge your commitment to be in "full compliance with all the applicable laws and regulations before proceeding."

如果你们计划恢复销售至美国市场的药品生产操作，则必须补救这些 CGMP 违规行为。我们了解你们承诺如果你们准备恢复向美国供货，你们会通知本办公室。我们了解你们承诺会“在继续之前全面符合所有适用法律法规”。

Quality Systems Guidance 质量体系指南

Your firm's quality systems are inadequate. See FDA's guidance document Quality Systems Approach to Pharmaceutical CGMP Regulations for help implementing quality systems and risk management approaches to meet the requirements of CGMP regulations 21 CFR, parts 210 and 211 at https://www.fda.gov/media/71023/download.

你公司的质量体系是不充分的。参见 FDA 指南文件“药物 CGMP 法规的质量体系方法”，帮助你们实施质量体系和风险管理方法，从而符合 21CFR 第 210 和 211 的 CGMP 规范要求。

Process Controls Guidance 工艺控制指南

Your firm lacks an ongoing program for monitoring process control to ensure stable manufacturing operations and consistent drug quality. See FDA's guidance document Process Validation: General Principles and Practices for general principles and approaches that FDA considers appropriate elements of process validation at https://www.fda.gov/media/71021/download.

你公司缺乏持续的工艺控制监测程序，无法确保稳定的生产操作和恒定的药品质量。参见 FDA 指南文件“工艺验证通则与规范”中 FDA 认为是工艺验证要素的方法。

CGMP Consultant Recommended CGMP 顾问建议

If you resume drug manufacturing operations for the U.S. market, based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualified as set forth in 21CFR 211.34 to assist your firm in meeting CGMP requirements. We also recommend that the qualified consultant perform a comprehensive audit of your entire operation for CGMP compliance and that the consultant evaluates the completion and efficacy of your corrective and preventive actions before you pursue resolution of your firm's compliance status with FDA.

鉴于我们在你公司所发现的违规情况，如果你们要继续为美国市场生产药品，我们强烈建议你们使用一位有 21 CFR 211.34 所述资质的顾问来协助你们公司符合 CGMP 要求。我们亦建议该具备资质的顾问对你们整体运营情况进行药品 CGMP 合规情况全面审计，并由其在你们寻求满足 FDA 合规要求之前对你们 CAPA 的完成情况和有效性进行评估。

Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

你们使用顾问并不能解除你们公司符合 CGMP 的义务。你们公司的高级管理层仍负有义务全面解决所有缺陷，确保持续 CGMP 符合性。

Conclusion 结论

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of other violations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

FDA placed your firm on Import Alert 66-40 on January 10, 2020.

FDA 已于 2020 年 1 月 10 日将你公司置于进口禁令 66-40 中。

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产的新申报和增补申报的批准。

Failure to correct these violations may also resultin the FDA continuing to refuse admission of articles manufactured at FICOSOTA LTD., Madara Boulevard 48, Shumen, Shumen, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Articles under this authority may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to COMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

28. 320-20-28 2020-03-10 Windlas Healthcare Private Limited 印度

Dear Mr. Windlass:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Windlas Healthcare Private Limited,FEI 3005339091, at Plot No. 183 & 192, Mohabewala Industrial Area, Dehradun, from August 26 to 30, 2019.

美国 FDA 于 2019 年 8 月 26 日至 29 日检查了你们位于印度的 WindlasHealthcare Private Limited（FEI3005339091）生产场所。

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See Title 21 Code of Federal Regulations (CFR), parts 210 and 211 (21 CFR parts 210 and 211).

本警告信总结了制剂生产严重违反 CGMP 的行为。参见 21CFR 第 210 与 211 部分。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drugs are adulterated within the meaning of section 501 (a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

由于你们的制剂生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的药品根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C. 351(a)(2)(B)被认为是掺假药品。

We reviewed your September 20, 2019, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

我们已详细审核了你公司 2019 年 9 月 20 日对 FDA483 表的回复，并此告知已收到后续通信。

During our inspection, our investigators observed specific violations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

1. Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to ensure compliance with established specifications and standards (21 CFR 211.194(a)).

你公司未能确保实验室记录中包括有为确保符合既定标准所需检测中得到的完整数据（21 CFR 211.194(a)）。

Your firm did not maintain complete and accurate data from all laboratory testing. Without reliable laboratory data, you cannot assure appropriate decisions regarding batch release, product stability, and other drug aspects of quality. For example:

你公司并未保存所有实验室检测的完整准确数据。没有可靠的实验室数据，你们就无法确保做出适当的批放行决策、产品稳定性及其它药品质量方面决策。例如：

a. On May 19, 2018, the peak detection function was disabled multiple times during the gas chromatography (GC) residual solvent testing of your incoming active pharmaceutical ingredient (API), (b)(4) batch (b)(4). After reviewing the chromatograms, our investigators noted unknown peaks that were not reported or integrated as required per your procedure.

2018 年 5 月 19 日，进厂 API 的 GC 残留溶剂检测期间峰检测功能被关闭了数次，我们检查员对色谱的审核注意到你们未按程序规定报告亦未积分这些未知峰。

Our investigators requested your firm to reprocess the sample set sequence, which subsequently showed > (b)(4)% total unknown impurity peaks. You used this batch of API to manufacture multiple batches of (b)(4) tablets which were released to the U.S. market.

我们调查员要求你公司重新处理样品序列，之后显示有>XX%的总未知杂质峰。你们使用该批 API 生产了多批 XX 片，并放行至美国市场。

This was not an isolated incident. Our investigators also noted unknown peaks which were not reported or integrated during the method transfer of related compounds testing for (b)(4) USP API batch (b)(4). Your firm did this study to support the (b)(4) for (b)(4) tablets.

这并不是孤立事件。我们检查员还发现在 XX USP API 批次有关物质检测方法验证期间，未报告亦未积分未知峰。你公司进行该项研究是为了支持 XX 片剂的 XX。

In your response, you attributed the root cause to "inadequate knowledge and awareness" by your laboratory personnel. You also stated that a contributing root cause was "the unavailability of a proper SOP on identification of extraneous peaks." Your response was inadequate. You did not discuss why your analysts did not follow your procedure to integrate known and unknown peaks. Your response also failed to identify the cause of the unknown peaks.

在你们的回复中，你们将根本原因归结为你们实验室人员“知识和意识不足”。你们还声称另一个可归结原因是“外源峰识别没有适当的 SOP”。你们的回复是不充分的。你们并未讨论为何你们的化验员没有遵守你们的程序对已知和未知峰进行积分。你们的回复亦未找出未知峰的根本原因。

b. On April 16, 2019, you cancelled a test sequence during 18-month related substances testing that included (b)(4) mg tablets batch (b)(4). Your investigation stated the cancellation was due to "oven leak error." The chromatogram for this initial run showed impurities that would yield an out-of-specifications (OOS) result. The initial run was invalidated, and you prepared and tested a new sample solution on April 17, 2019. The retest failed percent relative standard deviation (RSD) and you invalidated this second run too. On April 22, 2019, you prepared a third sample solution and repeated the test. The third sample solution also failed percent RSD and again you invalidated the run. On April 29, 2019, you prepared a fourth sample solution. This test yielded passing data. You reported the final, passing data after multiple testing failures. You did not adequately investigate the failing results as required by your laboratory incidents (LI) procedure. Your firm also did not identify clear root causes for the repeated analytical problems that caused you to invalidate the first three analyses.

2019 年 4 月 16 日，你们在 18 个月有关物质检测中取消了一个检测序列，其中包括 XXmg 片剂批次 XX。你们的调查说取消该序列是因为“柱温箱泄漏故障”。初始运行色谱图显示杂质会得出 OOS 结果。初次运行被宣布无效，你们在 2019 年 4 月 17 日重新配制样品并检测。复测时 RSD 不合格，你们又宣布第二次运行无效。2019 年 4 月 22 日，你们制备了第三份样品并重新检测，第三次检测中样品溶液 RSD 仍然不合格，你们又宣布运行无效。2019 年 4 月 29 日，你们第四次制备了样品溶液。这次检测得到了合格数据。你们在多次检测合格之后报告了最后这次合格数据。你们并未对失败结果按你们的实验室事件（LI）程序进行充分调查。你公司亦未找出导致你们宣布前面三次分析过程中反复发生的分析问题的明确根本原因。

In your response, you confirmed that batch (b)(4) was OOS, and stated it was potentially due to contaminated (b)(4) solution used as part of the test method and mobile phase preparation. However, you lacked adequate evidence demonstrating how the potential contamination of the (b)(4) solution was the root cause of the OOS. You did not discuss how, in the same sequence multiple samples were apparently not compromised. In addition, you lacked adequate· evidence concerning the scope and potential impact that these laboratory errors may have on other laboratory tests and results.

在你们的回复中，你们确认 XX 批次为 OOS，并声称可能是因为用作检测方法一部分和流动相配制的 XX 溶液受污染。但是你们缺少足够证据来证明 XX 溶液的可能污染是 OOS 的根本原因。你们并未讨论为何在相同序列多个样品明显都未受到影响。另外，你们亦缺乏足够证据证明实验室错误的范围及其可能对其它实验室检测和结果产生的潜在影响。

In your response to this letter provide the following:

在你们对本函的回复中请提交以下：

- A retrospective, independent, assessment of your OOS investigation into the 18-month related substances testing for (b)(4)mg tablets batch (b)(4).
  对你们 XX 批 XXmg 片剂 18 个月有关物质检测中 OOS 调查的独立回顾评估
- A comprehensive, independent assessment of your laboratory practices, procedures, methods, equipment, documentation, and analyst competencies. Based on this review, provide a detailed plan to remediate and evaluate the effectiveness of your laboratory system.
  一份对你们实验室规范、程序、方法、仪器、文件和化验员能力的全面独立评估。根据这些审核，提交一份详细的 CAPA 计划用于补救你们实验室系统的有效性。
- Your corrective action and preventive action (CAPA) plan to implement routine, vigilant quality management oversight of laboratory equipment. This plan should ensure, among other things, prompt detection of equipment performance issues, effective execution of repairs, and adherence to appropriate preventive maintenance schedules.
  你们对实验室设备执行日常严格质量管理监管的 CAPA 计划。该计划应确保（除其它事情外）快速发现设备性能问题、有效进行维修，并遵守适当的预防性维护计划。
- See the Data Integrity Remediation heading below. Part C requests a corrective action plan to ensure the reliability and completeness of all the data you have submitted to FDA in your approved and pending drug applications. It is essential that this retrospective review include an independent evaluation of raw data used for these application submissions.
  参见以下数据完整性补救措施项。第 C 部分要求制订整改计划以确保你们在你们已批准和审评中药品申报资料里提交给 FDA 的所有数据的可靠性和完整性。必须保证该回顾性审核包括对这些申报资料中所用原始数据的独立评估。
- A comprehensive, independent assessment of your overall system for investigating deviations, discrepancies, complaints, OOS results, and failures. Provide a detailed action plan to remediate this system. Your action plan should include, but not be limited to, significant improvements in investigation competencies, scope determination, root cause evaluation, CAPA effectiveness, quality unit oversight, and written procedures. Address how your firm will ensure all phases of investigations are appropriately conducted.
  一份对你们偏差、差异、投诉、OOS 结果和失败调查的全面系统的全面独立评估。提交一份详细的行动计划以补救该系统。你们的行动计划应包括但不仅限于对调查能力、范围界定、根本

原因评估、CAPA 有效性、质量部门监管和书面程序的重大改进。说明你们公司要如何确保恰当地执行了所有调查阶段。

- An independent assessment and remediation plan for your CAPA program. Provide a report that evaluates if it includes staff with proper investigation competencies, effectively conducts root cause analysis, assures CAPA effectiveness, regularly reviews investigations trends, implements improvements to the CAPA program when needed, ensures appropriate quality unit decision rights, and is fully supported by executive management.
  一份你们 CAPA 程序的独立评估及补救计划。提交一份报告评估其是否包括员工具备适当的调查能力、有效执行根本原因分析、确保 CAPA 有效性、定期审核调查趋势、必要时对 CAPA 程序进行改进，确保质量部门具备适当的决策权力，并得到高级管理层的全面支持。

2. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

你公司未彻底调查已销售和未销售批次产品或其组份未经解释的差异或不符合其标准（21 CFR 211.192）。

Your investigations into laboratory incidents (LI) testing results are inadequate. Multiple LI investigations lacked adequate scientific rationale for root cause determination. Without adequate scientific rationale, your firm invalidated the failing OOS results that were included in these LI. You subsequently reported the passing retest results.

你们对实验室事件（LI）检测结果的调查是不充分的。多个 LI 调查中根本原因确定中缺乏足够的科学合理性。在没有足够的科学合理性情况下，你公司宣布在这些 LI 中的不合格 OOS 结果无效。你们随后报告了合格的复测结果。

For example, during your analytical method verification for residual solvent for (b)(4) API, your firm initiated numerous LI concerning failures of the test's accuracy, method precision, or intermediate precision parameters. The probable root causes of these LI were attributed to contamination and analyst error. We note your retesting plans did not specify retesting by an analyst other than the one who performed the original test. In addition, samples were retested until passing results were achieved. Your CAPA for these LI stated "training on standard operating procedure (SOP) of 'Good laboratory practices of QC laboratory' shall be imparted to concern person [sic]." Your method verification report was approved on May 3, 2018. We note that on May 19, 2018, unknown peaks were observed using this test method which were not identified or integrated as discussed in Charge 1 of this letter.

例如，在你们的 XX API 残留溶剂分析方法确认过程中，你公司对检测准确性、方法精密度或中间精密度参数有无数 LI 相关的失败。这些 LI 的可能根本原因被归结到污染和化验员错误。我们注意到你们的复测计划并未指定由原化验员以外的化验员进行复测。还有你们对样品一直复测直到获得合格结果。你们对这些 LI 的 CAPA 说“应该为相关人员进行《QC 实验室的优良实验室规范》SOP 培训”。你们的方法确认报告是在 2018 年 5 月 3 日批准的，我们发现在 2018 年 5 月 19 日，采用该方法时发现有未知峰，但对这些未知峰并未进行鉴别或积分。见本函第 1 条缺陷所述。

In your response, you stated that the lack of adequate LI investigations was due to inadequate training on procedures, analysts not following procedures, and inadequate quality oversight and visibility to senior management. You committed to perform a retrospective evaluation of LI.

在你们的回复中，你们声称缺乏足够的 LI 调查是因为程序培训不充分，化验员未遵守程序，以及质量监管不够和高级管理层不重视。你们承诺会对 LI 进行回顾性评估。

However, your response failed to assess your entire laboratory system to ensure the competency of analysts. You also failed toprovide a retrospective review of all your drug products to determine if you are attributing root cause appropriately, reporting OOS results correctly, and implementing adequate CAPA to prevent recurrence.

但是你们的回复中并未对你们整个实验室系统进行评估，以保证化验员的能力。你们亦未提交对你们药品的回顾性审核，从而确定你们是否找到了正确的根本原因，正确地报告了 OOS 结果，以及实施了足够的 CAPA 防止其再次发生。

For more information about handling failing, out-of-specification, out-of-trend, or other unexpected results and documentation of your investigations, see FD A's guidance document Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production, at https://www.fda.gov/media/71001/download.

关于不合格、OOS、OOT 或其它非预期结果和调查文件记录，参见 FDA 指南“药物生产中 OOS 结果调查”。

In your response to this letter provide the following:

在你们对本函的回复中请提交以下：

- A retrospective, independent review of all invalidated laboratory incidents and OOS (including in-process and release/stability testing) results for U.S. products irrespective of whether the batch was ultimately distributed in the U.S. and a report summarizing the findings of the analysis, including the following for each OOS:
  对所有美国产品的宣布无效的实验室事件和 OOS（包括中控和放行/稳定性测试）结果的独立回顾审核，无论这些产品是否最终销售至美国，并提交一份报告总结分析中发现的情况，包括每个 OOS 的以下信息：
  - Determine whether the scientific justification and evidence relating to the invalidated OOS result conclusively or inconclusively demonstrates causative laboratory error.
    确定宣布无效的 OOS 结果的科学论证和证据是否可得出结论支持可归因的实验室错误
  - For investigations that conclusively establish laboratory root cause, provide rationale and ensure that all other laboratory methods vulnerable to the same or similar root cause are identified for remediation.
    对于可得出实验室根本原因的调查，提交理由并确保识别出所有其它易受到类似根本原因影响的实验室方法并进行补救
  - For all OOS results found by the retrospective review to have an inconclusive or no root cause identified in the laboratory, include a thorough review of production (e.g., batch manufacturing records, adequacy of the manufacturing steps, suitability of equipment/facilities, variability of raw materials, process capability, deviation history, complaint history, batch failure history). Provide a summary of potential manufacturing root causes for each investigation, and any manufacturing operation improvements.
    对于回顾审核中发现的所有 OOS 结果，在实验室未找到根本原因或不能得出结论的，要包括一份对生产（例如批生产记录，生产步骤是否充分，设备/设施适用性，原料波动性，工

艺能力，偏差历史，投诉历史，批不合格历史）的彻底审核。提交一份每个调查潜在生产根本原因的总结，以及所有生产操作改进措施。

- A comprehensive review and remediation plan for your OOS result investigation systems.
一份对你们 OOS 结果调查系统的全面审核和补救计划。

The CAPA should include but not be limited to addressing the following:

该 CAPA 应包括但不仅限于说明以下问题：

- Define what constitutes a laboratory incident or OOS.
规定实验室事件或 OOS 的形成要素
- Quality unit oversight of laboratory investigations.
质量部门对实验室调查的监管
- Identification of adverse laboratory control trends.
不良实验室控制趋势的识别
- Resolution of causes of laboratory variation.
实验室波动原因的解决方案
- Initiation of thorough investigations of potential manufacturing causes whenever a laboratory cause cannot be conclusively identified.
无论是否可发现可归结实验室原因，均要对潜在生产原因启动彻底调查
- Adequately scoping of each investigation and its CAPA.
对每个调查及其 CAPA 范围进行充分界定
- Revised OOS investigation procedures with these and other remediations.
包括上述要求及其它补救措施的修订后 OOS 调查程序

3.Your firm failed to establish an adequate quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging materials, labeling, and drug products (21 CFR 211.22(a)).

你公司未建立足够的质量部门，使其具备职责与权力可批准或拒收所有组份、药品容器密闭器、中间体、包装材料、标签和药品（21 CFR 211.22(a)）。

Your firm's quality unit (QU) failed to provide adequate oversight of your manufacturing activities. For example:

你公司的 QU 未对你们的生产活动执行充分监管，例如：

When our investigators arrived at your firm just 30 minutes after announcing our inspection, they observed numerous employees in the process of moving off-site cartloads of trash bags containing shredded and tom documents and binders. Upon closer examination, the investigators discovered batch reconciliation forms, cleaning and dispensing logs, training assessments, and scale balance printouts.

当我们检查员到达你们公司宣布我们检查后才 30 分钟，他们就发现大量员工在将装有切碎和撕掉的文件与文件夹的垃圾袋往厂外装运。检查员接近检查后发现有批平衡表、清洁和分料日志、培训评估和秤打印件。

In your response, your firm acknowledged that your employees violated your documentation procedure. You identified the root causeas inadequate awareness of data integrity principles, training and education, supervision, and problem-solving capabilities. Your response was inadequate in that it did not fully evaluate the scope of this deficiency. You also did not adequately address the major failure of operations management and quality unit management to conduct proper oversight over documentation and data integrity.

在你们的回复中，你公司承诺你们员工违反了你们的文件记录程序。你们将根本原因归结于数据完整性原则意识，培训和教育、监管和问题解决能力不够。你们的回复是不充分的，其中并未全面评估该缺陷的范围。你们亦未充分解决操作管理和质量部门管理未能对文件记录和数据完整性进行适当监管的重大问题。

Later in the inspection, our investigator noted that your live-feed cameras showed production staff expediently signing and passing documents to one another. Our investigator requested to visit the production staff location; however, our investigator was routed to an incorrect area. This incident delayed our investigator and prevented contemporaneous verification of the activities being performed.

在检查后期，我们检查员发现你们的实时录像显示生产员工快速地在文件上签名并传递给另一人。我们的检查员要求查看生产员工位置，但我们的检查员被带到了错误地方。该事件拖延了我们的检查员，使得他们未能在该活动正在进行时进行同步核查。

In your response, you stated that your firm's procedure for camera locations was incorrect. Your response is inadequate. You failed to address why two QU personnel reviewed and approved an incorrect camera location procedure approximately one week before the start of this inspection.

在你们的回复中，你们声称你公司的录像机放置位置的程序是不正确的。你们的回复是不充分的，

In response to this letter provide the following:

在回复本函时请提交以下内容：

- A comprehensive assessment and remediation plan to ensure your QU is given the authority and resources to effectively function.The assessment should also include, but not be limited to:
  一份确认你们 QU 被赋予权力和资源可有效运转的全面评估和补救计划。评估还应包括但不仅限于：
  - A determination of whether procedures used by your firm are robust and appropriate.
    确定你公司所用程序是否稳健恰当
  - Provisions for QU oversight throughout your operations to evaluate adherence to appropriate practices.
    QU 对你们整个操作进行监管并评估其是否遵守适当规范的条款
  - A complete and final review of each batch and its related information before the QU disposition decision.
    在 QU 批处置决策前对每个批次及其相关信息的完整最终审核
  - Oversight and approval of investigations and discharging of all other QU duties to ensure identity, strength, quality, and purity of all products.
    对调查的监管和批准，履行所有其它 QU 职责以确保所有产品的鉴别、含量、质量和纯度

- Also describe how top management supports quality assurance and reliable operations; including but not limited to timely provision of resources to proactively address emerging manufacturing/quality issues and to assure a continuing state of control.
  亦要说明高级管理层是如何支持质量保证和可靠操作的，包括但不仅限于及时提供资源，积极解决新发现的生产/质量问题，确保持续受控状态。

- A complete assessment of documentation systems used throughout your manufacturing and laboratory operations to determine where documentation practices are insufficient. Include a detailed CAPA plan that comprehensively remediates your firm's documentation practices to ensure you retain attributable, legible, complete, original, accurate, and contemporaneous records throughout your operation.
  一份你们整个生产和实验室操作所用文件的完整评估，以确定哪些文件记录规范不够充分。在其中要包括一份详细的 CAPA 计划，全面补救你公司的文件记录规范，确保你们保存了你们所有操作中可追溯的、清晰的、完整的、原始的、准确的和同步记录。

Data Integrity Remediation 数据完整性补救措施

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. See FDA's guidance document Data Integrity and Compliance With Drug CGMP for guidance on establishing and following CGMP compliant data integrity practices at https://www.fda.gov/media/97005/download.

你们的质量体系不能充分确保数据的准确性和完整性，无法支持你们生产的药品的安全性、有效性和质量。参见 FDA 指南文件“数据完整性和药品 GMP 合格”指导建立和遵守 CGMP 合格数据完整性规范。

In response to this letter, provide the following:

在回复此函时请提交以下信息：

A. A comprehensive investigation into the extent ofthe inaccuracies in data records and reporting. Your investigation should include:

一份对数据记录和报告不准确性程度的全面调查。你们的调查应包括

- A detailed investigation protocol and methodology; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
  详细的调查方案和方法学，所有实验室、生产操作和评估所覆盖的系统的总结，如有除外部分请论证
- Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
  对现有和已离职员工进行面谈，找出数据不准确的程度、范围和根本原因。我们建议这些面谈由有资质的第三方进行。
- An assessment of the extent of data integrity deficiencies at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses.

你们工厂数据完整性缺陷的程度的评估。识别出省略、修改、删除、记录销毁、不同步记录填写和其它缺陷。说明你们已发现的数据完整性问题所涉及的工厂操作。

- A comprehensive retrospective evaluation of the nature of the testing and any other data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluate all data integrity lapses.
  一份对检测和生产数据完整性缺陷情况的全面回顾性评估。我们建议由具备在已发现可能有问题的领域的专业能力的有资质的第三方对所有数据完整性问题进行评估。

B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity and analyses of the risks posed by ongoing operations.

你们药品质量中所发现的不合格情况的潜在影响的当前风险评估。你们的评估应包括由于受到数据完整性问题影响的药品放行导致的患者风险的分析，以及持续运营所具有的风险。

C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan.Your strategy should include:

你们公司的管理策略，包括你们全球 CAPA 计划详细情况。你们的策略应包括：

- A detailed corrective action plan that describe show you intend to ensure the reliability and completeness of all the data you generate including analytical data, manufacturing records, and all data submitted to FDA.
  详细的 CA 计划，描述你们准备如何确保你们生成的所有数据的可靠性和完整性，包括分析数据、生产记录和所有提交给 FDA 的数据。
- A comprehensive description of the root causes of your data integrity lapses including evidence that the scope and depth of the cw-rent action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related or drug application data at your firm.
  一份对你们数据完整性问题根本原因的全面描述，包括当前行动计划的范围和深度与调查和风险评估发现相称的证据。说明负责数据完整性的人员是否还有能力影响你公司与 CGMP 有关或药品申报数据。
- Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring.
  临时措施，描述你们已采取或将采取用来保护患者和确保你们药品质量的措施，如通知你们的客户、召回产品、执行额外检测、增加批次至稳定性计划以确保稳定性、药品申报措施和加强投诉监测。
- Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, control s, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data.
  长期措施，其中描述所有对用以确保你们公司数据完整性的程序、流程、方法、控制、系统、管理监管和人力资源（例如培训、员工提高）的弥补和提升。
- A status report for any of the above activities already underway or completed.

对上述活动已开展或已经完成的状态报告。

CGMP Consultant Recommended CGMP 顾问建议

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualified as set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements. We also recommend that the qualified consultant perform a comprehensive audit of your entire operation for CGMP compliance and that the consultant evaluates the completion and efficacy of your corrective actions and preventive actions before you pursue resolution of your firm's compliance status with FDA.

鉴于我们在你公司所发现的违规情况，我们强烈建议你们使用一位有 21 CFR 211.34 所述资质的顾问来协助你们公司符合 CGMP 要求。我们亦建议该具备资质的顾问对你们整体运营情况进行药品 CGMP 合规情况全面审计，并由其在你们寻求满足 FDA 合规要求之前对你们 CAPA 的完成情况和有效性进行评估。

Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

你们使用顾问并不能解除你们公司符合 CGMP 的义务。你们公司的高级管理层仍负有义务全面解决所有缺陷，确保持续 CGMP 符合性。

Conclusion 结论

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of other violations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately; at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C.356C(b). This also allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

如果你们在考虑要采取的措施可能会导致你们工厂所生产的药品供应中断，FDA 要求你立即联系 CDER 药品短缺负责人员，这样 FDA 可以与你们一起采用最为高效的方式引导你们的操作符合法规要求。联系药品短缺负责人员还能让你满足依据 21 U.S.C. 356C(b)你可能必须报告你们药品中止或中断的义务，让 FDA 尽快考虑是否需要采取何种措施来避免短缺，保护依赖于你们药品的患者健康。

FDA placed your firm on Import Alert 66-40 on January 21, 2020.

FDA 已于 2020 年 1 月 21 日将你公司置于进口禁令 66-40 中。

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产的新申报和增补申报的批准。

Failure to correct these violations may also resultin the FDA continuing to refuse admission of articles manufactured at Windlas Healthcare Private Limited at Plot No. 183 & 192 Mohabewala Industrial, Dehradun, into the United States under section 801(a)(3) of the FD&C Act,21 U.S.C. 381(a)(3). Articles under this authority may be subject to refusal of admission, in that the methods and controls used in their manufacture do notappear to conform to CGMP within the meaning of section 501(a)(2)(B) of theFD&C Act, 21 U.S.C. 351(a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to thisoffice in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

29. 320-20-29 2020-03-10 DermaPharm A/S 丹麦

Dear Mr. Mollerup:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, DermaPharm A/S, FEI 3005947959, at Europavej 10, Farup, Denmark from September 16 to 19, 2019.

美国 FDA 于 2019 年 9 月 16 日至 19 日检查了你们位于丹麦的 DermaPharm A/S 生产场所。

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See Title 21 Code of Federal Regulations (CFR), parts 210 and 211 (21 CFR parts 210 and 211).

本警告信总结了制剂生产严重违反 CGMP 的行为。参见 21CFR 第 210 与 211 部分。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug product is adulterated within the meaning or section501 (a)(2)(B) of the Federal Food, Drug, and Cosmetic Act(FD&C Act), 21 U.S.C. 351(a)(2)(B).

由于你们的制剂生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的药品根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C. 351(a)(2)(B)被认为是掺假药品。

We reviewed your October 24, 2019, response to our form FDA 483 in detail and acknowledge receipt of your subsequent correspondence. Your response is inadequate because it did not provide sufficient detail or evidence of corrective actions to bring your operations into compliance with CGMP.

我们已详细审核了你公司 2019 年 10 月 24 日的回复，并此告知已收到后续通信。

During our inspection, our investigator observed specific violations including, but not limited to the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

1. Your firm failed to have, for each batch of drug product, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release (21 CFR 211.165(a)).

你公司未在放行之前对每批药品进行适当的实验室检测，确定其满足药品的最终质量标准，包括每种活性成分的鉴别和含量（21 CFR 211.165(a)）。

Your firm failed to test your over-the-counter(OTC) (b)(4) drug product, (b)(4), for the identity and strength of the active ingredient prior to release for distribution. We note that this drug product is labeled for use on children. Testing is essential to ensure that the drug products you manufacture conform to all pre-determined quality attributes appropriate for their intended use. Because you lacked adequate testing of each batch of your drug products, you do not know whether they conform to all appropriate finished product specifications and are suitable for release to consumers.

你公司未在旅行销售之前检测你们的 OTC 药品 XX 中活性成分的鉴别和含量。我们注意到该药品标示为可用于儿童。为确保你们生产的药品符合其用途所需的所有既定的质量属性，检测是必要的。

因为你们对每批药品未进行充分检测，你们并不知道它们是否符合适当的成品质量标准，是否适合放行销售给消费者。

In your response, you stated that finished product testing of the (b)(4) will include an "assay/potency of (b)(4)" for any future release.

在你们的回复中，你们声称未来对 XX 成品检测会包括“XX 含量/效价”。

Your response is inadequate. You failed to address previously released batches of this finished drug product, including testing reserve samples for batches in commercial distribution in the United States.

你们的回复是不充分的。你们并未解决之前已放行的该产品批次问题，包括对已商业化销售至美国的批次的留样检测。

In response to this letter, provide:

在回复本函时请提交以下内容：

- A comprehensive, independent assessment of your laboratory practices, procedures, methods, equipment, documentation, and analyst competencies. Based on this review, provide a detailed plan to remediate and evaluate the effectiveness of your laboratory system.
  一份对你们实验室规范、程序、方法、设备、文件和化验员能力的全面独立评估。根据该审核结果，提交一份详细的计划补救和评估你们实验室系统的有效性
- An updated list of chemical and microbiological specifications, including test methods, used to analyze each batch of your drug products prior to a batch disposition decision.
  一份批处置之前对你们每批药品进行分析所用已更新化学和微生物标准清单，包括检测方法
- An action plan and timelines for conducting full chemical and microbiological testing of retain samples to determine the quality of all batches of drug product distributed to the United States within expiry as of the date of this letter.
  一份对留样进行化学和微生物全检的行动计划和时间表，以确定所有销售至美国且本函签发时仍在效期内的药品批次的质量
- A summary of all results obtained from testing retain samples from each batch. If such testing reveals substandard quality drug products, take rapid corrective actions, such as notifying customers and product recalls.
  一份对每批留样检测所得所有结果的总结。如果检测显示有药品质量不合格，则快速采取纠正措施如通知客户和召回产品

2. Your firm failed to conduct at least one test to verify the identity of each component of a drug product. Your firm also failed to validate and establish the reliability of your component supplier's test analyses at appropriate intervals (21 CFR 211.84(d)(1) and (2)).

你公司未检测每种组份样品的鉴别和相关项目，确保其符合所有书面的纯度、含量和质量标准。你公司亦未以适当时间间隔验证和建立你们组份供应商的检测分析可靠性(21 CFR 211.84(d)(1) and (2))。

Your firm receives raw material, "(b)(4)" as a component for use in production of (b)(4). This raw materialis a (b)(4) containing (b)(4), the active ingredient in your finished drug product. Though you

receive this raw material with a certificate of analysis from your supplier, you have not performed appropriate incoming analysis of component lots upon receipt, including confirming the identity prior to use in production of your finished drug product. You also relied on your supplier's Certificate of Analysis without establishing the reliability of your component supplier's test analyses at appropriate intervals.

你公司收到原料“XX”，将其作为原料用于 XX 的生产。该原料是一种含有 XX 的 XX，是你们成品中的活性成分。虽然你们收到该原料同时收到了供应商的 COA，但你们并在接收时对每批原料进行适当的进厂分析，包括在用于成品生产之前确认其鉴别。你们还在未以适当时间间隔建立你们原料供应商检测分析可靠性时依赖于你们供应商的 COA。

During the inspection, you stated that raw materials are sampled by the quality unit but are not fully tested, and that only an appearance test is performed. You further stated that, because the supplier of this component is ·qualified, you did not perform incoming testing of this material.

在检查期间，你们声称质量部门对该原料有采集样品，但未进行全检，只进行了外观检查。你们进一步声称因为已对该原料供应商进行了资格确认，因此你们未对该原料进行进厂检测。

In response to this letter, provide:

在回复本函时请提交以下内容：

- A comprehensive review of your material system to determine whether all suppliers of components, containers, and closures are each qualified, and the materials are assigned appropriate expiration or retest dates. The review should also determine whether incoming material controls are adequate to prevent use of unsuitable components, containers, and closures.
  对你们原料管理系统的综合审核，以确定是否所有原料、容器和密闭器的供应商均经过资质确认，是否所有原料均给定了适当的有效期或复验期。审核还应确定进厂原料控制是否足以防止使用不恰当的组份、容器和密闭器。
- The chemical and microbiological quality control specifications you use to test and release each incoming lot of component for use in manufacturing.
  你们用于检测和放行每批生产用进厂原料的化学和微生物质量控制标准。
- A description of how you will test each component lot for conformity with all appropriate specifications for identity, strength, quality, and purity. If you intend to accept any results from your supplier's Certificates of Analysis instead of testing each component lot for strength, quality, and purity, specify how you will robustly establish the reliability ofyour supplier's results through initial validation as well as periodic re-validation. In addition, include a commitment to always conduct at least one specific identity test for each incoming component lot.
  说明你们准备如何对每种原料进行检测，确定其符合所有恰当的鉴别、含量、质量和纯度标准。如果你们准备接受你们供应商的 COA 中所有结果，取代你们对每批进厂物料的含量、质量和纯度检测，请说明你们准备如何通过初始验证和定期重新验证稳固地建立你们供应商的结果可靠性。此外，要包括一份承诺保证你们会一直对每批进厂原料进行至少一项鉴别检查。

3. Your firm failed to establish adequate written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess (21 CFR 211.100(a)).

你公司未能建立书面生产和工艺控制程序，设计用以确保你们生产的药品具备其理当具备或显示具备的鉴别、含量、质量和纯度（21 CFR 211.100(a)）。

You did not validate the process used to manufacture your drug product, (b)(4), prior to distribution. During the inspection, you told our investigator that there are (b)(4) batch sizes for the production of (b)(4), approximately at (b)(4), and that neither batch size has been validated.

你们在销售之前并未验证你们药品 XX 生产所用工艺。检查期间，你们告诉我们检查员说有 XX 种批量分别为约 XX，你们的批量均未进行验证。

Process validation evaluates the soundness of design and state of control of a process throughout its lifecycle. Each significant stage of a manufacturing process must be designed appropriately and assure the quality of raw material inputs, in-process materials, and finished drugs.

工艺验证评估的是工艺生命周期中其设计合理性和受控状态。每个生产工艺的重大阶段均必须进行恰当设计，确保原料输入、中间体和成品的质量。工艺确认研究会确定是否建立初始的受控状态。

Process validation studies determine whether an initial state of control has been established. Successful process validation studies are necessary before commercial distribution. Thereafter, ongoing vigilant oversight of process performance and product quality is necessary to ensure you maintain a stable manufacturing operation throughout the product lifecycle.

工艺验证研究确定是否已建立了初始的受控状态。商业销售之前必须进行成功的工艺验证研究。之后要对工艺性能和产品质量进行持续警觉的监管，这是确保你们在产品生命周期中维护稳定的生产操作所必须的。

See FDA's guidance document, Process Validation:General Principles and Practices, for general principles and approaches that FDA considers appropriate elements of process validation at https://www.fda.gov/media/71021/download.

参见 FDA 指南文件“工艺验证通则与规范”。

In your response to this letter, provide:

在你们回复本函时请提交以下内容：

- A detailed summary of your validation program for ensuring a state of control throughout the product lifecycle, along with associated procedures. Describe your program for process performance qualification (PPQ), and ongoing monitoring of both intra-batch and inter-batch variation to ensure a continuing state of control.
  一份你们验证程序和相关程序的详细总结，确保整个产品生命周期中的受控状态。解释你们为确保持续受控状态而制订的工艺性能确认（PPQ）和对批间与批内波动的严格监测程序。
- A timeline for performing PPQ for each of your marketed drug products. Include your process performance protocol(s) and written procedures to qualify equipment and facilities.
  对你们所有已上市药品实施 PPQ 的时间表。包括你们确认设备与设施的工艺性能方案和书面程序。
- A detailed program for designing, validating, maintaining. controlling, and monitoring each of your manufacturing processes that includes vigilant monitoring of intra-batch and interbatch variation to ensure an ongoing state of control. Also, include your program for qualification of your equipment and facility.

一份你们所有生产工艺的详细设计、验证、维护、控制和监测计划，在其中要包括批内和批间波动严格监测，以确保持续受控状态。还要包括一份你们的设备与设施确认程序。

CGMP consultant recommended CGMP 顾问建议

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualifiedas set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements.We also recommend that the qualified consultant perform a comprehensive audit of your entire operation for CGMP compliance and that the consultant evaluates the completion and efficacy of your corrective actions and preventive actions before you pursue resolution of your firm's compliance status with FDA.

鉴于我们在你公司所发现的违规情况，我们强烈建议你们使用一位有 21 CFR 211.34 所述资质的顾问来协助你们公司符合 CGMP 要求。我们亦建议该具备资质的顾问对你们整体运营情况进行药品 CGMP 合规情况全面审计，并由其在你们寻求满足 FDA 合规要求之前对你们 CAPA 的完成情况和有效性进行评估。

Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

你们使用顾问并不能解除你们公司符合 CGMP 的义务。你们公司的高级管理层仍负有义务全面解决所有缺陷，确保持续 CGMP 符合性。

Conclusion 结论

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of other violations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

FDA placed your firm on Import Alert 66-40 on March 9, 2020.

FDA 已于 2020 年 3 月 9 日将你公司置于进口禁令 66-40 中。

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产的新申报和增补申报的批准。

Failure to correct these violations may also result in the FDA continuing to refuse admission of articles manufactured at DermaPharm A/S, Farup, Denmark into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Articles under this authority may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351 (a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

30. 320-20-30 2020-03-13 Hangzhou Linkweier Daily Chemicals Co. Ltd .杭州林柯韦尔日化有限公司

Dear Mr. Wenbing

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Hangzhou Linkweier Daily Chemicals Co. Ltd., FEI 3014324616, at 568 Dongfang Road, Yiqiao Town, Xiao Shan District, Hangzhou, Zhejiang, from September 11 to 17, 2019.

美国 FDA 于 2019 年 9 月 11 日至 17 日检查了你们位于浙江杭州市萧山区义桥镇东方路 568 号的杭州林柯韦尔日化有限公司生产场所。

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See Title 21 Code of Federal Regulations (CFR), parts 210 and 211 (21 CFR parts 210 and 211).

本警告信总结了制剂生产严重违反 CGMP 的行为。参见 21CFR 第 210 与 211 部分。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug product is adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

由于你们的制剂生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的药品根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C. 351(a)(2)(B)被认为是掺假药品。

We reviewed your September 24, 2019, response toour Form FDA 483 in detail. Your response is inadequate because it did not provide sufficient detail or evidence of corrective actions to bring your operations into compliance with CGMP.

我们已详细审核了你公司 2019 年 9 月 24 日的回复，并此告知已收到后续通信。

During our inspection, our investigator observed specific violations deviations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

1. Your firm failed to conduct, for each batch ofdrug product, appropriate laboratory testing, as necessary, required to be free of objectionable microorganisms (21 CFR 211.165(b)).

你公司未能在必要时对每批药品进行适当的致病菌实验室检测（21 CFR 211.165(b)）。

Your firm contract manufactures over-the-counter (OTC) (b)(4) drug products. Your firm released these products without ensuring that they are free of objectionable microorganisms.

你公司将 OTC 药品 XX 委外生产。你公司在未确保这些产品未检出致病菌情况下即放行销售。

Moreover, your finished product is formulated with (b)(4) which you also fail to adequately monitor for microbial contamination. Poorly controlled (b)(4) systems may harbor objectionable microorganisms, which may contribute to the contamination of your finished product.

另外，你们产品配制所用 XX 亦未进行足够的微生物污染监测。XX 系统控制不良可能会滋生致病菌，这可能会污染你们的成品。

Microbial testing of each batch is the last in aseries of essential CGMP controls that ensure a drug product is free of objectionable microorganisms and suitable for release.

对每个批次进行微生物检测是确保药品没有致病菌，可放行的一系列基本 CGMP 控制中最基本的要求。

In your response, you stated that you will establish specifications for your OTC drug products. However, your response is inadequate because you did not provide sufficient rationale that your established specifications are appropriate. Additionally, you did not perform a retrospective review and risk evaluation of OTC drug products currently in theU.S. market within expiry.

在你们的回复中，你们声称你们会为你们的 OTC 药品制订质量标准。但是你们的回复是不充分的，因为你们并未提交足够的理由说明你们所制订的质量标准是适当的。另外，你们亦未对当前仍在美国市场且在有效期内的 OTC 药品进行回顾性审核和风险评估。

In response to this letter, provide the following:

在回复本函时请提交以下内容：

- A comprehensive independent assessment of the design and control of your firm's manufacturing operations, with a detailed and thorough review of all microbiological hazards, not limited to your (b)(4) system.
  一份你们公司生产操作设计和控制的全面独立评价，连同对所有微生物危害（不仅限于你们的 XX 系统）的详细彻底审核。
- A detailed risk assessment addressing the hazards posed by distributing drug products with potentially objectionable contamination. Specify actions you will take in response to the risk assessment, such as customer notifications and product recalls.
  一份详细的风险评估，说明销售可能受致病菌污染的药品的危害。写明你们基于风险评估将采取的措施，例如通知客户和召回产品。
- All chemical and microbial test methods used to analyze each of your drug products.
  所有药品分析用化学和微生物检测方法
- Appropriate microbiological batch release specifications (i.e., total counts, identification of bioburden to detect objectionable microbes) for each of your drug products.
  每种药品恰当的微生物批放行标准（即，总计数，致病菌鉴别）
- A summary of results from testing reserve samples of all drug product batches within expiry. You should test all appropriate quality attributes including, but not limited to, identity and strength ofactive ingredients and microbiological quality (total counts and identification of bioburden to detect any objectionable microbes) of each batch. If testing yields an out-of-specification result, indicate the corrective actions you willtake, including notifying customers and initiating recalls.
  一份所有仍在效期内药品留样检测结果的汇总。你们应对所有适当的质量属性进行检测，包括但不仅限于所有批次的活性成分鉴别和含量和微生物质量（总计数和致病菌鉴别）。如果检测结果为 OOS 结果，应说明你们将要采取的纠正措施，包括通知客户和启动召回。
- A procedure governing your program for ongoing control, maintenance, and monitoring that ensures the system consistently produces (b)(4) that meets (b)(4) USP monograph specifications and appropriate microbial limits.

一份对你们实验室规范、程序、方法、设备、文件和化验员能力的全面独立评估。根据该审核结果，提交一份详细的计划补救和评估你们实验室系统的有效性

- A tabular summary of chemical and microbial monitoring results that you have collected from testing your (b)(4) system for the past two years. Within the table, also include the following:
  你们过去 2 年对 XX 系统检测中收集的化学和微生物结果，以表格方式汇总。在表格中请包括以下内容：
  - Specification for tested attribute
    所测属性的标准
  - Date of sampling
    取样日期
  - Point of use from which the sample was collected
    采集样品的使用点

2.Your firm failed to test samples of each component for identity and conformity with all appropriate written specifications for purity, strength, and quality.Your firm also failed to validate and establish the reliability of your component supplier's test analyses at appropriate intervals (21 CFR211.84(d)(1) and (2)).

你公司未检测每种组份样品的鉴别和相关项目，确保其符合所有书面的纯度、含量和质量标准。你公司亦未以适当时间间隔验证建立你们组份供应商的检测分析可靠性(21 CFR 211.84(d)(1) and (2))。

Your firm failed to adequately test your incoming components, including the active ingredient, for identity, strength, purity, and other appropriate quality attributes. Instead, your firm relied on certificates of analyses (COA) from unqualified suppliers. Identity testing for each component lot used in drug product manufacturing is required, and you can only rely on COA for other component attributes by appropriately validating the suppliers' test results at appropriate intervals. In addition, the COA for the incoming active ingredient lacks appropriate microbial testing.

你公司未对你们的进厂组份，包括活性成分进行足够的鉴定、含量、纯度和其它适当质量属性检测。相反，你公司依赖于未经确认的供应商的 COA。药品生产中所用每个批次组份均应进行鉴别测试，其它组份属性可在对供应商的检测结果以适当时间间隔进行适当验证之后依赖其 COA。另外，进厂活性成分的 COA 缺少适当的微生物检测。

Your response states you will ensure your suppliers send a "report of the percentage of each ingredient." Your response is inadequate because it lacks specificity regarding your supplier validation program or plans to test each lot of each shipment of incoming components. Additionally, your response did not address retrospective assessment of the OTC drug products distributed in the U.S. market with components that have not been adequately tested to ensure conformance to established specifications.

你们的回复中声称你们会确保你们的供应商发过来"每种组份的百分比报告"。你们的回复是不充分的，因为其中缺少了对你们供应商进行验证的程序说明，或对每次收到的进厂组份的每个批次进行检测的计划。另外，你们的回复亦未说明要对已销售至美国市场但未经过足够检测以确保其符合既定的标准的 OTC 药品进行回顾性评估。

In response to this letter, provide the following:

在回复本函时请提交以下内容：

- The chemical and microbiological quality control specifications you use to test and release each incoming lot of component foruse in manufacturing.
  你们用于检测和放行每批生产所用进厂组份的化学和微生物质量控制标准
- A description of how you will test each componentlot for conformity with all appropriate specifications for identity, strength, quality, and purity. If you intend to accept any results from your supplier's COA instead of testing each component lot for strength, quality, and purity, specify how you will robustly establish the reliability of your supplier's results through initial validation as well as periodic re-validation. Inaddition, include a commitment to always conduct at least one specific identity test for each incoming component lot.
  说明你们准备如何检测每种组份的每个批准，确保其符合所有适当的鉴别、含量、质量和纯度标准。如果你们准备接受你们供应商的所有 COA 结果，取代你们对每批进厂物料的含量、质量和纯度检测，则需说明你们准确如何通过初始验证和定期再验证稳固地建立你们供应商结果的可靠性。另外，在其中包括一份承诺，保证会一直对每批进厂物料执行至少一项特定鉴别项目。
- A summary of results obtained from testing all components to evaluate the reliability of the COA from each component manufacturer. Include your SOP that describes this COA validation program.
  一份所有组份检测所得结果的汇总，以评估来自每个组份生产商的 COA 的可靠性，其中要包括你们阐述该 COA 验证程序的 SOP。
- A summary of your program for qualifying and overseeing contract facilities that test the drug products you manufacture.
  对你们确认和监管检测你们所生产药品的合同场所的程序摘要
- A comprehensive assessment of your laboratory practices, procedures, methods, equipment, documentation, and analyst competencies. Based on this review, provide a detailed plan to remediate and evaluate the effectiveness of your laboratory system.
  一份对你们实验室规范、程序、方法、仪器、文件和化验员能力的全面独立评估。根据这些审核，提交一份详细的 CAPA 计划用于补救你们实验室系统的有效性。

3. Your firm failed to establish adequate written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess (21 CFR 211.100(a)).

你公司未能建立书面生产和工艺控制程序，设计用以确保你们生产的药品具备其理当具备或显示具备的鉴别、含量、质量和纯度（21 CFR 211.100(a)）。

Your firm failed to validate the processes used to manufacture your drug product. You have not performed process qualification studies, nor do you have a rigorous ongoing program for monitoring process control to ensure stable manufacturing operations and consistent drug quality.

你公司未对药品生产所用工艺进行验证。你们既未执行工艺确认研究，亦没有严格的工艺监测程序确保稳定的生产操作和一致的药品质量。

In your response you stated that you will draft an "operational guide for the process to control variability in the characteristics." Your response is inadequate because you did not provide sufficient details of the validation program for the process to ensure a robust and consistent process. You also did not discuss a plan to review previously manufactured products to ensure they were manufactured with appropriate process controls.

在你们的回复中，你们声称你们会起草一份“工艺操作指南以控制品质波动”。你们的回复是不充分的，因为你们并未提交能够确保工艺稳健和一致性的足够详细的工艺验证程序。你们亦未讨论制订一份计划对之前已生产药品进行审核，从而确保其生产符合适当的工艺控制。

Process validation evaluates the soundness of design and state of control of a process throughout its lifecycle. Each significant stage of a manufacturing process must be designed appropriately and ensure the quality of raw material inputs, in-process materials, and finished drugs. Failure to conduct these studies can result in product quality attribut efailures. Process qualification studies determine whether an initial state of control has been established. Before commercial distribution, successful process qualification studies are necessary. Thereafter, ongoing vigilant oversight of process performance and product quality is necessary to ensure you maintain a stable manufacturing operation throughout the product lifecycle. See FDA’s guidance document Process Validation: General Principles and Practices for general principles and approaches that FDA considers appropriate elements of process validation at http://www.fda.gov/media/71021/download.

工艺验证评估的是工艺生命周期中其设计合理性和受控状态。每个生产工艺的重大步骤均必须进行恰当设计，确保原料输入、中间体和成品的质量。未能实施这些研究可能会导致产品质量属性失败。工艺确认研究决定了是否已建立起初始受控状态。之后，要对工艺性能和产品质量进行持续警觉的监管，以确保你们能在整个产品生命周期中维持稳定的生产操作。参见 FDA 指南文件“工艺验证通则与规范”中 FDA 认为是恰当的工艺验证要素的通则与方法。

In response to this letter, provide the following:

在回复本函时请提交以下：

- A detailed program for designing, validating, maintaining, controlling, and monitoring each of your manufacturing processes that includes vigilant monitoring of intra-batch and inter-batch variation to ensure an ongoing state of control. Also, include your program for qualification of your equipment and facility.
  你们所生产的每个生产工艺的详细设计、验证、维护、控制和监测程序，其中包括对批间和批内波动的严格监测，以确保持续受控状态。还需包括你们的设备与设施确认计划。
- An assessment of each drug product process to ensure that there is a data-driven and scientifically sound program that identifies and controls all sources of variability, such that your production processes will consistently meet appropriate specifications and manufacturing standards. This includes, but is not limited to, evaluating suitability of equipment for its intended use, sufficiency of detectability in your monitoring and testing systems, quality of input materials, and reliability of each manufacturing process step and control.
  对每种药品工艺的评估，以确保根据数据和科学合理的计划识别所有波动来源并进行控制，使得你们的生产工艺可持续满足适当的标准和生产标准。其中包括但不仅限于评估设备是否合适其既定用途，你们监测和检测系统检测能力的充分性，输入物料的质量和每个生产工艺步骤和控制的可靠性
- Timelines for completed process performance qualification for marketed drug products for which a state of control has not been adequately/fully established.
  已上市但未充分/完全建立其受控状态的药品完成工艺性能确认的时间表

4. Your firm failed to establish and follow an adequate written testing program designed to assess the stability characteristics of drug products and to use results of stability testing to determine appropriate storage conditions and expiration dates (21 CFR211.166(a)).

你公司未建立和遵守足够的书面检测程序，设计用以评估药品的稳定性特性，以及使用稳定性测试结果确定适当的存贮条件和有效期（21 CFR 211.166(a)）。

Your firm does not have an adequate stability testing program to demonstrate that the chemical and microbiological properties of your drug product remain acceptable throughout the claimed expiry period of (b)(4). Without appropriate stability data, you cannot ensure your drug products meet established specifications and all pre-determined quality criteria throughout the drug product's assigned shelf-life.

你公司没有足够的稳定性测试程序证明你们药品在其声称的有效期 XX 内保持其化学和微生物品质仍可接受。没有适当的稳定性数据，你们就无法确保你们的药品在给定的货架期内满足既定的标准，和所有既定的质量标准。

In your response, you stated you will draft a "Product Stability Specification" and you will place a specific number of batches already distributed on stability. Your response is inadequate because you did not provide sufficient details, such as stability protocols that ensureall relevant quality criteria are incorporated in your new stability program. Furthermore, you did not indicate any actions to ensure or demonstrate that the chemical and microbiological properties of your drug product distributed in the United States remained stable throughout its 24-month expiry period.

在你们的回复中，你们声称你们会起草一份"产品稳定性质量标准"，并且你们会将一定数量的已销售批次放入稳定性考察中。你们的回复是不充分的，因为你们并未提交足够的详细内容，例如稳定性方案，确保将所有相关质量标准放入你们新稳定性计划。另外，你们说明为确保或证明你们已销售至美国的药品化学和微生物品质在 24 个月的有效期内保持稳定的措施。

In response to this letter, provide the following:

在回复本函时请提交以下内容：

- A comprehensive independent assessment and corrective action and preventive action (CAPA) plan to ensure the adequacy of your stability program. Your remediated program should include, but not be limited to:
  一份全面独立的评估和 CAPA 计划，以确保你们稳定性程序的充分性。你们改进后的程序应包括但不仅限于：
  - Stability-indicating methods
    稳定性指标性方法
  - Stability studies for each drug product in its marketed container-closure system before distribution is permitted
    允许销售之前每种药品模拟上市包装进行的稳定性研究
  - An ongoing program in which representative batches of each product are added each year to the program to determine if the shelf-life claim remains valid
    每年将每种药品的代表性批次加入稳定性考察计划，以确定货架期是否有效的持续性计划
  - Detailed definition of the specific attributes to be tested at each station (timepoint)
    在每个时间点要检测的具体项目的详细规定
- All procedures that describe these and other elements of your remediated stability program.
  阐述你们改进后稳定性程序的上述及其它要素的所有程序

Quality Systems 质量体系

Your firm's quality systems are inadequate. See FDA's guidance document Quality Systems Approach to Pharmaceutical CGMP Regulations for help implementing quality systems and risk management approaches to meet the requirements of CGMP regulations 21 CFR, parts 210 and211 at https://www.fda.gov/media/71023/download.

你公司的质量体系是不充分的。参见 FDA 指南文件"药物 CGMP 法规的质量体系方法"，帮助你们实施质量体系和风险管理方法，从而符合 21CFR 第 210 和 211 的 CGMP 规范要求。

CGMP Consultant Recommended CGMP 顾问建议

If your firm intends to resume manufacturing drugs for the U.S. market, based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualified as set forthin 21 CFR 211.34 to assist your firm in meeting CGMP requirements. We also recommend that the qualified consultant performs a comprehensive audit of your entire operation for CGMP compliance and evaluates the completion and efficacy of your corrective actions and preventive actions before you pursue resolution of your firm's compliance status with FDA.

鉴于我们在你公司所发现的违规情况，如果你公司准备继续为美国市场生产药品，我们强烈建议你们使用一位有 21 CFR 211.34 所述资质的顾问来协助你们公司符合 CGMP 要求。我们亦建议该具备资质的顾问对你们整体运营情况进行药品 CGMP 合规情况全面审计，并由其在你们寻求满足 FDA 合规要求之前对你们 CAPA 的完成情况和有效性进行评估。

Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

你们使用顾问并不能解除你们公司符合 CGMP 的义务。你们公司的高级管理层仍负有义务全面解决所有缺陷，确保持续 CGMP 符合性。

Responsibilities as a Contractor 作为合同商的义务

Drugs must be manufactured in conformance with CGMP. FDA is aware that many drug manufacturers use independent contractors such as production facilities, testing laboratories, packagers, and labelers.FDA regards contractors as extensions of the manufacturer.

药品生产必须符合 CGMP 要求。FDA 了解许多药品生产商使用独立合同方如生产场所、检测实验室、包装商和贴标商。FDA 将合同商作为生产商的外延部分来对待。

You and your customer (b)(4) have aquality agreement regarding the drugs you manufacture on their behalf. You are responsible for the quality of drugs you produce as a contract facility regardless of agreements in place with (b)(4) You are required to ensure that drugs are made in accordance with section 501(a)(2)(B) of the FD&C Act for safety, identity, strength, quality, and purity. See FDA's guidance document Contract Manufacturing Arrangements for Drugs: Quality Agreements at https://www.fda.gov/media/86193/download.

你们和你们的客户 XX 之间订有药品生产的质量协议。作为合同场所，虽然你们与药品所有者订有协议，但你们仍对你们所生产的药品负有义务。你们应确保药品生产符合 FDCA 第 501(a)(2)(B)条款对安全性、鉴别、剂量、质量和纯度的要求。参见 FDA 指南文件"药品合同生产安排：质量协议"。

Conclusion 结论

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of other violations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

FDA placed your firm on Import Alert 66-40 on March 09, 2020.

FDA 已于 2020 年 3 月 9 日将你公司置于进口禁令 66-40 中。

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产的新申报和增补申报的批准。

Failure to correct these violations may also result in the FDA continuing to refuse admission of articles manufactured at Hangzhou Linkeweier Daily Chemicals Co., Ltd., at 568 Dongfang Road, Yiqiao Town, XiaoShan District, Hangzhou, Zhejiang into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Articles under this authority may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

31. 320-20-31 2020-03-25 Pfizer Healthcare India 印度

Dear Mr. Bourla:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Pfizer Healthcare India Private Limited, FEI 3008316085, at Plots 116-117-118-119-111-123 (part), Jawaharlal Nehru Pharma City, Parawada, Visakhapatnam, Andhra Pradesh, India, from August29 to September 6, 2019.

美国 FDA 于 2019 年 8 月 29 日至 9 月 6 日检查了你们位于印度的 Pfizer Healthcare India Private Limited（辉瑞印度工厂）生产场所。

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See Title 21 Code of Federal Regulations (CFR), parts 210 and 211 (21 CFR parts 210 and 211).

本警告信总结了制剂生产严重违反 CGMP 的行为。参见 21CFR 第 210 与 211 部分。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

由于你们的制剂生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的药品根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C. 351(a)(2)(B)被认为是掺假药品。

We reviewed your September 27, 2019, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

我们已详细审核了你公司 2019 年 9 月 27 日对 FDA483 表的回复，并此告知已收到后续通信。

During our inspection, our investigator observed specific violations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

1. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

你公司未彻底调查已销售和未销售批次产品或其组份未经解释的差异或不符合其标准（21 CFR 211.192）。

Your facility manufactures (b)(4) injectable products. Your firm failed to conduct adequate investigations, including timely implementation of effective corrective action and preventive action (CAPA) plans.

你们场所生产 XX 注射剂。你公司未进行充分的调查，包括及时实施有效 CAPA 计划。

Failed Sterility Testing 无菌性检测不合格

You did not adequately investigate root causes and implement CAPA to address deficiencies regarding your sterility testing (b)(4). For example, in February 2019, you investigated the sterility failure of (b)(4) injection batch (b)(4). You determined the most probable root cause of this sterility failure was the “lack of robust (b)(4) integrity testing and possible non-integral drug product vials.”

You also stated that the source of the microbial contamination may have been a faulty (b)(4). This batchwas rejected. However, you continued to use the same (b)(4) and performed sterility testing for a substantial number of additional batches before you made corrections, including replacing the suspect (b)(4).

你们并未对根本原因进行充分调查，并执行 CAPA 解决你们无菌检测 XX 的缺陷。例如，2019 年 2 月，你们调查了 XX 注射剂批次 XX 的无菌检查不合格情况。你们认为最可能的根本原因是“缺乏稳健的 XX 完整性测试，药品西林瓶可能不完整”。你们还声称微生物污染来源可能是错误 XX。该批次被拒。但你们在整改包括替换可疑的 XX 之前继续使用相同的 XX，并对另外几批进行了大量无菌检测。

Your response stated that you will implement automated (b)(4) integrity testing, which is planned for July 2020. Previously, you lacked an automated integrity test, and instead relied on avisual check that was insufficient on its own to reliably detect (b)(4).

你们的回复声称你们将使用自动化 XX 进行完整性检测，计划实施时间为 2020 年 7 月。之前，你们缺少自动完整性检测，而是依赖于人工目视检查，仅靠人工目检无法可靠检出 XX。

You also indicated that, effective January 2020, you would inspect sterility test samples for integrity before introduction to the sterility (b)(4).

你们还说自 2020 年 1 月起，你们会在引入无菌 XX 之前对无菌性检测样品进行检查。

The timeliness of the CAPA to resolve these significant root causes was insufficient. Your response did not adequately address the delay in CAPA implementation. Your response also indicated that you had made revisions to the investigation and that these revisions were completed on September 27, 2019. However, your response lacked the revised investigation and the status of your CAPA progress.

解决这些重大根本原因的 CAPA 时间限是不充分的。你们的回复中并未充分说明为何延迟执行 CAPA。你们的回复亦说你们已对调查进行了修订，这些修订已于 2019 年 9 月 27 日完成。但是你们的回复中没的修订后的调查内容，以及你们的 CAPA 进度。

Environmental Monitoring Program 环境监测程序

You did not adequately investigate serious deficiencies in microbiology laboratory conditions and practices. Among the deficiencies were excessive occurrences of negative control plate contamination, high levels of contamination in environmental monitoring (EM) samples of the sterility test (b)(4), and disregarded EM data because of delayed plate readings. More specifically:

你们并未对微生物实验室条件和操作的严重缺陷进行充分调查。这些缺陷中，有阴性控制碟污染反复发生、无菌性检测 XX 环境监测（EM）样品有高水平污染、由于碟计数延迟弃除 EM 数据。更为具体的内容如下：

- You did not thoroughly investigate negative environmental trends observed in the (b)(4) used to support sterility testing. Repeated recoveries were observed in the (b)(4), including excessively high levels (e.g., (b)(4), too-numerous-to-count (TNTC)CFU/m3), in some cases, over a three month period.

你们并未对支持无菌性检测的 XX 中发现的不良环境趋势进行彻底调查。有过 3 个月时间里，在 XX 中观察到重复回收，包括有些检测中发现微生物水平超高（例如 XX，太多无法计数（TNTC）CFU/m3）。

- You did not adequately investigate numerous instances over a one year period of microbial growth on negative control plates. These plates were used to support the EM program in both your production and laboratory areas.
  你们并未对 1 年多时间里空白控制碟的大量事件进行充分调查。这些碟被用于支持你们生产和实验室区域的 EM 程序。
- You invalidated microbial results without adequate scientific justification. Between September 26 and December 23, 2018, your biological quality laboratory allowed EM and testing plates used for monitoring your facility to be incubated beyond the days established in procedures. You attributed this recurring issue to a lack of qualified personnel. These plates included but are not limited to EM of the (b)(4), negative control plates, and product bioburden analysis. The testing results were repeatedly invalidated as the counts were considered unreliable, although the risks posed by the potentially valid contamination findings and related impact were not sufficiently addressed. Approximately (b)(4) batches were made during this period.
  你们宣布微生物结果无效，却没有充分的科学论证。在 2018 年 9 月 26 日至 12 月 23 日之间，你们的生物质量实验室允许 EM 和检测碟用于监测你们要进行培养的设施，超出了程序中规定的天数。你们将该情况的发生归因于缺乏具备资质的人员。这些碟包括但不仅限于 XX 的 EM、空白控制碟和产品生物负载分析。虽然存在实际可能被污染的风险，并且也没有对相关影响进行科学说明，但你们因为认为计数不可靠而反复宣布检测结果无效。

Your investigation into the extended incubation of plates indicates that they were being read on a “(b)(4)” basis. While you indicate you were reading plates (b)(4), you lacked documentation of earlier readings performed before the extended incubation times. The investigation also discusses the commingling of media plates in the same bag that were overgrown to the point that one plate may have contaminated another plate.

你们对延长碟培养时间的调查说你们在 XX 基础上进行计数。虽然你们说你们对碟进行了计数，但你们缺少在延长培养时间之前的计数文件记录。调查还讨论了培养碟混装在相同袋子里，碟之间可能会接触而相互污染。

Laboratory data accuracy deficiencies were also cited in our September 2018 inspection.

实验室数据准确性问题在 2018 年 9 月我们的检查中已有指出。

In your response, you indicated there are ongoing investigations to address the root causes of the recurring growth on negative control plates. You indicated that you have taken initial measures such as adding a new media vendor and improving incubator maintenance.

在你们的回复中，你们说还在继续调查找出阴性控制碟反复长菌的根本原因。你们说你们已采取初步措施如增加新的培养基供应商和改进培养箱维护。

Regarding the significant adverse environmental monitoring trends in your sterility testing (b)(4), your response stated that no additional EM excursions had occurred in your (b)(4) since you initiated your CAPA. The CAPA steps included addition of a (b)(4) to the (b)(4), better disinfection of supplies, slower (b)(4) movements, and retraining.

关于你们无菌检测 XX 中的严重不良环境监测趋势，你们的回复说自从启动 CAPA 以来，在你们的 XX 中并未发生其它的 EM 超标。该 CAPA 步骤包括增加 XX 至 XX，对物品进行更好消毒，减慢 XX 动作和重新培训。

You also stated that you are improving overall laboratory capabilities and investigations systems.

你们还声称你们正在改进整体实验室能力和调查体系。

However, your response did not fully address how deficient laboratory controls, inadequate investigations, and delays in implementing CAPA compromised your firm's microbiological control program.

但是你们的回复并未全面说明有缺陷的实验室控制、不充分的调查以及 CAPA 执行延迟对你公司的微生物控制程序有何不良影响。

In response to this letter, provide the following:

在回复本函时请提交以下内容：

- A comprehensive assessment of your overall system for investigating deviations, discrepancies, complaints, out-of-limit results,out-of-specification results, and failures. Provide a detailed action plan to remediate this system. Your action plan should include, but not be limited to, significant improvements in investigation competencies, scope determination, root cause evaluation, CAPA effectiveness, quality assurance oversight, and written procedures. Address how your firm will ensure all phases of investigations are appropriately conducted.
  一份对你们偏差、差异、投诉、OOS 结果和失败调查的全面系统的全面独立评估。提交一份详细的行动计划以补救该系统。你们的行动计划应包括但不仅限于对调查能力、范围界定、根本原因评估、CAPA 有效性、质量部门监管和书面程序的重大改进。说明你们公司要如何确保恰当地执行了所有调查阶段。
- An assessment and remediation plan for your CAPA program. Provide a report that evaluates whether your firm effectively conducts root cause analysis, ensures CAPA effectiveness, regularly reviews investigations trends, implements improvements to the CAPA program when needed, ensures appropriate quality assurance decision rights, and is fully supported by executive management.
  对你们 CAPA 程序的评估和补救计划。提交一份报告评估你们公司是否有效执行了根本原因分析，确保 CAPA 有效性、定期审核调查趋势、必要时对 CAPA 程序进行改进、确保适当的质量保证决策权，以及执行管理层的全面支持。
- A complete assessment of documentation systems used throughout your manufacturing and laboratory operations to determine where documentation practices are insufficient. Include a detailed CAPA plan that comprehensively remediates your firm's documentation practices to ensure you retain attributable, legible, complete, original, accurate, contemporaneous records throughout your operation.
  一份在你们生产和实验室操作中所用的文件体系的完整评估，确定哪些文件记录做法不充分。要包括一份详细的 CAPA 计划，全面补救你们公司的文件记录规范，确保你们保持你们所有操作记录的可追溯性、清晰、完整性、原始性、准确度和同步性。
- A comprehensive, independent assessment of your laboratory practices, procedures, methods, equipment, documentation, analyst competencies, and resources. Regarding the latter, the

assessment should address the adequacy of qualified staff needed to produce reliable results within appropriate timelines as well as your practices for managing the tracking of samples and timely reading of test results. Based on this review, provide a detailed plan to remediate and evaluate the effectiveness of your laboratory system.

一份对你们实验室规范、程序、方法、设备和文件记录、化验员能力和资源的全面独立评估。关于后者，评估应说明在适当时间限内得到可靠结果所需的具备资质的员工的充分性，以及你们管理样品追踪和及时读取检测结果的规范。根据该审核，提交一份详细的计划补救和评估你们实验室系统的有效性。

- Your revised investigations regarding the sterility failure and the loss of environment control in the sterility testing (b)(4).The updated investigations should include, but not be limited to:

  你们修订后的无菌性不合格以及无菌性检测中环境控制缺失的调查。更新后的调查应包括但不仅限于:

  - A final summary of all factors that may have compromised (b)(4) integrity, corrective actions, and your re-qualification results.

    所有可能导致 XX 完整性、整改措施和你们重新确认结果的所有因素的最后总结。
  - Further explanation of the potential product container-closure integrityroot cause that appears to have been ruled out as a cause of the sterility failure. Provide a detailed summary of the defect and deviation rates that are relevant to container-closure integrity from your batch records over the last two years. In addition, explain the atypical manufacturing conditions that could impact container-closure integrity.

    对你们将可能的产品容器密闭器完整性根本原因排除是无菌性不合格原因的进一步解释。提交一份过去 2 年中你们批记录里与容器密闭器完整性有关的缺陷和偏差率的详细汇总。另外，解释一下可能影响容器密闭器完整性的异常生产条件。
- A summary of your completed negative control plate investigations that were ongoing at the close of the inspection.

  一份你们已完成的阴性控制碟调查的总结。在检查结果时你们正在进行该调查。
- Your response concerning extended incubation of media plates leading to the invalidation of EM results. Include a summary worksheet that documents the date that each plate was read, the date each plate was scheduled to be read, and the difference in the number of days between the actual date and the scheduled date. Clarify if you read and document microbial plates samples more than once during the incubation period and whether you document the results each time. Also provide your investigation for the TNTC result documented in PR#2466588. Include the methods used for bioburden, dilutions, and counting of microbes.

  你们关于延长培养碟培养时长导致 EM 结果无效的回复。包括一份记录每个碟计数的日期、每个碟计划计数日期以及实际计数与计划计数之间相关天数的表格汇总。说明你们在培养期间是否多次读取并记录了微生物碟样品计数结果，以及你们是否每次都记下结果。还请提交一份你们对 PR#2466588 中所记录的 TNTC 结果的调查，包括生物负载、稀释和微生物计数的方法。

Data Integrity Remediation 数据完整性补救措施

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. For guidance on establishing and following CGMP compliant data integrity practices, see FDA's guidance documents Data Integrity and Compliance With Drug CGMP at https://www.fda.gov/downloads/DRUGS/GuidanceComplianceRegulatoryInformation/Guidances/UCM495891.pdf and Questions and Answers on Current Good Manufacturing Practices—Laboratory

Controls at https://www.fda.gov/DRUGS/Guidances-Drugs/Questions-And-Answers-Current-Good-Manufacturing-Practices-Laboratory-Controls#17.

你们的质量体系不能充分确保数据的准确性和完整性，无法支持你们生产的药品的安全性、有效性和质量。参见 FDA 指南文件“数据完整性和药品 GMP 合规”及实验室控制 CGMP 问答指导建立和遵守 CGMP 合格数据完整性规范。

We acknowledge that you engaged a consultant to audit your operation and assist in meeting FDA requirements.

我们知悉你们正聘用顾问对你们的操作进行审计并协助你们符合 FDA 要求。

In response to this letter, provide the following:

在回复此函时请提交以下信息：

- A comprehensive investigation into the extent of the inaccuracies in data records and reporting including results of the data review for drugs distributed to the United States. Include a detailed description of the scope and root causes of your data integrity lapses.
  一份对数据记录和报告不准确性程度，包括销售至美国的药品的数据审核结果，的全面调查，要有一份对你们数据完整性问题范围与根本原因详细的描述。
- A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity and analyses of the risks posed by ongoing operations.
  你们药品质量中所发现的不合格情况的潜在影响的当前风险评估。你们的评估应包括由于受到数据完整性问题影响的药品放行导致的患者风险的分析，以及持续运营所具有的风险。
- A management strategy for your firm that includes the details of your global corrective action and preventive action plan. The detailed corrective action plan should describe how you intend to ensure the reliability and completeness of all data generated by your firm including microbiological and analytical data, manufacturing records, and all data submitted to FDA.
  你们公司的管理策略，包括你们全球 CAPA 计划详细情况。详细的纠正措施计划应说明你们准备如何确保你公司所生成的所有数据的可靠性与完整性，包括微生物和分析数据、生产记录和提交给 FDA 的所有数据。

Conclusion 结论

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility.You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of other violations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER’s Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug

manufacture under 21 U.S.C.356C(b). This also allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

如果你们在考虑要采取的措施可能会导致你们工厂所生产的药品供应中断，FDA 要求你立即联系 CDER 药品短缺负责人员，这样 FDA 可以与你们一起采用最为高效的方式引导你们的操作符合法规要求。联系药品短缺负责人员还能让你满足依据 21 U.S.C. 356C(b)你可能必须报告你们药品中止或中断的义务，让 FDA 尽快考虑是否需要采取何种措施来避免短缺，保护依赖于你们药品的患者健康。

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产的新申报和增补申报的批准。

Failure to correct these violations may also result in the FDA refusing admission of articles manufactured at Pfizer Healthcare India Private Limited, FEI 3008316085, at Plots 116-117-118-119-111-123 (part),into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C.381(a)(3). Articles under this authority may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

32. 320-20-32 2020-00-00 FDA 尚未发布

33. 320-20-33 2020-04-15 Shriram Institute for Industrial Research 印度

Dear Dr. Chacko:

The U.S. Food and Drug Administration (FDA) inspected your contract testing laboratory, Shriram Institute for Industrial Research, FEI 3002808145, at 19 University Road, University Campus, Delhi, from October 15 to 22, 2019.

美国 FDA 于 2019 年 10 月 15 日至 22 日检查了你们位于印度的 Shriram Institute for Industrial Research 生产场所。

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals, 21 CFR parts 210 and 211, and significant deviations from CGMP for active pharmaceutical ingredients (API).

本警告信总结了制剂生产严重违反 CGMP， 21CFR 第 210 与 211 部分，以及原料药生产严重违反 CGMP 的行为。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drugs are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

由于你们的生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的药品根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C.351(a)(2)(B)被认为是掺假药品。

We reviewed your November 7, 2019, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

我们已详细审核了你公司于 2019 年 11 月 7 日对 FDA 483 表格的回复，并此告知已收到后续通信。

During our inspection, our investigators observed specific violations and deviations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

Finished Drug Violations 制剂药品违规

1. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(a)).

你公司未对计算机或相关系统实施适当的控制，确保只有经过授权的人员才可修改主生产和检测记录，或其它记录（21 CFR 211.68(a)）。

Your firm serves as a contract testing laboratory analyzing both API and drug products. Your firm had not enabled the audit trail function on high-performance liquid chromatography (HPLC) units until on orabout October 11, 2019, when this FDA inspection was announced. Your analyst acknowledged during the inspection that the audit trail function on the HPLCs units was not enabled until October 2019. This was a repeat observation of your August 2016 FDA inspection.

你公司是一个合同检测实验室，分析 API 和制剂。你公司在 2019 年 10 月 11 日收到本次 FDA 检查通知以前均未激活 HPLC 上的审计追踪功能。你们的化验员在检查中承认在 2019 年 10 月之前 HPLC 上审计追踪功能未激活。这是 2016 年 8 月 FDA 检查中的重复缺陷。

Despite written commitments after that inspection to install audit trails, you failed to enable audit trail functions on multiple analytical instruments, including your HPLC units.

虽然在检查之后你们书面承诺要安装审计追踪，但你们有多台分析仪器（包括 HPLC 单元上）并未激活审计追踪功能。

Customers rely on the integrity of the laboratory data that you generate to make decisions regarding drug quality. It is important to maintain strict control over CGMP electronic data to ensure that all additions, deletions, or modifications of information in your electronic records are authorized and appropriately documented.

客户依赖于你们产生的实验室数据的完整性来做出药品质量方面的决策。为确保你们电子记录中所有信息增加、删除或修改均经过批准并有适当记录，保持对 CGMP 电子数据进行严格控制是很重要的。

In your response, your only corrective action was to designate an instrument engineer “to perform the routine inspection to proper performance of the equipment.” Your response is inadequate because it failed to describe specific controls you will implement to ensure audit trails remain enabled and the integrity of your data is not compromised.

在你们的回复中，你们仅有的纠正措施是指定一位仪器工程师“日常检查仪器是否工作正常”。你们的回复是不充分的，因为其中未说明你们为确保审计追踪保持激活，以及你们的数据完整性不受破坏而准备实施的具体控制措施。

In response to this letter, provide: 在回复本函时请提交

- A comprehensive, independent assessment of your laboratory practices, procedures, methods, equipment, documentation, and analyst competencies. Based on this review, provide a detailed plan to remediate and evaluate the effectiveness of your laboratory system.
  一份对你们实验室规范、程序、方法、设备、文件记录和化验员能力的全面独立评估。根据该评估，提交一份详细的补救计划，并评估你们实验室系统的有效性。

2. Your firm failed to establish adequate written responsibilities and procedures applicable to the quality control unit and to follow such written procedures (21 CFR 211.22(d)).

你公司未能制订并遵守书面的质量部门适用职责与程序（21 CFR 211.22 (d)）。

Your Quality Unit (QU) failed to ensure that your laboratory personnel follow written procedures. For example, our investigators observed at least (b)(4) samples tested between March 2019 and September 2019 in which out-of-specification (OOS) results were not investigated as required in your procedures. Your head of Quality Assurance informed our investigator during the inspection that failures are investigated only upon customer request. Additionally, our investigators observed procedures not followed for review of analytical logbooks and results.

你们的质量部门（QU）未能确保你们实验室人员遵守书面程序。例如，我们的检查员发现在 2019 年 3 月至 2019 年 9 月之间的检测中至少有 XX 个样品为 OOS 结果，但未按你们的程序要求进行调

查。你们的 QA 领导在检查期间告诉我们检查员只有在客户要求时才会对失败进行调查。另外，我们检查员发现你们亦未按程序要求对分析日志和结果进行审核。

These observations included: 这些缺陷包括：

- Documentation errors covered by adhering new paper over the original value.
  文件错误时在上面贴一张新纸盖住原始值
- Tests not recorded contemporaneously.
  未同步记录检测情况
- Sample identification not entered into your “Sample Record Register.”
  样品编号未录入你们的“样品记录登记本”
- Electronic data supporting analytical laboratory packets were not reviewed before you released final laboratory results.
  在最终放行实验室结果之前未审核支持分析实验室包的电子数据

In your response, you stated that the procedure for OOS was not followed, but going forward all OOS results will be investigated to identify root causes. Additionally, you committed to conduct further CGMP documentation practice training for your analysts. Your response is inadequate because you failed to perform a risk assessment of your lack of following OOS procedures and poor documentation practices on products you tested for commercial release.

在你们的回复中，你们声称未执行 OOS 程序，但将来会对所有 OOS 结果进行调查，找出根本原因。另外，你们承诺会对你们的化验员进行深入 CGMP 文件规范培训。你们的回复是不充分的，因为你们未对不遵守 OOS 程序和商业产品检测放行中不良文件规范进行风险评估。

In response to this letter, provide: 在回复本函时请提交

- A retrospective, independent risk assessment of documentation systems used throughout your manufacturing and laboratory operations to determine where documentation practices are insufficient. Includea detailed corrective action and preventive action (CAPA) plan that comprehensively remediates your firm’s documentation practices to ensure you retain attributable, legible, complete, original, accurate, and contemporaneous records throughout your operation. Specify actions you will take in response tothe risk assessment, such as customer notifications.
  一份对你们生产和实验室操作所用文件记录系统的回顾性独立风险评估，以确定哪些文件规范是不足的。要包括一份详细的 CAPA 计划，全面补救你公司的文件规范，确保你们会保存可追溯的、清晰的、完整的、原始的、准确的和同步的所有操作记录。说明你们对风险评估结果准备采取的措施，如通知客户。
- A retrospective, independent review of all OOS results for all tests. Identify any products which may be intended for the United States for the last three years from the initial date of inspection and a report summarizing the findings of the analysis, including the following for each OOS:
  一份对所有 OOS 检测结果的回顾性独立审核报告。找出所有在检查开始日之前三年内可能销售给美国的所有药品，汇总分析发现的问题，包括每个 OOS 的以下内容：

For all OOS results found by the retrospective review, identify any potential root cause and indicate if your customer was notified of the failure. Include the original test, date of test, testing result, customer, and reason for initiating an investigation.

对于回顾性审核中发现的所有 OOS 结果，找出所有潜在根本原因，说明是否将失败情况通知你们客户。要包括原始的检测信息、检测日期、检测结果、客户，以及启动调查的原因。

- The written response from your customers when notified of the testing failure(s).
  在告诉你们客户检测不合格时，客户的书面回复
- A comprehensive assessment and remediation plan to ensure your QU is given the authority and resources to effectively function.The assessment should also include, but not be limited to:
  一份全面的评估和补救计划，确保你们 QU 被授予权力和资源可有效运作。评估亦应包括但不仅限于以下：
  - A determination of whether procedures used by your firm are robust and appropriate
    确定你公司所用程序是否稳健恰当
  - Provisions for QU oversight throughout your operations to evaluate adherence to appropriate practices
    QU 对整体操作进行监管以评估是否遵守适当规范的条款
  - A complete and final review of each batch and its related information before the QU disposition decision
    QU 在批处置决策前对每个批次及其相关信息进行全面最终审核
  - Oversight and approval of investigations and discharging of all other QU duties to ensure identity, strength, quality, and purity of all products
    监管和批准调查，履行所有其它 QU 义务以确保所有产品的鉴别、含量、质量和纯度

Test Results Out-of-Specification 检测结果 OOS

For more information about handling failing, out-of-specification, out-of-trend, or other unexpected results and documentation of your investigations, see FDA's guidance document Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production at https://www.fda.gov/media/71001/download.

关于失败、OOS、OOT 或其它计划外结果处理和你们调查的文件记录更多信息，参见 FDA 指南文件"药品生产中 OOS 结果调查"。

Quality Systems 质量体系

Your firm's quality systems are inadequate. See FDA's guidance document Quality Systems Approach to Pharmaceutical CGMP Regulations for help in implementing quality systems and risk management approaches to meet the requirements of CGMP regulations 21 CFR, parts 210 and211 at https://www.fda.gov/media/71023/download.

你公司的质量体系是不充分的。参见 FDA 指南文件"药物 CGMP 法规的质量体系方法"，帮助你们实施质量体系和风险管理方法，从而符合 21CFR 第 210 和 211 的 CGMP 规范要求。

API Deviations API 偏差

3. Failure to ensure that all test procedures are scientifically sound and appropriate to ensure that your raw materials and API conform to established standards of quality and/or purity.

未能确保所有检测方法均科学合理恰当，能确保你们的原料和 API 符合既定质量标准和/或纯度要求。

Our investigators observed many examples of United States Pharmacopeia (USP) labeled material which were tested on your analytical instruments without the completion of system suitability testing prior to analysis. For example, a sample of (b)(4) USP, batch (b)(4), was tested using an atomic absorption spectrometer on January 15, 2019, without confirming system suitability testing. This was a repeat observation from the August 2016 FDA inspection.

我们的检查员发现许多标有 USP 的物料在你们分析仪器上检测时未完成系统适用性测试就开始进样。例如，一个 XX USP 样品批号为 XX，在 2019 年 1 月 15 日采用原子吸收光谱进行检测，检测前未进行系统适用性测试。这是 2016 年 8 月 FDA 检测中发现的重复缺陷。

After the previous inspection, your firm committed to performing system suitability testing on all analytical instruments “wherever required, prior to analysis” of USP tests. Additionally, your firm failed to document the testing method within laboratory records before issuing a certificate of analysis. You lacked adequate documentation to support that the USP labeled drug products were tested with USP methods.

上次检查后，你公司承诺会在所有仪器上在 USP 检测“需要时在分析之前”进行系统适用性测试。另外，你公司未在实验室记录中记录检验方法就签发了 COA。你们没有足够的文件记录支持标示为 USP 的该药品是采用 USP 方法检测的。

System suitability testing determines whether requirements for precision are satisfied and ensures that the analytical instrument is fit for the intended testing before analyzing samples. It is critical that your system be demonstrated as suitable for use to avoid the possibility of samples erroneously passing when an instrument is not working properly.

系统适用性测试决定系统是否满足精密度要求，在分析样品之前确保分析仪器适合于检测目的。证明你们的系统适合其用途，对于仪器工作不正常时避免样品被错判合格是非常关键的。

Customers rely on your laboratory data for critical information about the quality of drugs and their components. Thus, it is important that your analytical instruments are suitable for their intended use,and that you use appropriate test methods to enable your customers to make proper decisions (e.g., batch disposition).

客户依赖于你们的实验室数据中关于药品及其成分的关键质量信息。因此让你们的分析仪器适合其既定用途，并且使用适当的检测方法让你们的客户做出正确决策（例如批处置）是非常重要的。

In your response, you committed to perform system suitability testing on your laboratory equipment prior to analysis. Additionally, you committed to inform your clients of the need to performmethod verification before conducting analysis. Your response lacked sufficient interim measures to ensure equipment is suitable and methods are robust while you continue to test drug products. Additionally, you did not conduct a risk assessment for USP tests performed without system suitability testing.

在你们的回复中，你们承诺要在分析之前对你们的实验室仪器进行系统适用性检测。另外，你们承诺会告知你们客户在分析之前需要对方法进行确认。你们的回复中没有足够的临时措施确保你们继续检测药品时设备是适用的，方法是稳健的。还有你们未对无系统适用性的 USP 检测进行风险评估。

In response to this letter, provide: 在回复本函时请提交

- A retrospective, independent risk assessment addressing the hazards posed by providing USP test results of active pharmaceutical ingredients and drug products to clients without documenting the test method or performing system suitability testing on analytical instruments

prior to testing. Specify actions you will take in response to the risk assessment, such as customer notifications.
一份回顾性独立风险评估，说明向客户提供 API 和制剂的 USP 检测结果却没有记录检测方法或检测前在仪器上执行系统适用性测试的危害。说明你们应对风险评估结果准备采取的措施，如通知客户。

- A comprehensive, independent assessment of your laboratory practices, procedures, methods, equipment, documentation, and analyst competencies. Based on this review, provide a detailed plan to remediate and evaluate the effectiveness of your laboratory system. This assessment should include, but not be limited to:
一份对你们实验室规范、程序、方法、设备、文件记录和化验员能力的全面独立评估。根据此次审核，提交一份详细的补救计划，同时评估你们实验室系统的有效性。该评估应包括但不仅限于
  - Your procedure for carrying out system suitability testing prior to analysis on your laboratory equipment
  你们分析前在你们实验室仪器上执行系统适用性测试的程序
  - Your procedure for method verification for current and new methods performed within your laboratory
  你们在你们实验室对现有和新方法执行方法确认的程序
  - Your procedure for establishing responsibility for performing method verification between you and your clients
  划分你们和客户之间方法确认职责的程序

Repeat Observations at Facility 工厂重复缺陷

In a previous inspection, dated August 2-5, 2016, FDA cited similar CGMP observations. You proposed specific remediation for these observations in your response.

在之前 20160802--20160805 检查中，FDA 引用了类似的 CGMP 违规。在你们回程中，你们提出了对这些违规的具体补救方法。

Repeated failures demonstrate that executive management oversight and control over the manufacture of drugs is inadequate.

重复失败证明你们的执行管理监管和对药品生产的控制是不充分的。

CGMP Consultant Recommended CGMP 顾问建议

Based upon the nature of the violations and deviations we identified at your firm, we strongly recommend engaging a consultant qualified to evaluate your operations as set forth in 21 CFR 211.34to assist your firm in meeting CGMP requirements.

鉴于我们在你公司所发现的违规情况，我们强烈建议你们使用一位有 21 CFR 211.34 所述资质的顾问来协助你们公司符合 CGMP 要求。

Your use of a consultant does not relieve your firm’s obligation to comply with CGMP. Your firm’s executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

你们使用顾问并不能解除你们公司符合 CGMP 的义务。你们公司的高级管理层仍负有义务全面解决所有缺陷，确保持续 CGMP 符合性。

Data Integrity Remediation 数据完整性补救措施

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. See FDA's guidance document Data Integrity and Compliance With Drug CGMP for guidance on establishing and following CGMP compliant data integrity practices at https://www.fda.gov/media/119267/download.

你们的质量体系不能充分确保数据的准确性和完整性，无法支持你们生产的药品的安全性、有效性和质量。参见 FDA 指南文件"数据完整性和药品 GMP 合规"指导建立和遵守 CGMP 合格数据完整性规范。

We strongly recommend that you retain a qualified consultant to assist in your remediation. In response to this letter, provide the following:

我们强烈建议你们聘用顾问对你们的操作进行审计并协助你们符合 FDA 要求。在回复此函时请提交以下信息：

A. A comprehensive investigation into the extent of theinaccuracies in data records and reporting. Your investigation should include: 一份对数据记录和报告不准确性程度的全面调查。你们的调查应包括

- A detailed investigation protocol and methodology; a summary of alll aboratories and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
  详细的调查方案和方法学，所有实验室、生产操作和评估所覆盖的系统的总结，如有除外部分请论证
- Interviews of current and former employees to identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
  对现有和已离职员工进行面谈，找出数据不准确的程度、范围和根本原因。我们建议这些面谈由有资质的第三方进行。
- An assessment of the extent of data integrity deficiencies at yourfacility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe allparts of your facility's operations in which you discovered data integrity lapses.
  你们工厂数据完整性缺陷的程度的评估。识别出省略、修改、删除、记录销毁、不同步记录填写和其它缺陷。说明你们已发现的数据完整性问题所涉及的工厂操作。
- A comprehensive retrospective evaluation of the nature of the testing data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential breaches were identified should evaluateall data integrity lapses.
  一份对检测和生产数据完整性缺陷情况的全面回顾性评估。我们建议由具备在已发现可能有问题的领域的专业能力的有资质的第三方对所有数据完整性问题进行评估。

B. A current risk assessment of the potential effects of the observed failures on the quality of drugs you tested for commercial release. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity and analyses of the risks posed by ongoing operations.

你们药品质量中所发现的不合格情况的潜在影响的当前风险评估。你们的评估应包括由于受到数据完整性问题影响的药品放行导致的患者风险的分析，以及持续运营所具有的风险。

C. A management strategy for your firm that includesthe details of your global corrective action and preventive action plan. Your strategy should include: 你们公司的管理策略，包括你们全球 CAPA 计划详细情况。你们的策略应包括：

- A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all the data you generate including analytical data, and all data submitted to FDA.
  详细的 CA 计划，描述你们准备如何确保你们生成的所有数据的可靠性和完整性，包括分析数据、生产记录和所有提交给 FDA 的数据。
- A comprehensive description of the root causes of your data integrity lapses including evidence that the scope and depth of the current action planis commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related data at your firm.
  一份对你们数据完整性问题根本原因的全面描述，包括当前行动计划的范围和深度与调查和风险评估发现相称的证据。说明负责数据完整性的人员是否还有能力影响你公司与 CGMP 有关或药品申报数据。
- Interim measures describing the actions you have taken or will take to protect patients and to ensure the quality of drugs, such as notifying your customers and conducting additional testing.
  临时措施，描述你们已采取或将采取用来保护患者和确保你们药品质量的措施，如通知你们的客户、执行额外检测。
- Long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data.
  长期措施，其中描述所有对用以确保你们公司数据完整性的程序、流程、方法、控制、系统、管理监管和人力资源（例如培训、员工提高）的弥补和提升。
- A status report for any of the above activities already underway or completed.
  对上述活动已开展或已经完成的状态报告。

Conclusion 结论

The violations and deviations cited in this letterare not intended to be an all-inclusive list of violations and deviations that exist at your facility. You are responsible for investigating and determining the causes of these violations and deviations and for preventing their recurrence or the occurrence of other violations and deviations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

Until you correct all violations and deviations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a contract testing laboratory.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产的新申报和增补申报的批准。

Failure to correct these violations and deviationsmay also result in the FDA refusing admission of articles manufactured by your clients and tested at Shriram Institute for Industrial Research, 19 University Road, University Campus, Delhi into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Articles under this authority may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and deviations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

34. 320-20-34 2020-04-23 Kumar Organic Products Limited 印度

Dear Mr. Singh:

The U.S. Food and Drug Administration (FDA)inspected your drug manufacturing facility, Kumar Organic Products Limited, FEI 3009167769, at Plot No. 379, Canal Road, Maitri Marg, Village Luna,Taluka-Padra District, Vadodara, Gujarat, from November 11 to 14, 2019.

美国 FDA 于 2019 年 11 月 11 日至 14 日检查了你们位于印度的 Kumar Organic Products Limited 生产场所。

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See Title 21 Code of Federal Regulations (CFR), parts210 and 211 (21 CFR parts 210 and 211).

本警告信总结了制剂生产严重违反 CGMP 的行为。参见 21CFR 第 210 与 211 部分。

Our inspection noted that your firm produces theactive pharmaceutical ingredient (API) (b)(4). The (b)(4) by definition an in-process material for a finished drug product under Title 21, Code of Federal Regulations section 210.3(b)(9), and therefore subject to the CGMP regulations at 21 CFR 211.

我们检查中注意到你公司生产原料药（API）XX。该原料药根据 21CFR210.3(b)(9)定义为制剂的中间体，因此受 GMP 法规 21CFR211 监管。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug product is adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

由于你们的制剂生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的药品根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C. 351(a)(2)(B)被认为是掺假药品。

We reviewed your December 5, 2019, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

我们已详细审核了你公司 2019 年 12 月 5 日对我们 FDA483 表的回复，并此告知已收到后续通信。

During our inspection, our investigator observed specific violations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

1. Your firm failed to use equipment in the manufacture, processing, packing, or holding of drug products that is of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance (21 CFR211.63).

你公司在生产、加工、包装或保存药品时未使用经过适当设计、具备足够尺寸并适当定位安装的设备，便于其既定用途和清洁与维护（21 CFR 211.63）。

Your firm manufactures an over-the-counter topical drug product intended to treat (b)(4). You use (b)(4) produced at your facility as a component in manufacturing this drug product. Your firm's (b)(4) system was not adequately designed, maintained, or monitored to ensure that it consistently produces (b)(4) suitable for its intended use.

你公司生产治疗 XX 用的 OTC 局部用药品。你们在你们工厂使用 XX 作为组份生产该药品。你们公司的 XX 系统未进行充分的设计、维护或监测，无法确保其能持续生产出适合其既定用途的 XX。

Inadequate (b)(4) System Design Features and Maintenance

XX 系统设计特性和维护不够

Your (b)(4) distribution system had multiple design deficiencies and also lacked proper maintenance, both of which can foster the development of biofilms. For example:

你们的 XX 分配系统有多个设计缺陷，缺少适当的维护，这会导致生物膜生长。例如：

- You informed our investigator that you turn off your (b)(4) system when not in use.
  你们告诉我们的检查员说你们在不用的时候关闭了 XX 系统
- Your maintenance records indicate that the (b)(4) were last changed in August of 2014.
  你们的维护记录显示 XX 最后修改日期为 2014 年 8 月
- Your (b)(4) were found actively leaking when in use.
  你们的 XX 在使用时有泄漏
- Your cleaning procedures did not adequately addres show your storage tanks are sanitized.
  你们的清洁程序未能说明你们的贮罐是如何消毒的

Inadequate (b)(4) System Monitoring XX 系统监测不够

Your procedures for testing your (b)(4) system required (b)(4) point-of-use sampling for chemical analysis and (b)(4) sampling for microbiological analysis. Your (b)(4) sampling intervals were inadequate to ensure your (b)(4) meets its specifications before using it for production activities.

你们检测 XX 系统的程序要求在使用点取样进行化学分析，XX 取样用于微生物分析。你们的 XX 取样间隔不足以确保在用于生产活动之前你们的 XX 符合其质量标准。

In your response, you submitted drug product microbial test results. Your response is inadequate. Your results for microbial release testing of your drug product cannot be used to compensate for a poorly designed and maintained (b)(4) system.

在你们的回复中，你们提交了一份药品微生物检测结果。你们的回复是不充分的。你们的药品微生物放行检测结果不能用于补偿 XX 系统的设计和维护不良。

Further, you stated that you have not designed your system to control bioburden. However, you also stated that you rely on the (b)(4) system's filtration components and (b)(4) sanitization program to control the microbial load. You also committed to evaluate your (b)(4) system to identify needed design changes, implement the changes, and revalidate the system.

另外，你们声称你们并未设计你们的系统来控制生物负载。但是你们亦声称你们依赖于 XX 系统的过滤部件和 XX 消毒程序来控制微生物负载。你们亦承诺会评估你们的 XX 系统，找出设计所需的变更，执行变更并重新验证系统。

Your response is inadequate. Your response did not address leaks from your (b)(4) or the lack of continuous circulation.Your response also lacked scientific details of your overall maintenance program including but not limited to your sanitization program.

你们的回复是不充分的。你们的回复并未解决你们的 XX 的泄漏问题，亦未解决缺乏连续循环的问题。你们的回复亦缺乏你们整体维护计划的科学性细节，包括但不仅限于你们的消毒计划。

You also stated that your (b)(4) is tested on a (b)(4) basis. However, the revised sampling procedure included in your response did not revise your microbial monitoring interval. Your sampling intervals remain inadequate. Significantly more frequent microbial monitoring at all points of use for your (b)(4) system is necessary to ensure your (b)(4) meets its established limits before using it as a component for your drug product.

你们声称你们的 XX 检测周期为 XX。但是你们回复中修订后的取样程序并未修订你们的微生物监测时间间隔。你们的取样时间间隔仍是不充分的。有必要对你们 XX 系统的所有使用点均进行更为频繁的微生物监测，以确保你们的 XX 作为一种组份用于你们的药品生产之前符合其既定限度。

In response to this letter, provide the following: 在回复本函时请提交以下内容：

- A comprehensive remediation plan for the design, control, and maintenance of the (b)(4) system.
  一份对你们 XX 系统的设计、控制和维护全面补救计划
- A (b)(4) system validation report. Also include the summary of all improvements made to system design (e.g., newly installed equipment, elimination of deadlegs) and to the program for ongoing control and maintenance.
  XX 系统验证报告。还要包括对系统设计（例如新安装的设备、清除死管）的所有改进总结，以及持续控制和维护计划的改进总结
- Your total microbial count and objectionable microbes limits to monitor whether this system is producing (b)(4) suitable for the intended uses for each of your products and API.
  你们的总微生物计数和致病菌限度，监测该系统是否能为你们的制剂和 API 生产出适合其既定用途的 XX
- A detailed risk assessment addressing the potential effects of your inadequate monitoring on the quality of all drug product lots currently in U.S. distribution. Specify actions that you will take in response to the risk assessment, such as customer notifications and product recalls.
  一份说明你们监测不足对所有目前在美国销售的药品批次质量的可能影响的详细风险评估。写明你们应对风险评估结果准备采取的措施，例如通知客户和召回产品
- A procedure for your (b)(4) system monitoring that specifies routine microbial testing of (b)(4) points of use to ensure its acceptability for use in each batch of drug products produced by your firm.
  一份你们 XX 系统的监测程序，在其中说明 XX 使用点常规的微生物检测，确保其可用于你公司所生产的每批次药品
- A procedure governing your program for ongoing control, maintenance, and monitoring that ensures the remediated system consistently produces (b)(4) that meets (b)(4), USP monograph specifications and appropriate microbial limits.
  一份持续控制、维护和监测的管理程序，确保补救后的系统能持续产出符合 XX、USP 各论标准和适当微生物限度的 XX
- A comprehensive, independent assessment of your laboratory practices and competencies, with special focus on (b)(4) testing methods. Based on this review, provide a detailed plan to remediate and evaluate the effectiveness of your laboratory system.

一份对你们实验室规范和能力的全面独立评估，特别要关注 XX 的检测方法。根据该审核，提交一份详细的补救计划，并评估你们实验室系统的有效性

2. Your firm failed to test samples of each component for identity and conformity with all appropriate written specifications for purity, strength, and quality. Your firm also failed to validate and establish the reliability of your component supplier's test analyses at appropriate intervals (21 CFR 211.84(d)(1) and (2)).

你公司未检测每种组份样品的鉴别和相关项目，确保其符合所有书面的纯度、含量和质量标准。你公司亦未以适当时间间隔验证和建立你们组份供应商的检测分析可靠性(21 CFR 211.84(d)(1) and (2))。

Your failed to test incoming components (e.g., (b)(4)) for identity. Identity testing is required for each component lot before use in drug product manufacturing. For example, you did not conduct a specific identity test for (b)(4) used in the manufacture of (b)(4).

你公司未对你们的进厂组份 XX 进行鉴别检测。每种组份在用于药品生产之前应进行鉴别检测。例如，你们并未对 XX 生产所用 XX 进行鉴别检测。

In addition, your firm used a technical grade of (b)(4) as a component in your drug product. You failed to analyze incoming lots of (b)(4) for the presence of diethylene glycol (DEG) and (b)(4) before use in the manufacture of your drug product. Your (b)(4) supplier's certificate ofanalysis (COA) did not include testing for DEG (b)(4).

另外你们公司使用了工业级的 XX 作为你们药品的组份。你们在将其用于你们药品生产之前未分析进厂 XX 批次的 DEG 和 XX。你们的 XX 供应商 COA 中没有 DEG 的检测。

DEG contamination has resulted in various lethal poisoning incidents in humans worldwide. See FDA's guidance document Testing for Glycerin for Diethylene Glycol to help you meet the CGMP requirements when manufacturing drugs containing glycerin at https://www.fda.gov/media/71029/download.

DEG 污染已导致全球多次人类因毒致死事件。参见 FDA 指南"丙三醇中 EG 检测"，有助于你们满足 CGMP 要求前提下生产含有丙三醇的药品。

In your response, you stated that you reviewed all raw material specifications and committed to revise the specifications to include identity testing. You also revised the specifications for (b)(4) to include impurity testing for DEG and (b)(4) impurities with a specification limit of Not More Than (NMT) (b)(4). In addition, you committed to evaluating batches distributed to the U.S. for "this impurity" along with related substances. Lastly, you revised your vendor qualification procedure to require qualification of all raw material (component) manufacturers and associated suppliers to verify the reliability of the received COAs.

在你们的回复中，你们声称你们审核了所有原料质量标准，承诺会修订质量标准在其中加入鉴别检测。你们还修订了 XX 的质量标准，在其中包括了 DEG 和 XX 杂质的检测，标准限度规定为不得过（NMT）XX。另外，你们还承诺要评估已销售至美国的批准中"该杂质"和有关物质。最后，你们还修订了你们的供应商确认程序，要求对所有原料（组份）生产商和相关供应商均进行确认，核查所收到 COA 的可靠性。

Your response is inadequate. You did not commit to testing all component lots from your retain samples to ensure each were of expected quality for drug product batches within expiry. In addition, you did not provide a plan of action for any lots of components that failed to meet specifications. Lastly, your specifications for DEG and (b)(4) differed from the current USP monograph of NMT (b)(4).

你们的回复是不充分的。你们并未承诺对你们留样的所有组份进行检测，以确保效期内的所有药品批次具备预期质量。另外，你们亦未对不满足质量标准的组份批次采取的行动计划。最后，你们的 DEG 标准和 XX 与当前 USP 各论中 NMT XX 是有差异的。

In response to this letter, provide the following:

在回复本函时请提交以下内容：

- A comprehensive, independent review of your material system to determine whether all suppliers of components, containers, and closures are each qualified and the materials are assigned appropriate expiration or retest dates. The review should also determine whether incoming material controls are adequate to prevent use of unsuitable components, containers, and closures.
  一份对你们原料系统的全面独立审核，以确定是否所有组份、容器和密闭器的供应商均经过了确认，且物料有给定适当的有效期或复测期。审核后应确定进厂物料控制是否足以防止使用不适当的组份、容器和密闭器。
- The chemical and microbiological quality control specifications you use to determine disposition of each incoming lot of components before use in manufacturing.
  你们用于检测和放行每批生产所用进厂组份的化学和微生物质量控制标准
- A description of how you will test each component lot for conformity with all appropriate specifications for identity, strength, quality, and purity. If you intend to accept any results from your supplier's COA instead of testing each component lot for strength, quality, and purity, specify how you will robustly establish the reliability of your supplier's results through initial validation as well as periodic re-validation. In addition, include a commitment to always conduct at least one specific identity test for each incoming component lot.
  说明你们准备如何检测每种组份的每个批准，确保其符合所有适当的鉴别、含量、质量和纯度标准。如果你们准备接受你们供应商的所有 COA 结果，取代你们对每批进厂物料的含量、质量和纯度检测，则需说明你们准确如何通过初始验证和定期再验证稳固地建立你们供应商结果的可靠性。另外，在其中包括一份承诺，保证会一直对每批进厂物料执行至少一项特定鉴别项目。
- A summary of test results obtained from comprehensive testing of all incoming components to validate the COA from each manufacturer of raw material.
  一份所有组份检测所得结果的汇总，以评估来自每个组份生产商的 COA 的可靠性，其中要包括你们阐述该 COA 验证程序的 SOP。
- A commitment that you will use only pharmaceutical-grade components going forward.
  承诺你们往后只会使用药用级的组份
- Results of tests for DEG and (b)(4) in retain samples of all (b)(4) lots used to manufacture your drug products.
  你们药品生产所用的所有 XX 批次中的留样中 XX 和 DEG 检测结果
- A full risk assessment for drug products that contain (b)(4) and are within expiry in the U.S. market. Take prompt corrective actions and preventive actions, and detail your future actions

to ensure appropriate selection of your suppliers, ongoing scrutiny of their supply chain, and appropriate incoming lot controls.
一份对含有 XX 的药品在美国仍在效期内批次的全面风险评估。采取立即纠正措施和预防措施，以及详细说明你们未来的措施，以确保对供应商的适当选择，对其供应链的持续严格审查，以及对进厂批次的适当控制

- A full risk assessment for drug products manufactured with component lots that did not include testing for identification that are within expiry in the U.S. market. Take prompt corrective actions and preventive actions, and detail your future actions to ensure appropriate selection of your suppliers, ongoing scrutiny of their supply chain, and appropriate incoming lot controls.
对于采用未检测鉴别项的组份批次生产的销往美国且在有效期内的药品的全面风险评估。立即采取纠正和预防措施，详细说明你们未来的措施，以确保对供应商的适当选择，对其供应链的持续严格审查，以及对进厂批次的适当控制

CGMP Consultant Recommended CGMP 顾问建议

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualifiedas set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements.

鉴于我们在你公司所发现的违规情况，我们强烈建议你们使用一位有 21 CFR 211.34 所述资质的顾问来协助你们公司符合 CGMP 要求。

Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

你们使用顾问并不能解除你们公司符合 CGMP 的义务。你们公司的高级管理层仍负有义务全面解决所有缺陷，确保持续 CGMP 符合性。

Conclusion 结论

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of other violations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产的新申报和增补申报的批准。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

35. 320-20-35 2020-05-13 Samchundang Pharm 韩国

Dear Mr. Chun:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Samchundang Pharm Co., Ltd., FEI3008425092, at Hyangnam Pharmaceutical Industries Complex, 71 Jeyakgongdan2-Gil, Hyangnam-Eup, Hwaseong, si Gyeonggi, from October 17 to 25, 2019.

美国 FDA 于 2019 年 10 月 17 日至 25 日检查了你们位于韩国的 SamchundangPharm Co., Ltd.生产场所。

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See Title 21 Code of Federal Regulations (CFR), parts 210 and 211 (21 CFR parts 210 and 211).

本警告信总结了制剂生产严重违反 CGMP 的行为。参见 21CFR 第 210 与 211 部分。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug product is adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

由于你们的制剂生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的药品根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C. 351(a)(2)(B)被认为是掺假药品。

We reviewed your November 14, 2019, response to ourForm FDA 483 in detail and acknowledge receipt of your subsequent correspondence. We note that you have discontinued production of over-the-counter (OTC) (b)(4) drug products intended for distribution to the United States (U.S.); however, you failed to have adequate interim measures in place for products currently on the market within expiry.

我们已详细审核了你公司 2019 年 11 月 14 日对我们 483 表的回复，并此告知已收到后续通信。我们注意到你们已停止生产销售至美国市场的 XX OTC 药品，但你们并未对当前仍在市场且未失效的药品采取临时措施。

During our inspection, our investigators observed specific violations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

1. Your firm failed to establish and document the accuracy, sensitivity, specificity, and reproducibility of its test methods (21CFR 211.165(e)).

你公司未能建立和记录检验方法的准确性、灵敏度、专属性和重复性（21 CFR 211.165(e)）。

Your firm manufactures and aseptically fills (b)(4) drug products for distribution to the U.S. You did not establish the suitability of the sterility test method used for final release testing of (b)(4) of your finished drug products. In addition, you did not determine the suitability of the in-process bioburden test performed for each of your drug products.

你公司生产和无菌灌装 XX 药品，销售至美国。你们并未建立成品最终放行检测所用无菌性检测方法的适用性。另外，你们未确定每种药品中控生物负载检测的适用性。

Suitability testing must be performed for each drug product to ensure the sterility test method is valid. Suitability testing establishes that contamination, if present, will be detected. When inhibitionis encountered during suitability testing, test method modifications allow for optimized recovery.

每种药品均必须执行方法适用性测试，以确保无菌性检测方法有效。适用性测试证明如果有污染则能检出。如果在适用性测试中发现有抑菌性，则需要对方法进行修改优化回收率。

Your response stated that method validation had not been performed “due to lack of specific requirements” in your contract agreements. We remind you that you are responsible for the quality of drugs you produce and test as a contract facility, regardless of agreements in place with product owners. You are required to ensure that drugs are made in accordance with section 501(a)(2)(B) of the FD&C Act for safety, identity, strength,quality, and purity. See FDA’s guidance document Contract Manufacturing Arrangements for Drugs: Quality Agreements at https://www.fda.gov/media/86193/download.

你们的回复声称在因为委托协议中“没有特定要求”，因此未对方法进行验证。我们提醒你们对你们生产的药品负有义务，无论是否与产品所有者签订有协议，均应作为受托工厂进行检测。你们要确保生产的药品符合 FDCA 的 501(a)(2)(B)条款要求的安全性、鉴别、剂量、质量和纯度。参见 FDA 指南文件“药品委托生产协议：质量协议”。

Your response further stated that you would prepare and execute a “sterility method validation protocol” for each OTC product manufactured for the U.S. market by March 30, 2020. You proposed to have all marketed lots retested using the suitable method by May 30, 2020.

你们的回复说你们会为 2020 年 3 月 30 日之前销往美国市场的每种 OTC 药品起草并执行“无菌性方法验证方案”。你们提出使用 2020 年 5 月 30 日起使用适用的方法对所有已销售批次进行复测。

Your response is inadequate. You failed to address the interim risk posed to product released and distributed in the U.S. prior to establishing the suitability of your sterility testing methods. Similarly, you also failed to address the potential impact from your failure to ensure the suitability of the in-process bioburden test.

你们的回复是不充分的。你们未解决在建立你们无菌性检测方法适用性之前已放行销售至美国产品的临时风险。同样，你们亦未解决你们失败对确保中控生物负载检测适用性的潜在影响。

In response to this letter, provide:

在回复本函时请提交：

- A comprehensive assessment of your laboratory practices, procedures, methods, equipment, documentation, and analyst competencies. Based on this review, provide a detailed plan to remediate and evaluate the effectiveness of your laboratory system.
  一份对你们实验室做法、程序、方法、设备、文件和化验员能力的全面评估。根据该审核结果，提交一份详细的计划补救和评估你们实验室系统的有效性
- Your updated methods and a summary of any changes made to the previously established methods based on the results of your validation studies (including suitability testing).
  你们更新后的方法，以及根据你们验证研究的结果（包括适用性测试）对之前已建立方法的所有变更汇总

- Results of the retrospective sterility testing of all reserve batches of U.S. marketed drug products within expiry as of the dateof this letter. Include your protocol and timeline for testing the reserve batches, and a summary of all results. If testing yields an OOS result, indicate the corrective actions you will take, including notifying customers and initiating recalls.
  所有销售至美国在签发本函时尚未过期的批次的留样的回顾性无菌性测试结果。包括你们对留样进行检测的方案和时间表，以及所有结果的汇总。如果检测发现有 OOS 结果，则应说明你们要采取的纠正措施，包括通知客户和启动召回。
- A risk assessment of the U.S. marketed batches of drug product in distribution and within expiry as of the date of this letter.
  一份对已销往美国在签发本函时尚未过期的药品批次的风险评估。

2. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR211.42(c)(10)(iv)).

你公司未能建立足够的系统监测无菌加工区域的环境条件（21 CFR 211.42(c)(10)(iv)）。

You did not routinely identify isolates recovered during environmental monitoring of your aseptic processing areas where your sterile drug products are filled. Per your procedure, SOP for Microbial Identification Management (QS-508), recovered isolates are grouped according to visual morphology. From the grouping of isolates with similar morphology, only one isolate is routinely identified for species determination.

你们日常没有鉴别无菌灌装区域环境监测过程中回收分离的菌。根据你们的程序"微生物鉴别管理SOP（QS-508）"，回收分离菌应根据目视形态进行分类。在将类似形态分离菌分类时，只有一种分离菌在日常进行了种鉴定。

In addition, your personnel monitoring program specifies alert and action limits of three CFU/plate and four CFU/plate, respectively, for personnel working in the aseptic processing operation, including (b)(4) samples. Manufacturing personnel who perform operationsin aseptic processing spaces should normally maintain contamination-free (b)(4) throughout operations. It is important to set action limits accordingly.

另外，你们的人员监测程序规定无菌加工操作工作人员的警戒限和行动限分别为 3CFU/碟和 4CFU/碟，包括 XX 样品。在无菌加工空间进行操作的生产人员应在整个操作过程中保持不受 XX 污染。设置相应的行动限是非常重要的。

Inadequate environmental and personnel monitoring practices may obscure the type and level of microbiological contamination in your aseptic processing facility. Vigilant environmental and personnel monitoring provides ongoing information on the state of control of your facility. Growth observed on (b)(4) samples taken from personnel who can perform any activities within the ISO 5 areas should trigger an appropriate investigation.

环境和人员监测不足可能会模糊化你们无菌加工设施中的微生物污染类型和水平。对环境和人员监测保持警惕能为你们工厂保持受控状态持续提供信息。在 ISO5 级区域内从事任何活动的人员上取的 XX 样品上发现有菌生长均应触发适当的调查。

In response, you stated you would revise your procedure for microbial identification to require the the identification of all isolates from your "Grade A" and "Grade B" areas, and documentation of the morphology and microscopic inspection of all other isolates. You further proposed to refine isolate

grouping based on “area, operational condition, area classification, different means of collection (settle plate, air sample, surface monitoring and personnel monitoring) and type of morphology.”

在回复中你们声称你们会修订你们的微生物鉴别程序，要求对所有 A 级和 B 级区分离的菌进行鉴别，并记录所有其它分离菌的形态和镜检结果。你们还提出要根据“区域、操作条件、区域级别、不同采集方式（沉降碟、浮游菌、表面监测和人员监测）和形态类型”重新规定分离菌的分组。

Your response is inadequate because you did not comprehensively address the environmental and personnel monitoring deficiencies and the effect of such deficiencies on the quality of distributed drug products. You also failed to include requirements for frequent identification of microorganisms to the species (or, where appropriate, genus) level in the ancillary clean rooms beyond your aseptic processing room to maintain a current and valid database.

你们的回复是不充分的，因为你们并未全面解决环境和人员监测缺陷问题，以及此类缺陷对已销售产品的质量缺陷影响。你们亦未包括将在你们无菌加工室外辅助洁净区经常发现微生物鉴定至种的要求（或者适当时鉴别至属），以维持现行有效的数据库。

In response to this letter, provide a comprehensive, independent and retrospective review of personnel and environmental monitoring data since 2018. This review should include your assessment and corrective action and preventive action (CAPA) for your environmental monitoring program (including personnel monitoring) to ensure the CAPA supports robust environmental control of your aseptic processing facility. The assessment and CAPA, including any recommendations from the independent review, should include justification of sampling locations, frequency of sampling, alert and action limits, adequacy of sampling techniques, and the trending program.

在回复本函时，请提交一份对 2018 年至今的人员和环境监测数据的全面独立回顾性审核。该回顾应包括你们对环境监测程序（包括人员监测）的评价和纠正与预防措施（CAPA），从而确保 CAPA 支持对你们无菌加工设施进行稳健的环境控制。该评估和 CAPA，包括所有来自独立回顾的建议应包括有取样点位置、取样频次、警戒限和行动限、取样技术充分性和趋势分析程序的论证。

See FDA’s guidance document, Sterile Drug Products Produces by Aseptic Processing – Current Good Manufacturing Practice, to help you meet the CGMP requirements when manufacturing sterile drugs using aseptic processing, at https://www.fda.gov/media/71026/download.

参见 FDA 指南文件“无菌工艺生产的无菌药品 CGMP”。

3. Your firm failed to ensure that each person engaged in the manufacture, processing, packing, or holding of a drug product has the education, training, and experience, or any combination thereof, to enable that person to perform his or her assigned functions (21 CFR 211.25(a)).

你公司未能确保每个从事生产、加工、包装或保存药品的人员具备教育背景、培训和经验，或这些的结合，以使得这些人员能够执行指定给其的职能（21 CFR 211.25(a)）。

Your firm failed to ensure that all personnel are trained as appropriate. Training deficiencies were noted for personnel operating in management, production, quality assurance, and quality control positions. For example, employees engaged in the manual visual inspection of (b)(4) drug products were not trained at the intervals specified in your SOP; analysts who perform foreign matter (visible particulate) testing were not certified as required by your SOP; and some personnel lacked training records.

你公司未能确保所有人员均接受了恰当的培训。我们发现管理人员、生产人员、质量保证人员和质量控制岗位人员的培训缺陷。例如，从事人工目检 XX 药品的人员未按你们 SOP 规定的时间间隔接受培训，执行异物检测（可见颗粒）的化验员未按你们的 SOP 得到认可，还有一些人员缺少培训记录。

We also observed laboratory data deficiencies during the inspection, which you attributed to inadequate SOPs, software, and training.

我们还发现实验室数据缺陷，你们将其归因于 SOP、软件和培训不足。

Training is essential to ensure proper performance of job functions by your firm's employees, including those responsible for oversight and management of personnel.

培训对于确保你们员工（包括那些负责人员监管和管理的职员）很好履行岗位职责来说至关重要。

In your response, you stated that you had initiated an investigation into the failure to conduct training as specified, and that you would update the training matrices of all employees. You further stated that you would ensure all training is provided as required.

在你们的回复中你们声称你们已启动调查程序，对未按规定执行培训进行调查，你们会更新所有员工的培训矩阵。你们还说你们会确保按规定提供所有培训。

Your response is inadequate. You did not addressthe reasons for the lapse in oversight of your training program, and you did not provide a detailed plan for assessing the effectiveness of your training.

你们的回复是不充分的。你们并未解决你们培训程序监管错漏的理由，你们亦未提交评估你们培训有效性的详细计划。

In response to this letter, provide:

在回复本函时请提交：

- A complete assessment of documentation systems usedthroughout your manufacturing and laboratory operations to determine where documentation practices are insufficient. Include a detailed CAPA plan that comprehensively remediates your firm's documentation practices to ensure you retain attributable, legible, complete, original, accurate, and contemporaneous records throughout your operation.
  一份生产和实验室操作所用文件记录系统的全面评估，以确定文件记录规范是否存在不足。要包括一份详细的 CAPA 计划，全面补救你公司的文件记录规范，以确保你们保存了所有操作的可追溯、清晰、完整、原始、准确和同步的记录。
- A comprehensive assessment and CAPA for your training program, including practices, records, staff competencies, and effectiveness throughout your operations. Specific gaps should be identified for remediation after assessing the capability of your program to ensure:
  一份你们培训程序的全面评估和 CAPA，包括规范、记录、员工能力和你们操作有效性。在评价了你们程序的能力之后，应识别出需要补救的差距，以确保：
  - job functions and training needs are reviewed on an ongoing basis to monitor whether staff competencies are robust
    会持续审核岗位说明和培训需求，监测员工能力是否足够

- training is conducted with sufficient frequency to assure employees maintain understanding of all applicable CGMP requirements
  按足够的频次进行培训，以确保员工保持了解所有适用 CGMP 要求
- all staff who conduct or supervise CGMP functions are properly trained in CGMP, so that your operations are performed in a manner that assures drug safety, identity, strength, quality, and purity
  所有执行或监督 CGMP 工作的员工均接受了适当的 CGMP 培训，这样你们的操作能确保药品安全性、鉴别、剂量、质量和纯度
- qualified individuals perform training
  有资质的人员执行培训
- provisions are implemented for evaluating staff comprehension, training effectiveness, and ensuring appropriate modifications where needed
  有条款评估员工理解情况、培训有效性和确保在必要时进行适当的修改

- A summary of your current training program.
  一份对你们现行培训程序的摘要
- Your plan to improve oversight of your training program.
  你们对培训程序的改进监管计划
- An assessment of the impact of the lack of appropriate training on marketed drug products.
  缺少恰当培训对已上市药品的影响评估

Drug Production Ceased 停止药品生产

We acknowledge your commitment to cease production of drugs for the U.S. market. In response to this letter, clarify whether you intend to resume manufacturing drugs for the U.S. market at this facility in the future.

我们知悉你们承诺要停止为美国市场生产药品。在回复本函时，请澄清你们未来是否准备恢复在该场所为美国市场生产药品。

If you plan to recommence manufacturing drugs for the U.S. market, notify this office before resuming your operations.

如果你们计划继续为美国生产药品，请在恢复运行之前通知本办公室。

CGMP consultant recommended CGMP 顾问建议

If your firm intends to resume drug manufacturing for the U.S. market, we strongly recommend engaging a consultant qualified asset forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements.

如果你公司准备恢复为美国市场生产药品，我们强烈建议你们使用一位有 21 CFR 211.34 所述资质的顾问来协助你们公司符合 CGMP 要求。

Your use of a consultant does not relieve your firm’s obligation to comply with CGMP. Your firm’s executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

你们使用顾问并不能解除你们公司符合 CGMP 的义务。你们公司的高级管理层仍负有义务全面解决所有缺陷，确保持续 CGMP 符合性。

Conclusion 结论

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of other violations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产的新申报和增补申报的批准。

Failure to correct these violations may also result in the FDA refusing admission of articles manufactured at Samchundang PharmCo., Ltd., 71 Jeyakgongdan 2-Gil, Hyangnam-Eup, Hwaseong, si Gyeonggi, Republicof Korea, into the United States under section 801(a)(3) of the FD&C Act,21 U.S.C. 381(a)(3). Articles under this authority may be subject to refusal ofadmission, in that the methods and controls used in their manufacture do notappear to conform to CGMP within the meaning of section 501(a)(2)(B) of theFD&C Act, 21 U.S.C. 351(a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

36. 320-20-36 2020-05-29 Cosmaceutical Research Lab 加拿大

Dear Mr. Ghuman:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Cosmaceutical Research Lab Inc., FEI3003878590, at 12920 84th Avenue, Surrey, BC, Canada, from November 18 to 22,2019.

美国 FDA 于 2019 年 11 月 18 日至 22 日检查了你们位于加拿大的 Cosmaceutical Research Lab Inc.（FEI3003878590）生产场所。

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See Title 21 Code of Federal Regulations (CFR), parts210 and 211 (21 CFR parts 210 and 211).

本警告信总结了制剂生产严重违反 CGMP 的行为。参见 21CFR 第 210 与 211 部分。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

由于你们的制剂生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的药品根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C. 351(a)(2)(B)被认为是掺假药品。

In addition, you manufacture OTC drug products “Dr.Numb® Lidocaine Cream 4% - Topical Anesthetic” and “Dr. Numb® Lidocaine Cream.”“Dr. Numb® Lidocaine Cream 4% - Topical Anesthetic” is an unapproved new drugin violation of section 505(a) of the FD&C Act, 21 U.S.C. 355(a) and isalso misbranded under section 502(j) of the FD&C Act, 21 U.S.C. 352(j). Introduction or delivery for introduction of such a product into interstate commerce is prohibited under sections 301(a) and (d) of the FD&C Act, 21U.S.C. 331(a) and (d). “Dr. Numb® Lidocaine Cream” is an unapproved new drug inviolation of section 505(a) of the Federal Food, Drug, and Cosmetic Act(FD&C Act), 21 U.S.C. 355(a). Introduction or delivery for introduction of such a product into interstate commerce is prohibited under section 301(d) of the FD&C Act, 21 U.S.C. 331(d). These violations are described in more detail below.

另外，你们生产 OTC 药品“Dr. Numb® Lidocaine Cream 4% - Topical Anesthetic”和“Dr.Numb® Lidocaine Cream.”。前者是一种未经批准的新药，违反 FDCA 第 505(a)款 21 U.S.C. 355(a)，且根据 FDCA 第 502(j)款 21 U.S.C. 352(j)为冒牌药品。引入或输送此类药品至州际贸易是被 FDCA 第 301(a)款 21 U.S.C. 331(a) 和 (d)禁止的。后者是一种未经批准的新药，违反 FDCA 第 505(a)款 21U.S.C. 355(a)，引入或输送此类药品至州际贸易是被 FDCA 第 301(a)款 21 U.S.C. 331(a) 和 (d)禁止的。这些违规情况在下文中将详细说明。

We reviewed your December 13, 2019, response to our Form FDA 483 in detail.

我们已详细审核了你公司 2019 年 12 月 13 日的回复。

During our inspection, our investigator observed specific violations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

CGMP Violations CGMP 违规

1. Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to ensure compliance with established specifications and standards (21 CFR 211.194(a)).

你公司未能确保实验室记录中包括有为确保符合既定标准所需检测中得到的完整数据（21 CFR 211.194(a)）。

Your firm performed extra injections without aclearly identified purpose and using ambiguous nomenclature.

你公司在没有清楚写下目的情况下即进行了额外进样，并使用了模糊的命名。

You injected samples with the intention of obtaining an “unofficial” result and/or failed to clearly indicate if the single injections were standards to determine whether high-performance liquid chromatography (HPLC) instruments were fit for use. For example:

你们进样目的是获得一个“非正式”结果和/或未能清楚说明某个进样是否用于确定 HPLC 仪器是否符合其用途的对照品，例如：

a) On April 25, 2019, at 3:37pm, you performed an HPLC injection with a blank “sample name” field. Afterwards, you ran a sample set of(b)(4), lot (b)(4), at (b)(4). Both the initial injection and the (b)(4) sample set had similar chromatograms and retention times. Only the results from (b)(4) were reported as the final results.

2019 年 4 月 25 日下午 3:37，你们进样 HPLC，“样品名称”为空。之后，你们在 XX 运行了一个样品序列。首针进样和 XX 样品序列有着相似的图谱和保留时间，只有 XX 的结果被报告为最终结果。

b) On September 19, 2019, at 2:52pm, you performed an HPLC injection with a name of “(b)(4)” in the “sample name” field. Afterwards, you ran (b)(4) for (b)(4) pain reliever (b)(4),lots (b)(4), at 4:19pm and (b)(4). All (b)(4) in this series of injections performed that day had similar chromatograms and retention times. Only the results from 4:19pm and (b)(4) were reported as the final results.

2019 年 9 月 19 日，下午 2:52，你们进样 HPLC，“样品名称”为“XX”。之后，你们在 4:19 和 XX 进样止痛药批号 XX 样品。当天该进样序列中所有 XX 的色谱图和保留时间均相似，但只有 4:19 和 XX 的结果报告为最终结果。

We also found torn documents in the trash related to quality and production.

我们还在垃圾中发现了撕碎的质量和生产相关文件。

In response, you stated that you will file adeviation and take corrective action regarding the unofficial injection issue.

在回复中，你们声称你们会提交非正式进样问题的偏差，采取纠正措施。

You stated that the injection named “(b)(4)” was a standard. However, other standards run on that day were labeled as “Std.”

你们声称命名为“XX”的进样为一个对照品。但是当天其它的对照品样品标记为“Std.”。

You also committed to reviewing your audit trialson a (b)(4) basis.

你们还承诺要每 XX 审核你们的审计追踪。

Regarding the improper disposal of quality and production documents, you stated you would revise your procedures on controlling, duplicating, and archiving documents and will retrain all staff. Your brief response lacked details regarding corrective and preventive actions, including but not limited to, a comprehensive review of laboratory and documentation system vulnerabilities.

关于质量和生产文件的不当处置，你们声称你们会修改你们的文件控制、复制和归档程序，并重新培训所有员工。你们的简单回复缺乏纠正预防措施方面的细节，包括但不仅限于对实验室和文件记录系统薄弱情况的全面审查。

Unofficial sample injections are not acceptable. All analytical data must be retained and reviewed as part of the official record.

非正式样品进样是不可接受的。所有的分析数据都必须作为正式记录的一部分保存并审核。

In response to this letter, provide:

在回复本函时请提交：

- An update on the unofficial injection assessment and other data integrity assessments performed by your third party. Include acopy of your protocols, and any interim and final reports. See the Data Integrity Remediation heading on page six of this letter for additional requests.
  一份由第三方执行的更新后的非正式进样评估，以及其它数据完整性评估。包括一份你们的方案，以及所有临时和最终报告。参见本函第 6 页数据完整性补救标题下其它要求。
- A complete assessment of documentation systems used throughout your manufacturing and laboratory operations to determine where documentation practices are insufficient. Include a detailed corrective action and preventive action (CAPA) plan that comprehensively remediates your firm's documentation practices to ensure you retain attributable, legible, complete, original, accurate, contemporaneous records throughout your operation.
  一份对你们生产和实验室操作所用文件记录系统的完整评估，确定哪些文件记录规范有不足之处。要包括一份详细的纠正和预防措施（CAPA）计划，全面补救你们公司的文件系统规范，确保保存你们所有操作的可追溯、清晰、完整、原始、准确同步记录。

2. Your firm failed to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity (21 CFR 211.160(b)).

你公司未能建立实验室控制，在其中包括科学合理和恰当的质量标准、取样计划和检测方法，以确保组份、药品容器、密闭器、中控物料、标签和成品符合恰当的鉴别、剂量、质量和纯度标准（21 CFR 211.160(b)）。

You lacked impurity testing and used deficient testing methods for your products. For example:

你们产品没有杂质检测，有些检测方法有缺陷。例如，

a) You lacked impurity testing for your products, including, but not limited to, (b)(4) and (b)(4). (b)(4) may contain a potentially carcinogenic impurity called (b)(4). Becauseyou did not test for (b)(4), you do not know the amount of (b)(4) in the final product to which a user might be exposed.

你们产品没有杂质检测，包括但不仅限于 XX 和 XX。XX 可能含有 XX 潜在基因毒性杂质。因为你们并未测试 XX，你们并不知道成品中使用者可能会暴露于 XX 的数量。

b) Your analytical test methods were deficient, including but not limited to, AM-011 Determination of (b)(4) in Raw Material and (b)(4) by HPLC, for your (b)(4). Range was not evaluated adequately with respect to accuracy and precision. It did not appear that accuracy was conducted on spiked placebo formulations. Accuracy testing was conducted on standard solutions whose composition is not representative of the final product. Furthermore, precision was not reported for the low or high concentrations used to determine the calibration function for range analysis.

你们的分析方法有缺陷，包括但不仅限于 AM-011“HPLC 方法检测原料和 XX 中的 XX”。该方法的准确度和精密度未进行充分评估。该方法未采用加标制剂测试准确度。准确度测试是采用标准溶液测试的，其组成不能代表成品。另外，未报告范围分析中校正函数计算所用的高低浓度的精密度。

In your response, you stated that you will investigate impurity testing on finished products. You stated that you willtest your raw materials method against the USP method. Your response lacked details, such as specific plans for finished product impurity testing and how you revised or intend to revise your raw material and finished product testing.

在你们的回复中，你们声称你们会对成品的杂质检测进行调查。你们声称你们会根据 USP 要求测试你们的原料分析方法。你们的回复不够详细，例如具体的成品杂质检测计划，以及你们已经如何修订了或准备如何修订你们的原料和成品检测。

In your response, provide: 在你们的回复中请提交：

- A list of chemical and microbial specifications, including test methods, used to analyze each lot of your drug products before a lot disposition decision.
  一份用于批处理决策前分析你们每批药品所用的化学和微生物的检测方法及其标准清单
- An action plan and timelines for conducting full chemical and microbiological testing of retain samples to determine the qualityof all batches of drug product distributed to the United States that are within expiry as of the date of this letter.
  一份执行留样全面化学和微生物检测的行动计划与时间表，以确定销售至美国且在签发本函时仍在效期内的所有批次药品的质量
- A summary of all results obtained from testing retain samples from each batch. If such testing reveals substandard quality drug products, take rapid corrective actions, such as notifying customers and product recalls.
  一份所有批次留样检测结果的总结。如果检测发现有药品质量不合格，则应立即采取纠正措施如通知客户和召回产品
- A comprehensive, independent assessment of your laboratory practices, procedures, methods, equipment, documentation, and analyst competencies. Based on this review, provide a detailed plan to remediate and evaluate the effectiveness of your laboratory system.
  一份对你们实验室规范、程序、方法、设备、文件记录和化验员能力的全面独立评估。根据此审核，提交一份补救和评估你们实验室系统有效性的详细计划

- A progress update on your raw material and finished drug product testing procedure revisions, and status of all method validation and verification studies.
  你们原料和成品检测程序修订进展，以及所有方法验证和确认研究的状态

See FDA's guidance document Analytical Procedures and Methods Validation for Drugs and Biologics for general principles and approaches that FDA considers appropriate elements of method validation at: https://www.fda.gov/media/87801/download.

参见上述网址中的 FDA 指南文件"药品和生物制品分析方法验证"中的一般性原则和方法，FDA 认为这些是方法验证的基本要素。

3. Your firm failed to establish and follow an adequate written testing program designed to assess the stability characteristics of drug products (21 CFR 211.166(a)).

你公司未建立和遵守足够的书面检测程序，设计用以评估药品的稳定性特性，以及使用稳定性测试结果确定适当的存贮条件和有效期（21 CFR 211.166(a)）。

Your firm lacked stability-indicating methods for testing your finished drug products. You also lacked forced degradation studies for your finished drug products.

你公司成品检测用方法没有稳定性指示性。你们亦未对你们的成品进行强降解研究。

In your response, you stated that you performed accelerated stability and (b)(4) stability on your (b)(4) productand will perform them on your (b)(4) product. Your response is inadequate because it did not address your firm's lack of stability-indicating test methods.

在你们的回复中，你们声称你们对你们的 XX 产品进行了加速稳定性和 XX 稳定性，并且会对你们的 XX 产品执行同样的稳定性试验。你们的回复不充分，因为回复并未能解决你公司缺少稳定性指示性检测方法的问题。

In response to this letter, provide: 在回复本函时请提交：

- A comprehensive, independent assessment and CAPA plan to ensure the adequacy of your stability program. Your remediated program should include, but not be limited to:
  一份全面独立的评估和 CAPA 计划，确保你们的稳定性试验计划的充分性。你们补救后的计划应包括但不仅限于：
  - Stability indicating methods
    稳定性指示性方法
  - Stability studies for each drug product in its marketed container-closure system before distribution is permitted
    批准销售之前每种药品在其市售包装中的稳定性研究
  - An ongoing program in which representative batches of each product are added each year to the program to determine if the shelf-life claim remains valid
    每年将每种药品代表批次加入程序以确定货架期声明是否保持有效的持续计划
  - Detailed definition of the specific attributes to be tested at each station(time point)
    在每个时间点要检测的具体属性的详细规定
- All procedures that describe these and other elements of your remediated stability program.
  阐述你们经过补救的稳定性计划中这些和其它要素的所有程序

4. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

你公司未彻底调查已销售和未销售批次产品或其组份未经解释的差异或不符合其标准（21 CFR 211.192）。

Your investigations into out-of-specification (OOS) results were inadequate. For example, you obtained OOS results for active pharmaceutical ingredient (API) assay during raw material testing for both (b)(4). In your OOS Number 169 investigation report, you attributed the root cause to assumed dilution error, prepared new sample solutions, and performed new tests.The new tests for (b)(4) API passed and you used the (b)(4) to manufacture (b)(4) for the U.S. market. Before performing the new tests, you noticed that the (b)(4) on the original sample had been damaged during testing. Yet you did not test the original sample or investigate the damaged (b)(4). Your investigation did not involve hypothesis testing to scientifically show dilution error was the root cause of the OOS results.

你们对 OOS 结果的调查是不充分的。例如，你们在原料检测时得到 API 含量结果为 OOS。在你们编号 169 的 OOS 调查报告中，你们将根本原因归因于假设稀释错误，制备了新的样品溶液，并进行了新的测试。新的 XX API 测试结果合格，你们使用了 XX 用于生产美国市场的 XX。在进行新测试之前，你们注意到原始样品上的 XX 在检测期间已经受损。你们没有检测原样，亦未对受损的 XX 进行调查。你们的调查并未使用假设性测，科学地证明稀释错误是该 OOS 结果的根本原因。

Re-analysis of the actual solutions, test units, and glassware is an integral part of an investigation to determine whether alaboratory error may have occurred. This assessment, in tandem with hypothesis testing if initial re-examinations do not reveal a root cause, is instrumental in determining whether there was a causative laboratory error. Whenever an investigation lacks conclusive evidence of laboratory error, a thorough investigation of potential manufacturing quality causes must be conducted either internally or with your supplier, depending on the source of the material being tested.

对实际溶液、测试单元和玻璃仪器进行重新分析是调查不可分割的一部分，用以确定是否可能发生了实验室错误。该评估（如果初次复检未发现根本原因则要与假设性检测一起）是采用仪器方式确定是否有偶发性实验室错误。无论调查是否发现有证据支持实验室错误，则必须根据所检物料来源，在内部或与你们供应商一起对潜在生产质量原因进行彻底调查。

In your response, you acknowledged there was no justification for invalidating the original sample and that you will retrain your analysts to conduct proper investigations before preparing a new sample for retest. Your response is inadequate because review of your OOS results was limited to the examples described by our investigator. You did not broaden your assessment to comprehensively identify any additional inadequate OOS investigations.

在你们的回复中，你们承诺未对宣布初始样品无效的动作进行论证，还说你们会重新培训你们的化验员，要求在制订新样品用于复测之前进行适当的调查。你们的回复是不充分的，因为你们的 OOS 结果审核仅限于我们检查员所述的例子。你们并未将你们的评估扩展至全面识别其它不充分的 OOS 调查。

For more information about handling failing, OOS,out-of-trend, or other unexpected results and documentation of your investigations, see FDA's guidance document Investigating Out-of-

Specification (OOS) Test Results for Pharmaceutical Production at https://www.fda.gov/media/71001/download.

关于不合格、OOS、OOT 或其它非预期结果和调查文件记录，参见 FDA 指南“药物生产中 OOS 结果调查”。

In response to this letter, provide: 在你们对本函的回复中请提交以下：

- A retrospective, independent review of all invalidated OOS (including in-process and release/stability testing) results for U.S.products currently in the U.S. market and within expiry as of the date of this letter for the last three years from the initial date of inspection and a report summarizing the findings of the analysis, including the following for each OOS:
  对所有美国产品的宣布无效的实验室事件和 OOS（包括中控和放行/稳定性测试）结果的独立回顾审核，无论这些产品是否最终销售至美国，并提交一份报告总结分析中发现的情况，包括每个 OOS 的以下信息：
  - Determine whether the scientific justification and evidence relating to the invalidated OOS result conclusively or inconclusively demonstrates causative laboratory error.
    确定宣布无效的 OOS 结果的科学论证和证据是否可得出结论支持可归因的实验室错误
  - For investigations that conclusively establish laboratory root cause, provide rationale and ensure that all other laboratory methods vulnerable to the same or similar root cause are identified for remediation.
    对于可得出实验室根本原因的调查，提交理由并确保识别出所有其它对类似根本原因易受影响的实验室方法并进行补救
  - For all OOS results found by the retrospective review to have an inconclusive or no root cause identified in the laboratory, include a thorough review of production (e.g., batch manufacturing records, adequacy of the manufacturing steps, suitability of equipment/facilities, variability of raw materials, process capability, deviation history, complaint history, batch failure history). Provide a summary of potential manufacturing root causes for each investigation, and any manufacturing operation improvements.
    对于回顾审核中发现的所有 OOS 结果，在实验室未找到根本原因或不能得出结论的，要包括一份对生产（例如批生产记录，生产步骤是否充分，设备/设施适用性，原料波动性，工艺能力，偏差历史，投诉历史，批不合格历史）的彻底审核。提交一份每个调查潜在生产根本原因的总结，以及所有生产操作改进措施。
- A comprehensive review and remediation plan for your OOS result investigation systems. The CAPA should include, but not be limited to, addressing the following:
  一份对你们 OOS 结果调查系统的全面审核和补救计划。该 CAPA 应包括但不仅限于说明以下问题：
  - Quality unit oversight of laboratory investigations
    质量部门对实验室调查的监管
  - Identification of adverse laboratory control trends
    不良实验室控制趋势的识别
  - Resolution of causes of laboratory variation
    实验室波动原因的解决方案
  - Initiation of thorough investigations of potential manufacturing causes whenever a laboratory cause cannot be conclusively identified

无论是否可发现可归结实验室原因，均要对潜在生产原因启动彻底调查

- Adequate scoping of each investigation and its CAPA
  对每个调查及其 CAPA 范围进行充分界定
- Revised OOS investigation procedures with these and other remediations
  包括上述要求及其它补救措施的修订后 OOS 调查程序

Unapproved New Drug and Misbranding Violations 未批准新药和冒牌违规（略）

CGMP Consultant Recommended CGMP 顾问建议

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualified as set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements. Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

鉴于我们在你公司所发现的违规情况，我们强烈建议你们使用一位有 21 CFR 211.34 所述资质的顾问来协助你们公司符合 CGMP 要求。你们使用顾问并不能解除你们公司符合 CGMP 的义务。你们公司的高级管理层仍负有义务全面解决所有缺陷，确保持续 CGMP 符合性。

Data Integrity Remediation 数据完整性补救措施

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. See FDA's guidance document Data Integrity and Compliance With Drug CGMP for guidance on establishing and following CGMP compliant data integrity practices at https://www.fda.gov/media/119267/download.

你们的质量体系不能充分确保数据的准确性和完整性，无法支持你们生产的药品的安全性、有效性和质量。参见 FDA 指南文件"数据完整性和药品 GMP 合规"指导建立和遵守 CGMP 合格数据完整性规范。

We strongly recommend that you retain a qualified consultant to assist in your remediation. In response to this letter, provide the following:

我们强烈建议你们聘用顾问协助你们进行补救。在回复此函时请提交以下信息：

A. A comprehensive investigation into the extent ofthe in accuracies in data records and reporting including results of the data review for drugs distributed to the United States. Include a detailed description of the scope and root causes of your data integrity lapses.

一份对数据记录和报告不准确性程度的全面调查，包括对销售至美国的药品的数据审核的结果。在其中还要包括一份对你们数据完整性问题范围和根本原因的详细说明。

B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity and analyses of the risks posed by ongoing operations.

你们药品质量中所发现的不合格情况的潜在影响的当前风险评估。你们的评估应包括由于受到数据完整性问题影响的药品放行导致的患者风险的分析，以及持续运营所具有的风险。

C. A management strategy for your firm that includes the details of your global CAPA plan. The detailed corrective action plan should describe how you intend to ensure the reliability and completeness of all data generated by your firm including microbiological and analytical data, manufacturing records, and all data submitted to FDA.

你们公司的管理策略，包括你们全球 CAPA 计划详细情况。详细的纠正措施计划应阐述你们准备如何确保你公司所生成的所有数据的可靠性和完整性，包括微生物和分析数据、生产记录和所有提交给 FDA 的数据。

Conclusion 结论

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility.You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of other violations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产商的新申报和增补申报的批准。

Failure to correct these violations may also result in the FDA refusing admission of articles manufactured at Cosmaceutical Research Lab Inc., 12920 84th Avenue, Surrey, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Articles under this authority may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

37. 320-20-37 2020-05-29 Takeda Pharmaceutical Company Limited 日本

Dear Mr. Weber,

The U.S. Food and Drug Administration (FDA)inspected your drug manufacturing facility, Takeda Pharmaceutical Company Limited, FEI 3004664162, at Takeda 4720, Mitsui, Hikari, Yamaguchi, from November 18 to 26, 2019.

美国 FDA 于 2019 年 11 月 18 日至 26 日检查了你们位于日本的武田药品工业株式会社（FEI 3004664162）生产场所。

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See Title 21 Code of Federal Regulations (CFR), parts 210 and 211 (21 CFR parts 210 and 211).

本警告信总结了制剂生产严重违反 CGMP 的行为。参见 21CFR 第 210 与 211 部分。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

由于你们的制剂生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的药品根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C. 351(a)(2)(B)被认为是掺假药品。

We reviewed your December 18, 2019, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence. Your response is inadequate because it did not provide sufficient detail or evidence of corrective actions to bring your operations into compliance with CGMP.

我们已详细审核了你公司 2019 年 12 月 18X 日对我们 FDA483 表的回复，并此告知已收到后续通信。你们的回复是不充分的，因为其中并未提供足够详细的内容或证据，证明纠正措施可使得你们的运营转入 CGMP 合规状态。

During our inspection, our investigators observed specific violations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

1. Your firm failed to establish adequate written responsibilities and procedures applicable to the quality control unit and to follow such written procedures (21 CFR 211.22(d)).

你公司未建立适用于质量部门的书面职责和程序，并遵守这些书面程序（21 CFR 211.22(d)）。

Our inspection found that your Quality Unit (QU) did not take appropriate steps prior to resumption of aseptic manufacturing after a shutdown that included multiple significant activities that compromised cleanroom control. Your QU allowed manufacturing operations to resume for (b)(4) filling operations without performing an aseptic process simulation (i.e.,media fill) as indicated by your procedure. Your firm manufactured and shipped several batches of (b)(4) to the U.S. market after this deviation.

我们的检查发现你们质量部门（QU）在洁净区关闭并执行了多项操作使得洁净区控制受到影响之后，继续无菌生产之前并未采取恰当的措施。你们的 QU 允许继续 XX 的灌装生产操作，但并未按你们程

序所要求进行无菌工艺模拟（即，培养基灌装）。在发生该偏差之后，你们公司生产了几批 XX 并发运至美国市场。

In your response, you committed to perform an aseptic process simulation for the (b)(4) manufacturing line and stated that you will strengthen your systems to ensure post-shutdown process simulations are performed. You stated your belief that there was no adverse impact to product because your procedure for restarting production requires that environmental monitoring data and utility results are available before product release.

在你们的回复中，你们承诺要对 XX 生产线执行无菌工艺模拟，并声称你们会强化你们的系统，确保在关闭之后会执行工艺模拟。你们声称你们相信对产品并没有不良影响，因为你们重启生产的程序要求在产品放行之前有环境监测数据和公用设施结果。

Your response is inadequate because you failed to adequately assess the impact on sterility assurance of the products manufactured in a facility after a shutdown in which cleanroom control was compromised. Environmental monitoring and utility data alone are not sufficient to support that appropriate cleanroom control has been restored to ensure drug sterility.

你们的回复是不充分的，因为你们并未充分评估洁净区关闭控制受影响之后，在该设施里生产的产品的无菌保证受到的影响。环境监测和公用设施数据单独不足以支持已恢复了恰当的洁净区控制，能确保药品无菌性。

In response to this letter, provide:

在回复本函时请提交：

- A comprehensive assessment and remediation plan to ensure your QU is given the authority and resources to effectively function. The assessment should also include, but not be limited to:
  一份全面评估和补救计划，确保你们的 QU 被授予了权力和资源可有效运作。评估还应包括但不仅限于：
  - A determination of whether procedures used by your firm are robust and appropriate.
    确定你公司所用的程序是否稳健和恰当
  - Provisions for QU oversight throughout your operations to evaluate adherence to appropriate practices.
    QU 监管你们整个操作，评估是否遵守恰当规范的条件
  - A complete and final review of each batch and its related information before the QU disposition decision.
    QU 在批处置决策前对每个批次及其相关信息进行全面最终审核
  - Oversight and approval of investigations and discharging of all other QU duties to ensure identity, strength, quality, and purity of all products.
    监管和批准调查，履行所有其它 QU 义务以确保所有产品的鉴别、含量、质量和纯度
- A description of how top management supports quality assurance and reliable operations, including but not limited to timely provision of resources to proactively address emerging manufacturing/quality issues and to assure a continuing state of control.
  说明高级管理级是如何支持质量保证和可靠操作的，包括但不仅限于及时提供资源，积极解决新出现的生产/质量问题，确保持续受控状态

- Your risk assessment of distributed products processed under conditions which did not provide adequate assurance of appropriate aseptic processing conditions.
  你们对在未能为合适的无菌加工条件提供足够保障的情况下生产且已销售产品的风险评估

2. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

你公司未建立和遵守适当的书面程序，防止微生物污染理当无菌的药物，亦未包括对所有无菌和灭菌工艺的验证（21 CFR 211.113(b)）。

You have not established adequate practices for your process simulations.

你们没有为你们工艺模拟制订足够的规范。

Inadequate Aseptic Processing Simulations (Media Fills) 无菌工艺模拟不充分（培养基灌装）

Your media fill program lacked assurance that aseptic processing operations are adequately performed to prevent microbial contamination.

你们的培养基灌装程序无法保证无菌工艺操作足以防止微生物污染。

Your firm removed integral units (i.e., units with intact container-closure systems) from media fills. For example, during media fill lot (b)(4), conducted in (b)(4), you removed (b)(4) intact vials and did not incubate them. You lacked adequate justification for removing these integral vials. While you indicated that the units were removed for a routine analytical test, this test could have been done after incubation.

你们公司从培养基灌装中取出了完整的单位（即，有完整无损容器-密闭系统的单位）。例如，在 XX 中执行的培养基灌装批次 XX 过程中，你们取出了 XX 个完整的小瓶，没有培养它们。你们对于取出这些完整的小瓶并没有足够的论证。你们说这些小瓶取出是用作常规分析检测，培养之后是有可能进行检测的。

In addition, your media fills did not sufficiently incorporate the contamination risks of commercial production, including the significant hazard posed by the (b)(4) operation. This operation includes manually intensive aseptic material transfers from a (b)(4).

另外，你们的培养基灌装并未包括足够的商业生产污染风险，包括 XX 操作具有严重危害。该操作包括从一个 XX 手动集中转移无菌材料。

Our review of media fill records also found that multiple personnel had not, at least (b)(4), performed interventions that adequately simulate the functions they are responsible for in production operations. For example, all aseptic processing personnel who perform the manually intensive (b)(4) step were not required to simulate this operation each (b)(4).

我们对培养基灌装记录的审核亦发现多位人员并未充分模拟他们所负责的生产操作的职能中的干预情况。例如，所有执行人工强化 XX 步骤的无菌加工人员并未被要求模拟每个 XX 的该操作。

In your response, you confirmed that withholding integral vials from incubation was in violation of your process simulation SOP. You indicated that the media fill batch remained valid because no critical interventions occurred before you filled these particular vials. Your responseis inadequate

because omission of these vials undermines the sensitivity of the process simulation to detect contamination hazards in your operation.

在你们的回复中，你们确认预先取出完整的小瓶不做培养确实违反了你们的工艺模拟 SOP。你们指出培养基灌装批次仍然有效，因为在你们灌装这些特殊小瓶时并没有发生关键性干预。你们的回复是不充分的，因为遗漏这些小瓶削弱了工艺模拟发现你们操作中污染危害的灵敏度。

Your response also stated an assessment will be performed for the (b)(4) operation to determine the worst-case (b)(4) of containers to more accurately reflect the production process. We acknowledge that you revised your process simulation procedure and are performing new process simulations. However, your response is deficient because you did not assess the risk to product sterility for products manufactured when process simulations were insufficient.

你们的回复还声称会对 XX 操作进行一次评估，确定容器的最差情形，以更为准确地反映生产工艺。我们了解你们修订了你们的工艺模拟程序，正在执行新的工艺模拟。但是，你们的回复是有缺陷的，因为你们并未评估当工艺模拟不充分时所生产的产品无菌性的风险。

Poor Aseptic Behavior 无菌行为不良

Critical aseptic processing operations are not appropriately controlled. Our investigator observed that operators who performed ISO 5 manipulations exhibited poor aseptic practices during production of (b)(4) Lot (b)(4). For example, operators:

关键无菌工艺操作受控不恰当。我们的检查员观察了你们在 ISO.5 操作的员工，他们在 XX 批次 XX 的生产过程中显示出很差的无菌做法。例如，操作员：

- failed to sanitize gloved hands after touching surfaces such as curtains and computer touch screens.
  在接触了如帘子和计算机触屏等表面之后并未对戴手套的手进行消毒
- conducted manipulations using rapid movements, rather than slow and deliberate aseptic technique.
  操作时动作很快，而不是慢而小心的动作技巧

We acknowledge from your response that you have retrained your operators in aseptic behavior, but you did not extend this training to supervisory staff. You also did not address how you would verify the effectiveness of the training.

我们从你们的回复中了解到你们对你们的操作员进行了无菌行为方面的重新培训，但你们并未将培训延伸至主管人员。你们亦未说明你们要准备如何核查培训的有效性。

Inadequate controls over materials used in aseptic processing area 无菌加工区域中所用物料控制不足

There was a lack of traceability over the (b)(4) wipes, which are used in the aseptic processing cleanroom with disinfectant to wipe equipment surfaces. The (b)(4) certificate you provided to our investigator did not reconcile with the material identification numbers for the wipes in use. Your Quality Unit also did not adequately maintain records for the receipt and approval of wipes.

对 XX 擦布缺少追踪，这些擦布是在无菌加工洁净区醮消毒剂用于擦拭设备表面的。你们向我们的检查员提交的 XX 证书与在用擦拭用的物料识别号不一致。你们的质量部门并未充分保存擦布接收和批准记录。

We acknowledge that you performed a risk assessment to determine the impact of potentially introducing (b)(4) wipes into your aseptic processing cleanroom, and you concluded it to have low risk for product sterility. However, your assessment is inadequate because you relied upon disinfectant use, environmental monitoring, and a sterilization qualitative indicator in lieu of adequate controls over material receipt and evaluation before transfer into the cleanroom. Furthermore, your response acknowledged the lack of traceability of lot numbers to an irradiation certificate.

我们了解你们进行了风险评估，确定了 XX 抹布可能被引入你们无菌加工洁净区的影响，得出结论说对产品无菌性的风险很低。但是，你们的评估是不充分的，因为你们依赖于消毒剂的使用、环境监测以及灭菌定性指示剂，而不是在转移至洁净区之间对物料接收进行充分控制和评估。另外，你们的回复承认无法追溯放射证书的批号。

See FDA's guidance document Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practiceto help you meet CGMP requirements for manufacturing sterile drugs using aseptic processing at https://www.fda.gov/media/71026/download

参见 FDA 指南文件"采用无菌工艺生产的无菌药品 CGMP"。

In response to this letter, provide:

在回复本函时请提交：

- A risk assessment of all contamination hazards with respect to your aseptic processes, equipment, and facilities, including an independent assessment that includes, but is not limited to:
  对你们无菌工艺、设备和设施方面所有污染危害的风险评估，包括一份独立评估，其中应包括但不仅限于：
  - All human interactions within the (b)(4) area
    在 XX 区域内所有人员互动
  - Equipment placement and ergonomics
    设备放置和人体工程学
  - Personnel flows and material flows (throughout all rooms used to conduct and support sterile operations)
    人流和物流（通过所有执行和支持无菌操作的房间）
  - Sourcing consumable materials that are appropriate for use in cleanrooms(e.g., ready-to-use sterile wipes)
    寻找适合于洁净区使用的耗材来源（例如，直接使用的无菌抹布）
  - Receipt, evaluation, and aseptic handling of all consumable items in ISO 5areas
    ISO5 区域内所有耗件接收、评估和无菌处理
- A comprehensive, independent retrospective reviewof all batches that remain within expiry in the U.S. market, which incorporates the knowledge of hazards gained from your risk assessment. Include any additional actions you intend to initiate because of the retrospective review.

一份仍在美国市场且在效期内的所有批次的回顾性全面独立审核，在其中包括从你们风险评估中获得的危害知识。要包括你们由于回顾性审核而准备启动的其它措施

- Environmental monitoring data for the past two years, details of total counts and microbial identifications when excursions were observed, and a summary of investigations performed.
过去 2 年的环境监测数据，微生物总计数和发现超标时微生物鉴别的详细信息，以及所实施调查的总结
- Your plan to ensure appropriate aseptic practices and cleanroom behavior during production. Include steps to ensure routine and effective supervisory oversight for all production batches. Also describe the frequency of quality unit oversight (e.g., audit) during aseptic processing andits support operations.
你们确保生产期间无菌做法和洁净区行为适当的计划，包括确保对所有生产批次进行常规和有效监管的措施。还要说明无菌加工及其支持性操作期间质量部门监管（例如审计）的频次

3. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether the batch has already been distributed (21CFR 211.192).

你公司未彻底调查未经解释的已放行和未放行批次或其成分偏离或不符合其质量标准的事件（21 CFR 211.192）。

You lacked adequate investigations into equipment malfunctions. Several investigations were concluded without sufficiently addressing root causes or ensuring adequate scope, allowing manufacturing risks to persist for extended periods.

你们对设备故障未进行充分调查。几次调查的结论均未圆满解决根本原因或确保调查范围是足够的，使得生产风险延续了较长时间。

Occurrence of black particles 发现黑色颗粒物

Your investigations into the occurrence of black particles in more than (b)(4) batches of (b)(4) vials were deficient. These investigations identified the particles as (b)(4).

你们对 XX 余批次的 XX 西林瓶 XX 中发现黑色颗粒物的调查是有缺陷的。这些调查将颗粒物认定为 XX。

For example, deviation report TW67805, initiated on August 23, 2019, did not include a thorough investigation of these recurring incidents. Although the investigation lacked a CAPA plan, you concluded that there was no product impact because the particles were easily detected sincethey settled at the bottom of the vials.

例如，调查报告 TW67805 于 2019 年 8 月 23 日启动，其中并未对这些重复发生的事件的彻底调查。尽管该调查并没有 CAPA 计划，但你们仍得出结论说没有产品受到影响，因为颗粒物沉在瓶底，所以易于检出。

Your response stated there is no product impactfrom black particle contamination because all vials for lots manufactured during this timeframe were rejected during finished product inspection, and all lots passed AQL inspection. Your response is inadequate because you did not explain how you could confidently rely only upon visual inspection to detectmetal particles embedded in lyophilized

cake. You also allowed manufacturing operations to continue without performing a risk assessment for products already released to the U.S. market.

你们在回复中说没有产品受到黑色颗粒物污染的影响，因为在该时间段生产批次的所有瓶在成品检查时均被拒收了，并且所有批次均通过了 AQL 检查。你们的回复是不充分的，因为你们并未解释你们怎么就能这么信任地仅仅依赖于目视检查来发现嵌入冻干饼状产品中的金属颗粒物。你们还在没有对已放行至美国市场的产品进行风险评估的前提下就允许继续生产。

(b)(4) malfunction XX 故障

You failed to assure that your (b)(4) was properly maintained and functioning as intended. Maintenance issues were identified as contributing to the increase in the (b)(4) between May 2018 through May 2019. As a result, several in-process batches were rejected. Although multiple investigations were conducted, the correct root cause of the problem was not promptly identified and remediated. Subsequently, during the (b)(4) requalification of this (b)(4) all (b)(4) bioindicators tested positive.

你们未能确保对你们的 XX 进行适当维护，确保其正常运转。所发现的维护问题被归因于 2018 年 5 月至 2019 年 5 月之间 XX 的增加。由于该原因，有几批在制品被拒收了。尽管执行了多次调查，但并未及时发现问题的真正根本原因并进行补救。后来，在该 XX 的重新确认期间，所有的生物指示剂测试均呈阳性。

In your response you stated that the root cause of the (b)(4) problem was a (b)(4). However, you failed to adequately explain why the malfunctioning (b)(4) was used for aprotracted period to sterilize components of your injectable product. You alsolacked a sufficiently comprehensive commitment to improve management oversightover maintenance and investigations.

在你们的回复中，你们声称 XX 问题的根本原因就是一个 XX。但是你们并未充分解释为什么有故障的 XX 被延长使用时间用于你们注射用产品组份的灭菌。你们亦未做出全面足够的承诺，表示愿意改进对维护和调查的管理监管。

In response to this letter, provide:

在回复本函时请提交：

- A comprehensive, retrospective, independent reviewof all (b)(4) batches manufactured since May 2018, for the impact of (b)(4) particles undetected in (b)(4) product.
  一份对 2018 年 5 月以来生产的所有批次 XX 的回顾性全面独立审核，评估 XX 产品中未检出 XX 颗粒物的影响
- A comprehensive, retrospective, independent review of all batch components sterilized using (b)(4) ID (b)(4) that were distributed in the U.S. market and remain within expiry.
  一份对销售于美国市场且仍在有效期的，使用 XX 编号 XX 灭菌的所有批次组份的回顾性独立全面审核
- An assessment of the suitability of (b)(4) equipment and cycles, including but not limited to:
  对 XX 设备和灭菌周期适用性的评估，包括但不仅限于
  - Review of your (b)(4) parameters, including time, (b)(4), and (b)(4) settings to ensure a sterility assurance level of (b)(4) or more.

对你们的 XX 参数，包括时间、XX 和 XX 设置的审核，以确保 XX 或更高的无菌保证水平

- Evaluation of the adequacy of maintenance and engineering controls associated with (b)(4) used for sterilization processes.
  对灭菌工艺用 XX 有关的维护和工程控制充分程度所做的评估

- A comprehensive and independent assessment of your system for investigating deviations and failures. Provide a detailed action plan to remediate this system. Your action plan should include, but not be limited to, significant improvements in investigation competencies, scope determination, root cause evaluation, CAPA effectiveness, quality unit oversight, and written procedures. Address how your firm will ensure all phases of investigations are appropriately conducted.
  一份对你们偏差和失败调查系统的全面独立评估。提交补救该系统的详细行动计划。你们的行动计划应包括但不仅限于调查能力、范围确定、根本原因分析、CAPA 有效性、质量部门监管和书面程序方面的重大改进。说明你们公司准备如何确保恰当执行了所有的调查阶段
- Your CAPA plan to implement routine, vigilant operations management oversight of facilities and equipment. This plan should ensure, among other things, prompt detection of equipment/facilities performance issues, effective execution of repairs, adherence to appropriate preventive maintenance schedules, timely technological upgrades to the equipment/facility infrastructure, and improved systems for ongoing managementreview.
  你们补救设施和设备常规、警戒操作管理监管的 CAPA 计划。该计划应确保快速发现设备/设施性能问题、进行有效维修、遵守恰当的维保计划、对设备/设施及时进行技术升级，以及改进持续管理审评体系

Conclusion 结论

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the causes of these violations and for preventing their recurrence or the occurrence of other violations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to reportdis continuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b).This also allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

如果你们在考虑要采取的措施可能会导致你们工厂所生产的药品供应中断，FDA 要求你立即联系 CDER 药品短缺负责人员，这样 FDA 可以与你们一起采用最为高效的方式引导你们的操作符合法规要求。联系药品短缺负责人员还能让你满足依据 21 U.S.C. 356C(b)你可能必须报告你们药品中止或中断的义务，让 FDA 尽快考虑是否需要采取何种措施来避免短缺，保护依赖于你们药品的患者健康。

Until you correct all violations completely and weconfirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产商的新申报和增补申报的批准。

Failure to correct these violations may also result in the FDA refusing admission of articles manufactured at Takeda Pharmaceutical Company Limited, at Takeda 4720, Mitsui, Hikari, into the United States undersection 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Articles under this authority may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

38. 320-20-38 2020-05-29 046255 Canada Inc.加拿大

Dear Mr. Emond:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, 8046255 Canada Inc., doing business as (dba) Viatrexx, FEI 3010033797, at 1360 Rue Louis-Marchand, Beloeil, fromSeptember 16 to 24, 2019.

美国 FDA 于 2019 年 9 月 16 日至 24 日检查了你们位于加拿大的 8046255 Canada Inc（dba Viatrexx）生产场所。

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See Title 21 Code of Federal Regulations (CFR), parts 210 and 211 (21 CFR parts 210 and 211).

本警告信总结了制剂生产严重违反 CGMP 的行为。参见 21CFR 第 210 与 211 部分。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

由于你们的制剂生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的药品根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C. 351(a)(2)(B)被认为是掺假药品。

In addition, FDA reviewed your labeling obtained from the inspection. Based on our review, your injectable homeopathic products“Articula,” “Mesenchyme,” “Connectissue,” “MuSkel-Neural,” “Ouch,” “Ithurts,”“Adipose,” “Systemic Detox,” “Hair,” “Neuro 3,” “Infla,” “Collagen,” “Prolo,”“Lymph 1,” “GI,” “Neuro,” “Arthros,” “Male+,” “Immunexx,” “Relief+,”“Intra-Cell,” “Facial,” and “ANS/CNS” (“injectable homeopathic products”) are unapproved new drugs under section 505 of the Federal Food, Drug, and CosmeticAct (FD&C Act), 21 U.S.C. 355. Introducing or delivering these products for introduction into interstate commerce violates section 301 of the FD&C Act,21 U.S.C. 331.

此外，FDA 还审核了检查中获取的标签内容。根据我们的审核，你们的注射用顺势疗法药品 “Articula,” “Mesenchyme,” “Connectissue,” “MuSkel-Neural,”“Ouch,” “Ithurts,” “Adipose,” “Systemic Detox,” “Hair,” “Neuro 3,” “Infla,”“Collagen,” “Prolo,” “Lymph 1,” “GI,” “Neuro,” “Arthros,” “Male+,” “Immunexx,”“Relief+,” “Intra-Cell,” “Facial,” 和 “ANS/CNS”（“顺势疗法注射剂”）根据 FDCA 第 505 条款 21U.S.C. 355 均为未批准的新药。引入或输送此类药品至州际贸易是被 FDCA 第 301(a)款 21 U.S.C. 331(a) 和 (d)禁止的。

These products are especially concerning from apublic health perspective because injectable drug products can pose risks of serious harm to users; these risks are less likely to occur with topical or ingested products, i.e., those applied to the skin or taken by mouth. Injectable products are delivered directly into the body, sometimes directly into the bloodstream, and therefore, bypass some of the body’s key defenses against toxins and microorganisms that can lead to serious and life-threatening conditions. Your injectable products are further concerning because they are labeled to contain potentially toxic or otherwise harmful ingredients, such as “Nux Vomica” (contains strychnine), “Rectum,” and “Belladonna,” thereby presenting additional risk of serious harm to patients when delivered directly into the body. Your firm’s significant violations of current good manufacturing practice regulations, as described below, enhances the risk of harm to patients even further.

这些药品在公众健康角度尤其令人担忧，因为注射剂可能会对使用者带来严重伤害风险，这些风险不太可能发生在消化道用药或局部用药，因为这些药品仅用于皮肤或经口摄入。注射剂是直接注入身体，有时直接进入血液，因此，绕开了人体的一些关键毒物和微生物防御系统，这样可能导致危及生命的严重情形。你们的注射剂有着更多担忧，因为其标示为含有潜在毒性或有害成分，例如“Nux Vomica”（含有马钱子碱），“Rectum”和“Belladonna”，因此当直接输入体内时对患者具有额外的严重伤害风险。如下所述，你公司严重违反了 CGMP 法规，更是大大增加了对患者的危害风险。

We reviewed your October 16, 2019, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

我们已详细审核了你公司 2019 年 10 月 16 日对我们 FDA483 表的回复，并此告知已收到后续通信。

During our inspection, our investigator observed specific violations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

1. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

你公司未遵守适当的书面程序，设计用于防止既定无菌的药品微生物污染，并包括所有无菌和灭菌工艺的验证（21 CFR 211.113(b)）。

You manufactured and distributed sterile injectable homeopathic drug products without adequately validating your aseptic manufacturing processes.

你们生产和销售无菌注射用顺势疗法药品，但并没有充分验证你们的无菌生产工艺。

Process Simulations (Media Fills) 工艺模拟（培养基灌装）

You failed to establish appropriate procedures and perform media fills to evaluate your manual aseptic filling and stoppering operations.

你们并未建立起适当的程序并执行培养基灌装，以评估你们的人工无菌灌装和加塞操作。

Filter Suitability 过滤器适用性

You failed to qualify the use of an appropriate filter for sterile filtration of your injectable drug products. Rather than using a sterilizing filter suitable for sterile drug manufacturing you used a (b)(4) filter for the sterile filtration. You also failed to test the filter integrity after use.

你们并未确认你们注射药品中除菌过滤时使用的是恰当的过滤器。你们使用了 XX 过滤器用于除菌过滤，而不是使用适合于无菌药品生产的除菌过滤器。你们在使用之后亦未检测过滤器完整性。

Poor Aseptic Techniques 无菌技巧不良

You failed to ensure use of appropriate aseptic technique for manufacturing sterile injectable drug products. Our investigator observed personnel behaviors in the manual filling and stoppering operations that blocked the path of (b)(4) airflow.

你们未能确保使用适当的无菌技巧用于生产无菌注射药品。我们的检查员观察了你们人工灌装和加塞操作员工的行为，他们挡住了 XX 气流的路径。

On October 14, 2019, your firm recalled all sterile injectable drug products you manufactured. However, your proposed corrective actions permitted continued use of an unsuitable filter to sterilize your drug product. Your response also failed to address the frequency for conducting media fills.

在 2019 年 10 月 14 日，你公司召回了你们生产的所有无菌注射产品。但是你们提出的纠正措施允许继续使用不适当的过滤器对你们的药品灭菌。你们的回复亦未解决培养基培养执行频次问题。

Validation of aseptic processing requires establishing documented evidence with a high degree of assurance that a particular process consistently produces a product meeting its predetermined specifications and quality attributes. Media fills, and various systemic controls including, but not limited to, daily adherence to strict aseptic processing standards, suitable facilities, robust environmental control, and satisfactory product sterility testing, combine to ensure that an injectable drug is sterile. If injectable drugs are not sterile, they pose unacceptable risks to patients, including infection.

无菌工艺的验证需要建立具有高度保证的文件化证据，保证具体的工艺可持续生产出符合其既定标准和质量属性的产品。培养基灌装和各种系统控制，包括但不仅限于日常遵守严格的无菌工艺标准、稳定的设施、稳健的环境控制，和令人满意的产品无菌性检测，联合起来确保注射药品是无菌的。如果注射药品不是无菌的，则它们会对患者有着不可接受的风险，包括感染风险。

In response to this letter, provide the following:

在回复本函时请提交以下内容：

- Comprehensive risk assessment of all contamination hazards with respect to your aseptic processes, equipment, and facilities, including an independent assessment that includes, but is not limited to:
  对你们无菌工艺、设备和设施所有污染危害的全面风险评估，包括一份包括但不仅限于以下内容的独立评估：
  - All human interactions within the ISO 5 area
    ISO5 区域内所有人间互动
  - Equipment placement and ergonomics
    设备安装位置和人体工程学
  - Air quality in the ISO 5 area and surrounding room
    ISO5 区域和周边房间的空气质量
  - Facility layout
    设施平面布局图
  - Personnel flows and material flows (throughout all rooms used to conduct and support sterile operations)
    人流和物流（执行和支持无菌操作的所有房间之间）
- A detailed remediation plan with timelines to address the findings of the independent contamination hazards risk assessment. Describe specific tangible improvements to be made to aseptic processing operation design and control.

一份详细的补救计划及时间表，解决独立污染危害风险评估期间发现的问题。阐明准备对无菌工艺操作设施和控制所做的具体实际的改进

- Your plan to ensure appropriate aseptic practices and cleanroom behavior during production. Include steps to ensure routine and effective supervisory oversight for all production batches. Also describe the frequency of quality unit oversight (e.g., audit) during aseptic processing andits support operations.
  你们确保生产期间的无菌操作和洁净间行为恰当的计划。包括确保对所有生产批次进行日常和有效监管的措施。亦请说明质量部门在无菌加工及其支持性操作期间的监管（例如审计）频次
- Your plan to ensure robust sterilization processes for all sterilization methods. Provide your program for qualification and validation of all sterilization operations. Also, regarding sterilizing filtration, provide a corrective action and preventive action (CAPA) plan that ensures:
  你们确保所有灭菌方法有着稳健灭菌工艺的计划。提交你们的所有灭菌操作确认和验证计划。
  另外，关于除菌过滤，请提交一份 CAPA 计划以确保：
  - Selection of a suitable (b)(4) filter for drug sterilization
    选择了适当的 XX 过滤器用于药品除菌
  - Appropriate filtration efficacy validation study protocols for each product and that incorporates the worst-case filtration conditions
    对每个产品进行恰当的过滤器效率验证研究的方案，要包括最差过滤情形
  - Proper responsibilities for proper conduct, full documentation, review, and approval of these studies
    恰当执行、全面记录、审核和批次这些研究的人员职责
  - Products will not be distributed before complete and adequate studies are performed
    在完成充分的研究之前不会将销售产品

2. Your firm failed to ensure that manufacturing personnel wear clothing appropriate to protect drug product from contamination (21 CFR 211.28(a)).

你公司未能确保生产人员穿着适合于保护药品不受污染的服装（21 CFR 211.28(a)）。

You failed to have appropriate gowning for manufacturing sterile injectable homeopathic drug products. With the exception of gloves, you used non-sterile gowning and also re-used these gowning materials to perform aseptic operations. Our investigator also observed exposed facial skin and the operator donning sterile gloves over bare hands when right next to the ISO 5 hood where aseptic processing is performed.

你们没有顺势疗法注射剂生产的适当着装程序。除了手套外，你们使用了非无菌服装，还重复使用这些服装材料进行无菌操作。我们的检查员亦观察到有面部皮肤暴露，操作员在紧邻无菌操作 ISO5 气流罩的地方将无菌手套戴到裸手上。

Your response stated that you will use sterile gowning for production. However, the gowning pictured in your response is not adequate for sterile injectable drug manufacturing because, for example, skin is exposed on the operator's face.

你们回复声称你们会在生产中使用无菌服装。但是你们回复中的服装图片不足以用于无菌注射药品生产，因为例如，操作员面部皮肤有暴露。

In response to this letter, provide the following:

在回复本函时请提交以下内容：

- A list of the gowning materials you intend to use(e.g. sterilized nonshedding gowns and covers for the skin and hair, such as,face-masks, hoods, beard/moustache covers, protective goggles, and gloves).
  一份你们装备使用的服装材料的清单（例如，已灭菌无脱落物的服装，遮住皮肤和毛发，如面罩、兜帽、胡须套、保护性手套和手套）
- A gowning qualification program that establishes, both initially and on a periodic basis, the capability of an individual to adequately don the complete sterile gown in an aseptic manner.
  一份更衣确认程序，首次和定期证明个人可以无菌方式穿戴完整的无菌服装的能力
- The role of the quality unit in gown supplier selection and ongoing qualification decisions. Ensure that the quality unit makes final decisions including supplier selection, release of raw materials and supplies (e.g., garments) used in production, and other ongoing decisions about supplier reliability.
  质量部门在服装供应商选择和持续确认决策方面的作用。确保是质量部门做出最终决策，包括生产用供应商选择、原料和供应商放行（例如，洁净服），以及其它供应商可靠性的持续决策
- Details regarding how you will establish adequate gowning, training, gowning qualification, and supervision on an ongoing basis.
  关于你们准备如何建立足够的更衣、培训、更衣确认和持续监管的详细信息

3. Your firm failed to establish a system for monitoring environmental conditions in aseptic processing areas and an adequate system for cleaning and disinfecting the room and equipment to produce aseptic conditions (21 CFR 211.42(c)(10)(iv) and (v)).

你公司未能建立一个用于监测无菌加工区域的环境条件的体系，以及一个清洁和消毒产生无菌条件的房间与设备的体系（21 CFR 211.42(c)(10)(iv) 和(v)）。

Cleaning and Disinfecting 清洁和消毒

Your procedures for cleaning and disinfecting are inadequate. For example, you lacked procedures to ensure frequent use of a (b)(4) agent. You also failed to consistently document cleaning and disinfecting.

你们的清洁和消毒程序不充分。例如，你们缺少程序确保 XX 剂的使用频次。你们亦未能持续记录清洁和消毒操作。

Environmental Conditions 环境条件

You performed environmental monitoring during the initial qualification of your facility in May 2019. However, you continued production through September 2019 with no routine environmental monitoring. You also lacked written procedures for environmental monitoring.

你们在 2019 年 5 月初次确认时进行了环境监测。但是你们在 2019 年 9 月连续生产，没有进行常规环境监测。你们亦缺少环境监测书面程序。

An environmental monitoring program provides meaningful information about the quality of the aseptic processing environment, as well as additional clean areas.

环境监测计划应提供无菌加工环境以及其它洁净区域质量的有意义的信息。

Your response is inadequate because it did not provide sufficient details or procedures for your environmental monitoring program. You also did not provide any evidence that your manufacturing environment is under an ongoing state of control.

你们的回复是不充分的，因为其中并未提供你们环境监测程序的足够的详细信息或程序。你们亦未提交任何证据证明你们的生产环境持续处于受控状态。

In response to this letter, provide the following:

在回复本函时请提交以下内容：

- A CAPA plan, based on a retrospective assessment of your cleaning and disinfection program, that includes appropriate remediations to your cleaning/disinfection processes and practices, and timelines for completion. Provide a detailed summary of vulnerabilities in your process for lifecycle management of equipment cleaning and disinfection. Describe improvements to your cleaning and disinfection program, including enhancements to cleaning effectiveness, improved ongoing verification of proper cleaning and disinfection execution for all products and equipment, and all other needed remediations.
  一份 CAPA 计划，基于你们清洁和消毒程序的回顾性评估，其中包括对你们清洁/消毒工艺和做法的适当补救措施，以及完成时间表。提交一份你们工艺中设备清洁和消毒生命周期管理方面薄弱点的详细综述，包括改进清洁有效性，改进所有产品和设备的清洁和消毒执行方面的持续确认，以及所有其它所需补救措施。
- A comprehensive environmental monitoring program for your facility, including but not limited to, frequency, location, types,and methods of monitoring. The program should include provisions to vigilantly monitor both daily results and trends.
  一份对你们设施的全面环境监测计划，包括但不仅限于监测频次、监测点、监测类型和方法。计划应包括严格监测日常结果和趋势的条款。
- A comprehensive personnel monitoring program for operators involved in aseptic processing operations.
  一份对参与无菌工艺操作的操作员的全面人员监测计划。

4. Your firm failed to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity (21 CFR 211.160(b)).

你公司未能建立实验室控制，在其中包括科学合理和恰当的质量标准、取样计划和检测方法，以确保组份、药品容器、密闭器、中控物料、标签和成品符合恰当的鉴别、剂量、质量和纯度标准（21 CFR 211.160(b)）。

You failed to validate your sterility test method and also failed to use suitable media for sterility testing of your sterile injectable homeopathic drug products. Furthermore, you failed to perform endotoxin and particulate matter testing for your sterile injectable homeopathic drug products.

你们并未验证你们的无菌检测方法，亦未使用适当的培养基对你们的无菌顺势疗法注射药品进行无菌性检测。另外，你们并未对你们的无菌顺势疗法注射药品进行内毒素和颗粒物检测。

Your response included certificates of analysis for third-party testing of multiple products, but did not address validation of your sterility test method. The sterility testing of each batch is the last ina series of essential CGMP controls that ensure that a drug product is sterile and suitable for release.

你们的回复包括有第三方对多个产品的分析报告，但并未解决你们无菌检测方法验证的问题。对每个批次进行无菌检测是确保药品是无菌并适合放行的一系列基本 CGMP 控制的最后一部分。

In response to this letter, provide the following:

在你们的回复中请提交：

- A comprehensive, independent assessment of your laboratory practices, procedures, methods, equipment, documentation, andanalyst competencies. Based on this review, provide a detailed plan to remediate and evaluate the effectiveness of your laboratory system.
  一份对你们实验室规范、程序、方法、设备、文件记录和化验员能力的全面独立评估。根据此审核，提交一份补救和评估你们实验室系统有效性的详细计划
- An update of all testing methods used by your firm and your method validation status.
  你们所用所有检测方法的更新情况，以及方法验证的状态

Additional Guidance on Aseptic Processing 其它无菌加工指南

See FDA's guidance document Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practiceto help you meet the CGMP requirements when manufacturing sterile drugs using aseptic processing at https://www.fda.gov/media/71026/download.

参见上述链接 FDA 的指南文件"采用无菌加工生产的无菌药品 CGMP"，帮助你们在采用无菌工艺生产无菌药品时符合 CGMP 要求。

In addition to addressing the above CGMP violations, any drug marketed by your firm must conform with all applicable requirements of the FD&C Act, including those outlined in the Unapproved New Drug Charges section below.

除了要解决上述 CGMP 违规问题外，所有你公司销售的药品必须符合所有适用的 FDCA 要求，包括在以下未批准新药指挥部分中所列要求。

Unapproved New Drugs 未批准新药（略）

Conclusion 结论

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility and in connection with your marketed products. You are responsible for investigating and determining the causes of these violations and for preventingtheir recurrence or the occurrence of other violations. It is your responsibility to ensure that your firm complies with all requirements of federal law and FDA regulations. You should take prompt action to correct the violations cited in this letter.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。你们有义务确保你公司符合所有的联邦法律和 FDA 法规要求。你们应即刻采取措施纠正本函中所引用的违规情况。

FDA placed your firm on Import Alert 66-40 on October 9, 2019.

FDA 已于 2019 年 10 月 9 日将你公司置于进口禁令 66-40 中。

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产商的新申报和增补申报的批准。

Failure to correct these violations may also result in the FDA continuing to refuse admission of articles manufactured at 8046255 Canada Inc., dba Viatrexx, FEI 3010033797, at 1360 Rue Louis-Marchand, Beloeilinto the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C.381(a)(3). Articles under this authority may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of theFD&C Act, 21 U.S.C. 351(a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

39. 320-20-39 2020-06-17 Vega Life Sciences 印度

Dear Mr. Kurre:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Vega Life Sciences Private Limited, FEI 3015658387, at Plot No. D-15, 16, 21 & 22, Phase-I, I.D.A.Pashamylaram, Patencheru (M), Sangareddy District, Telangana, from November 25 to 28, 2019.

美国 FDA 于 2019 年 11 月 25 日至 28 日检查了你们位于印度的 Vega Life Sciences Private Limited（FEI 3015658387）生产场所。

This warning letter summarizes significant deviations from current good manufacturing practice (CGMP) for active pharmaceutical ingredients (API).

本警告信总结了原料药生产严重违反 CGMP 的行为。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your API are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food,Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

由于你们的原料药生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的原料药根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C.351(a)(2)(B)被认为是掺假药品。

We reviewed your December 19, 2019, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

我们已详细审核了你公司 2019 年 12 月 19 日对我们 FDA483 表格的回复，并此告知已收到后续通信。

During our inspection, our investigators observed specific deviations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

1. Failure to control and monitor solvent recovery procedures to ensure that solvents meet appropriate standards before reuse in API manufacturing.

未能控制和监测溶剂回收程序，从而确保溶剂在重新用于 API 生产之前符合适当的标准。

Our inspection found that your firm acts as acontract solvent recovery facility for your customer's (b)(4) API manufacturing operations. Solvents recovered at your facility include (b)(4).

我们检查发现你公司受委托为你们客户的 XX API 生产操作回收溶剂。在你们场所回收的溶剂包括 XX。

Your firm failed to establish and follow procedures to evaluate and control impurity risks associated with your solvent recovery operations. For example:

你公司未能建立和遵守评估和控制与你们溶剂回收操作有关的杂质风险的程序。例如

Inadequate Testing of Recovered Solvents 对回收溶剂检测不充分

Your firm failed to follow your gas chromatography (GC) test method procedure for recovered (b)(4). The procedure requiresuse of a standard for ensuring the batch meets the Identification by GC recovered solvent specification. We reviewed analytical data packages for approximately (b)(4) batches of recovered (b)(4) processed by your firm in 2019 and found they lacked chromatograms representing the use of a standard. Furthermore, your firm stated to the investigators that standards were never run during GC analysis of recovered (b)(4) in 2018 and 2019.

你公司未能遵守你们对回收 XX 的 GC 检测方法。该方法要求使用一种对照品确保批次符合回收溶剂质量标准中的 GC 鉴别。我们审核了你公司在 2019 年约 XX 批次回收 XX 的分析数据包，发现其中缺少使用对照品的图谱。另外，你公司向检查员承诺 2018-2019 年间在 GC 分析时从未使用对照品运行 GC 分析。

In your response, you provided no explanation for this deviation and made no commitment to investigate the scope of this deficiency to determine if other test methods or procedures were not followed. Your response also lacked a risk assessment to determine potential product impact.

在你们的回复中，你们没有为该偏差提交解释，亦未承诺要调查该缺陷的范围，从而确定是否未遵守其它检测方法或程序。你们的回复亦未进行风险评估来确定对产品的潜在影响。

Failure to Establish an Impurity Profile for Recovered Solvents or Investigate Extraneous Peaks in Chromatograms 未能建立回收溶剂的杂质概况或调查色谱图中的外源峰

Your firm failed to establish an impurity profilefor recovered solvents and maintain appropriate oversight of your operations for the control of unknown impurities. Extraneous peaks were observed in morethan (b)(4) batches of recovered (b)(4) processed at your facility between 2018 and 2019. The batches were released by your firm without investigation and you failed to inform your customer of any potential impurities. You stated that your customer instructed you to focus only on the peak representing the recovered solvent, however this is not adequate. Unknown peaks observed in chromatograms of recovered solvents may represent unanticipated impurities that can impact the quality of your customer's API and should be thoroughly investigated.

你公司未能建立回收溶剂杂质谱，并对你们操作中未知杂质的控制进行适当监管。在 2018-2019 年间在你们场所加工的多个批次回收 XX 中发现有外源峰。你们未进行调查就放行这些批次，你们未将潜在杂质问题通知给你们客户。你们声称你们的客户指令你们仅关注回收溶剂峰，但这是不够的。回收溶剂色谱图中的未知峰可能代表了意外杂质，可能会影响你们客户 API 的质量，应进行彻底调查。

Your response is inadequate. Your evaluation of the extraneous peaks observed in recovered solvent chromatograms was not comprehensive and did not include a thorough manufacturing evaluation to determine if your solvent recovery operations contributed impurities to the recovered solvent.

你们的回复是不充分的。你们对回收溶剂色谱图中外源峰的评估不全面，其中未包括彻底的生产评估，从而确定你们的溶剂回收操作是否影响了回收溶剂的杂质。

During the inspection, your firm provided a written statement indicating that you had terminated processing recovered solvents for customers. However in your response you indicated that all future customer products would include quality agreements, which suggests that you may resume such operations in the future. Your firm has not provided sufficient details or procedures to

demonstrate the capability of predicting, controlling, testing, and preventing impurities or cross contamination associated with your solvent recovery processes.

在检查期间，你们公司提交了一份书面声明，说你们已停止为客户回收溶剂。但是在你们的回复中，你们说所有未来客户产品会包括有质量协议，这表示你们未来可能恢复此类操作。你公司未提交足够详细的信息或程序，来证明你们预测、控制、检测和预防溶剂回收工艺杂质与交叉污染的能力。

In response to this letter, provide the following: 在回复本函时请提交以下资料

- A comprehensive investigation into your firm'sfailure to follow internal procedures including test methods. Include a detailed description of the scope and root causes of your lapses and list all associated corrective actions with timeframes for completion.
  一份对你们公司未遵守内部程序，包括检测方法的全面调查。包括对你们问题范围和根本原因的详细描述，以及所有相关纠正措施和完成时限的清单
- A detailed plan describing how you will implement an ongoing program for evaluating the effectiveness of your solvent recovery operations monitoring process control to ensure stable manufacturing and prevention of unanticipated impurities during solvent recovery operations.
  一份详细的计划，说明你们会持续评估你们溶剂回收操作有效性，监测工艺控制，以确保生产的稳定性，防止溶剂回收操作中的意外杂质
- A procedure requiring an impurity profile analysis and risk assessment for all solvent recovery operations. The scope of the procedure should include recovered solvents for internal and external use.
  一份要求进行杂质概况分析，对所有溶剂回收操作进行风险评估的程序。程序的范围应包括内部和外部使用的回收溶剂。
- An updated procedure for handling unknown peaks in chromatograms.
  一份处理色谱中未知峰的程序

2. Failure to have adequate cleaning procedures to prevent contamination or carry-over of a material that would alter the quality of the API.

未制订足够的清洁程序，防止可能改变 API 质量的污染或物料残留

The cleaning of your nondedicated manufacturing equipment used to recover customer solvents including (b)(4) is inadequate. Your firm failed to ensure that your cleaning procedure was sufficient to prevent carryover or contamination for nondedicated equipment used to recover spent solvents. Your firm stated during the inspection that these requirements were not met. Additionally, your firm stated that there were no records to document cleaning of nondedicated equipment used to process recovered solvents including product changeover cleaning.

你们用于回收客户溶剂的非专用生产设备的清洁包括 XX 是不充分的。你公司未能确保你们的清洁程序足以防止用于回收废溶剂的非专用设备的残留或污染。你公司在检查期间声称不符合这些要求。另外，你公司声称没有记录回收溶剂的非专用设备的清洁，包括更换产品的清洁。

In your response, you provided examples of equipment cleaning records but did not include an explanation or justification regarding why you told our investigators during the inspection that these documents did not exist.

在你们的回复中，你们提交了一份设备清洁记录的例子，但并未解释或说明为何你们在检查期间告诉我们检查员没有记录。

Your response also failed to include a thorough evaluation designed to ensure that all equipment including nondedicated storage, receiving, and charging tanks were properly cleaned according to approved procedures.

你们的回复亦未对设计用以确保所有设备包括非专用存贮、接收和加料罐未能按已批准程序进行恰当清洁进行彻底评估。

In response to this letter, provide the following:

在回复本函时请提交以下资料：

- A corrective action and preventive action (CAPA) plan, based on the retrospective assessment, that includes appropriate remediations to your cleaning processes and practices, and timelines for completion. Providea detailed summary of vulnerabilities in your process for lifecycle management of equipment cleaning. Describe improvements to your cleaning program including enhancements to cleaning effectiveness, improved ongoing verification of proper cleaning execution for all products and equipment, and all other needed remediations.
  一份基于回顾性评估的 CAPA 计划，其中要包括对你们清洁工艺和做法的适当补救，以及完成时限。提交一份对你们工艺在设备清洁生命周期管理中的薄弱点。说明对你们清洁程序的改进，包括改进清洁有效性，改进所有产品和设备执行适当清洁的持续确认，以及其它所需补救措施
- Appropriate improvements to your cleaning program,with special emphasis on incorporating conditions identified as worst case in your drug manufacturing operation. In addition, describe the steps that must be taken in your change management system before introduction of new manufacturing equipment or new manufacturing operations.
  对你们清洁程序的适当改进，特别要强调你们药品生产操作的最差情形。另外，说明你们变更管理体系中在引入新的生产设备或新的生产操作之前必须采取的措施
- A summary of updated SOPs that ensure an appropriate program is in place for cleaning procedures for products, processes, and equipment.
  一份更新后的 SOP 摘要，确保制订有适当的产品、工艺和设备清洁程序
- A comprehensive investigation into your firm's CGMP documentation practices. Include a detailed description of the scope and root causes of your documentation lapses and list all associated corrective actions with timeframes for completion.
  一份对你们公司 CGMP 文件规范的全面调查。包括一份对你们文件问题范围和根本原因的详细描述，以及所有相关纠正措施的清单及完成时限

3. Failure to exercise sufficient controls over computerized systems to prevent unauthorized access or changes to data and failure to have adequate controls to prevent omission of data.

未能对计算机化系统进行足够的控制从而防止未经授权进入或改变数据，未能充分防止数据遗漏

Your firm failed to implement adequate controls to ensure the integrity of data generated at your facility including:

你公司未能实施足够的控制，从而确保在你们工厂所生产的数据的完整性，包括：

- Missing raw data files associated with recovered solvent testing were observed in folders on the local hard drive of the operating system connected to the GC instrument. Your firm indicated that the files appear to have been deleted.
  在连接 GC 仪器的操作系统的本地硬盘文件夹中发现与回收溶剂检测有关的原数据文件缺失，你公司说文件已删除
- Quality Control analysts shared the same user name and password for the operating system on each workstation and the analytical software for the GC.
  QC 化验员共用工作站操作系统和 GC 分析软件的用户名和密码
- Recovered solvent data on the stand-alone computerized system for the GC were not backed up as required per your approved procedure.
  单机版本计算机化系统中的回收溶剂 GC 分析数据未按你们已批准的程序备份
- Your firm did not have a procedure governing the audit trail or its retention. During the inspection, the GC analytical software was configured to retain the audit trail for only (b)(4).
  你公司没有程序对审计追踪及其保存情况进行管理。在检查期间，GC 分析软件的参数设置为审计追踪仅保存 XX

Your firm failed to include a comprehensive, systematic plan for evaluating your practices and procedures to ensure data integrity controls are applied throughout your firm. Additionally, you failed to conduct a risk assessment addressing potential impacts to product as a result of the inadequate data integrity controls.

你公司未包括一份评估你们做法和程序的全面系统化计划，从而确保在整个公司对数据完整性进行了控制。另外，你们未能执行风险评估，解决数据完整性控制不充分对产品的潜在影响问题。

Data Integrity Remediation 数据完整性补救措施

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. See FDA's guidance document Data Integrity and Compliance With Drug CGMP for guidance on establishing and following CGMP compliant data integrity practices at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/data-integrity-and-compliance-drug-cgmp-questions-and-answers-guidance-industry.

你们的质量体系不能充分确保数据的准确性和完整性，无法支持你们生产的药品的安全性、有效性和质量。参见 FDA 指南文件"数据完整性和药品 GMP 合规"指导建立和遵守 CGMP 合格数据完整性规范。

We strongly recommend that you retain a qualified consultant to assist in your data integrity remediation. In response to this letter, provide the following:

我们强烈建议你们正聘用顾问对你们的操作进行审计并协助你们符合 FDA 要求。在回复此函时请提交以下信息：

- A comprehensive investigation into the extent of the inaccuracies in data records and reporting including results of the data review for drugs distributed to the United States. Include a detailed description of the scope and root causes of your data integrity lapses.
  一份对数据记录和报告不准确性程度的全面调查。其中要包括一份对你们数据完整性问题范围和根本原因的详细说明。

- A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity and analyses of the risks posed by ongoing operations.
  你们药品质量中所发现的不合格情况的潜在影响的当前风险评估。你们的评估应包括由于受到数据完整性问题影响的药品放行导致的患者风险的分析，以及持续运营所具有的风险。
- A management strategy for your firm that includesthe details of your global CAPA plan. The detailed corrective action plan should describe how you intend to ensure the reliability and completeness of all data generated by your firm including microbiological and analytical data, manufacturing records, and all data submitted to FDA.
  你们公司的管理策略，包括你们全球 CAPA 计划详细情况。应有一份详细的 CA 计划，说明你们准备如何确保你们生成的所有数据的可靠性和完整性，包括分析数据、生产记录和所有提交给 FDA 的数据。

CGMP Consultant Recommended CGMP 顾问建议

Based upon the nature of the deviations we identified at your firm, we strongly recommend engaging a consultant qualified to evaluate your operations and to assist your firm in meeting CGMP requirements if your firm intends to resume manufacturing drugs for the U.S.market. We also recommend that the qualified consultant perform a comprehensive audit of your entire operation for CGMP compliance and that the consultant evaluates the completion and efficacy of your corrective actions and preventive actions before you pursue resolution of your firm's compliance status with FDA.

鉴于我们在你公司所发现的违规情况，我们强烈建议你们使用一位有 21 CFR 211.34 所述资质的顾问来协助你们公司符合 CGMP 要求。我们亦建议该具备资质的顾问对你们整体运营情况进行药品 CGMP 合规情况全面审计，并由其在你们寻求满足 FDA 合规要求之前对你们 CAPA 的完成情况和有效性进行评估。

Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

你们使用顾问并不能解除你们公司符合 CGMP 的义务。你们公司的高级管理层仍负有义务全面解决所有缺陷，确保持续 CGMP 符合性。

Solvent Recovery Operations Terminated 停止溶剂回收操作

We acknowledge your commitment to terminate processing recovered solvents for customers at this facility for the U.S.market. If you plan to resume producing recovered solvents for the U.S. supply chain, notify this office in writing.

我们了解到你们承诺会停止在该场所为美国市场客户回收溶剂。如果你们计划继续为美国供应链回收溶剂，请书面通知本办公室。

Conclusion 结论

The deviations cited in this letter are not intended to be an all-inclusive list of deviations that exist at your facility.You are responsible for investigating and determining the causes of these deviations and for preventing their recurrence or the occurrence of other deviations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

FDA placed your firm on Import Alert 66-40 on April14, 2020.

FDA 已于 2020 年 4 月 14 日将你公司置于进口禁令 66-40 中。

Until you correct all deviations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产商的新申报和增补申报的批准。

Failure to correct these deviations may also resultin the FDA continuing to refuse admission of articles manufactured at Vega Life Sciences Private Limited at Plot No. D-15, 16, 21 & 22, Phase-I, I.D.A.Pashamylaram, Patencheru (M), Sangareddy District, Telangana into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3).Articles under this authority may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C.351(a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your deviations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

40. 320-20-40 2020-07-14 Signa S.A. de C.V.墨西哥

Dear Mr. Watson:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Signa S.A. de C.V., FEI 3002808161,at Avenida Industria Automotriz No. 301, Fracc. Delegación Santa Ana Tlapaltitlan, Toluca, Toluca De Lerdo, Mexico, from December 16 to 20, 2019.

美国 FDA 于 2019 年 12 月 16 日至 20 日检查了你们位于墨西哥的 Signa S.A. deC.V., FEI 3002808161 生产场所。

This warning letter summarizes significant deviations from current good manufacturing practice (CGMP) for active pharmaceutical ingredients (API).

本警告信总结了原料药生产严重违反 CGMP 的行为。

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your API are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food,Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

由于你们的原料药生产、加工、包装或保存的方法、场所或控制不符合 CGMP 要求，你们的原料药根据 FDCA 的 501(a)(2)(B)以及 21 U.S.C.351(a)(2)(B)被认为是掺假药品。

We reviewed your January 13, 2020, response to our Form FDA 483 in detail and acknowledge receipt of your subsequent correspondence.

我们已详细审核了你公司 2020 年 1 月 13 日对 FDA483 表的回复，并此告知已收到后续通信。

During our inspection, our investigator observed specific deviations including, but not limited to, the following.

检查期间，我们的调查人员发现的具体问题包括但不仅限于以下：

Failure to adequately investigate out-of-specification results and implement appropriate corrective actions. 未对 OOS 结果进行充分调查，并执行恰当的纠正措施。

Your investigations into out-of-specification (OOS) test results were inadequate. You failed to appropriately justify potential root causes, expand investigations to all potentially affected batches, and implement adequate corrective actions and preventive actions (CAPA).

你们对 OOS 结果的调查是不充分的。你们未能恰当地论证潜在根本原因，未将调查扩展至所有可能影响的批次，并实施恰当的 CAPA。

a. You obtained OOS results for related substances (b)(4) during the release testing of (b)(4) USP, batch (b)(4), performed in January 2018 as part of a process validation study. Your Phase I laboratory investigation confirmed the OOS results. You opened a manufacturing investigation that listed multiple hypotheses as root causes for an inadequate (b)(4) reaction. Your investigation ultimately concluded, without adequate supporting evidence, that the potential root cause for the impurity OOS was inadequate (b)(4).

你们 2018 年 1 月工艺验证时，在 XX USP 规格批号 XX 的放行检测中，有关物质项结果为 OOS。你们的第一阶段实验室调查中确认了 OOS 结果。你们启动了生产调查，列出了多个假设作为 XX 反

应不充分的根本原因。你们的调查最后在没有足够支持性证据的情况下得出结论说杂质 OOS 可能的根本原因是 XX 不充分。

You later found this root cause was unsupported because you were using the maximum (b)(4). Your investigation was inadequate and did not include appropriate corrective action.

后来你们发现无法支持该根本原因，因为你们正在使用的是最大 XX。你们的调查是不充分的，其中未包括恰当的纠正措施。

In response to the FDA-483, you reopened the manufacturing investigation. Your firm emphasized temperature profile and material charging in the updated investigation. Specifically, while the batch was within operational temperatures ranges, your firm found that it exhibited an “anomalous pattern.” Your firm had previously identified temperature range as acritical control parameter with the potential for quality impact. Your investigation also noted that the yield was slightly lower for this batch, which may have been related to material (b)(4) errors. Your CAPA after the renewed investigation included tightening the temperature range from (b)(4),but it remained uncertain whether the root cause was adequately resolved.

在回复 FDA483 表时，你们重启了生产调查。你公司在更新后的调查中侧重于温度概况和物料投料。具体来说，当该批次在操作温度范围内时，你公司发现其呈现“异常模式”。你公司之前识别了温度范围是一个关键控制参数，对质量有潜在影响。你们在调查中亦注意到该批次收率略低，这可能与物料 XX 错误有关。在重启调查之后，你们的 CAPA 包括有收紧温度范围，但仍不确定是否充分解决了根本原因。

The failing impurity data obtained for this batch was intended to support (b)(4) process validation studies. Notably, your firm has experienced several additional failures during the production history of this API.

该批次的不合格杂质数据原准备用于支持 XX 工艺验证研究。值得注意的是，你公司该 API 的生产历史中有好几次其它失败经历。

At least one of the finished API batches from these validation studies was released for the U.S. market.

这些验证研究中至少有一批 API 成品被放行到了美国市场。

In your response, you stated that your firm will conduct additional experimental design studies to ensure evaluation of multivariate combinations that replicate the failure mode. However, your response lacked sufficient information about the scope, timeline, and plans to ensure CAPA effectiveness.

在你们的回复中，你们声称你们的公司会进行更多的试验设计研究，以确保对多变量组合进行评估，重现失败模式。但是你们的回复缺少了足够的范围、时间表和计划方面资料，无法确保 CAPA 的有效性。

b. You obtained an OOS assay result during the release testing of (b)(4) USP, batch (b)(4), performed in October 2018.You then obtained passing retest results and invalidated the original OOS result. Your firm indicated that a likely root cause was instability of the analytical balance due to the presence of too many analysts in the weighing room.There was no evidence that the

presence of multiple analysts in the room affected the sensitivity of the analytical balance and therefore contributed to the OOS results.

你们在 X2018 年 10 月工艺验证时，在 XX USP 规格批号 XX 的放行检测中，含量结果为 OOS。然后你们复测并得到合格结果，宣布了原始 OOS 结果无效。你公司说可能的根本原因是因为称重间里化验员太多，所以分析天平不稳定。但没有证据证明当时房间里有多个化验员，对分析天平的灵敏度产生了影响，从而导致 OOS 结果。

Your laboratory investigation also indicated that your Plant Manager reported no deviations that could be related to the OOS results. No further documentation of the manufacturing evaluation was available or provided to the investigator during the inspection.

你们的实验室调查亦显示你们的工厂经理没有报告可能与 OOS 结果有关的偏差。生产评估没有更多的文件记录，在检查期间未提交给检查员。

Your firm lacked a meaningful or formal Phase 2 manufacturing investigation, and batch (b)(4) was subsequently released.

你公司没有执行有意义的正式第二阶段生产调查，之后放行了批号 XX。

Whenever an investigation lacks conclusive evidence of laboratory error, a thorough investigation of potential manufacturing causes must be performed.

如果调查缺少有力证据证明实验室错误，则必须彻底调查可能的生产原因。

We acknowledge that you have initiated efforts to remediate and improve your investigation programs. However, your response lacked adequate details of the remediation approach. In addition, the scope of your assessment is insufficient.

我们了解到你们已开始执行补救工作，准备改进你们的调查程序。但是你们的回复没有足够详细的补救方法。此外，你们的评估范围是不充分的。

In response to this letter, provide the following.

在回复本函时请提交以下内容：

- A comprehensive, independent assessment of your overall system for investigating deviations, discrepancies, complaints, OOS results, and failures. Provide a detailed action plan to remediate this system. Your action plan should include, but not be limited to, significant improvements in investigation competencies, scope determination, root cause evaluation, CAPA effectiveness, quality assurance unit oversight, and written procedures. Address how your firm will ensure all phases of investigations are appropriately conducted.
  一份对你们偏差、差异、投诉、OOS 结果和失败调查的全面系统的全面独立评估。提交一份详细的行动计划以补救该系统。你们的行动计划应包括但不仅限于对调查能力、范围界定、根本原因评估、CAPA 有效性、质量部门监管和书面程序的重大改进。说明你们公司要如何确保恰当地执行了所有调查阶段。
- An independent assessment and remediation plan for your CAPA program, including whether your firm assures CAPA effectiveness, regularly reviews investigations trends, implements improvements to the CAPA program when needed, ensures appropriate quality assurance unit decision rights, and is fully supported by executive management.

一份你们 CAPA 程序的独立评估及补救计划。提交一份报告评估其是否包括员工具备适当的调查能力、有效执行根本原因分析、确保 CAPA 有效性、定期审核调查趋势、必要时对 CAPA 程序进行改进，确保质量部门具备适当的决策权力，并得到高级管理层的全面支持。

- A retrospective, independent review of all invalidated OOS (including in-process and release/stability testing) results for U.S. products, irrespective of whether the batch was ultimately distributed in the U.S. and a report summarizing the findings of the analysis, including a detailed chart with the following for each OOS:
  对所有美国产品的宣布无效的实验室事件和 OOS（包括中控和放行/稳定性测试）结果的独立回顾审核，无论这些产品是否最终销售至美国，并提交一份报告总结分析中发现的情况，包括每个 OOS 的以下信息：
  - Determine whether the scientific justification and evidence relating to the invalidated OOS result conclusively or inconclusively demonstrates causative laboratory error.
    确定宣布无效的 OOS 结果的科学论证和证据是否可得出结论支持可归因的实验室错误
  - For investigations that conclusively establish laboratory root cause, provide rationale and ensure that all other laboratory methods vulnerable to the same or similar root cause are identified for remediation.
    对于可得出实验室根本原因的调查，提交理由并确保识别出所有其它对类似根本原因易受影响的实验室方法并进行补救
  - For all OOS results found by the retrospective review to have an inconclusive or no root cause identified in the laboratory, include a thorough review of production (e.g., batch manufacturing records, adequacy of the manufacturing steps, suitability of equipment/facilities, variability of raw materials, process capability, deviation history, complaint history, and batch failure history). Summarize potential manufacturing root causes for each investigation, and any manufacturing operation improvements.
    对于回顾审核中发现的所有 OOS 结果，在实验室未找到根本原因或不能得出结论的，要包括一份对生产（例如批生产记录，生产步骤是否充分，设备/设施适用性，原料波动性，工艺能力，偏差历史，投诉历史，批不合格历史）的彻底审核。提交一份每个调查潜在生产根本原因的总结，以及所有生产操作改进措施。
  - This review should cover the past three years (i.e., since January 2017) and evaluate any other common issues found beyond that period.
    该审核应覆盖过去 3 年时间（即自 2017 年 1 月起），并评估在该时间段以外所发现的所有其它一般问题
- Provide the full batch history of (b)(4) andof its (b)(4), batch disposition decisions, and details regarding any failing results that occurred at any stage or processing.
  提交一份 XX 及其 XX 的所有批次历史、批处置决策，以及在任何阶段或工艺处理中发生的失败结果的所有详细信息
- A comprehensive review and remediation plan for your OOS result investigation systems. The CAPA should include but not be limited to addressing the following:
  一份对你们 OOS 结果调查系统的全面审核和补救计划。CAPA 应包括但不仅限于解决以下问题：
  - Quality unit oversight of laboratory investigations.
    质量部门对实验室调查的监管
  - Identification of adverse laboratory control trends.
    不良实验室控制趋势的识别
  - Resolution of causes of laboratory variation.

实验室波动原因的解决方案

- Initiation of thorough investigations of potential manufacturing causes whenever a laboratory cause cannot be conclusively identified.
  无论是否可发现可归结实验室原因，均要对潜在生产原因启动彻底调查
- Adequately scoping each investigation and its CAPA.
  对每个调查及其 CAPA 范围进行充分界定
- Revised OOS investigation procedures with these and other remediations.
  修订后 OOS 调查程序，其中要包括上述要求及其它补救措施

Repeat Violations and Deviations at Multiple Sites 多场所重复违规和偏差

FDA cited similar CGMP deviations at other facilities in your company's network. These repeated failures at multiple sites demonstrate that management oversight and control over the manufacture of drugs is inadequate.

FDA 在你公司旗下其它场所亦发现有相似的 CGMP 违规情况。多场所重复违规证明你们对药品生产的监管和控制是不充分的。

Your executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance.

你们的高级管理人员有义务全面解决所有缺陷，确保持续符合 CGMP 要求。

Conclusion 结论

The deviations cited in this letter are notintended to be an all-inclusive list of deviations that exist at your facility. You are responsible for investigating and determining the causes of these deviations and for preventing their recurrence or the occurrence of other deviations.

此函中所引用的违规并不是全部。你们有责任对这些偏差进行调查，确定原因，防止其再次发生，防止你们设施内其它偏差的发生。

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effectiveway to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b). This also allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

如果你们在考虑要采取的措施可能会导致你们工厂所生产的药品供应中断，FDA 要求你立即联系 CDER 药品短缺负责人员，这样 FDA 可以与你们一起采用最为高效的方式引导你们的操作符合法规要求。联系药品短缺负责人员还能让你满足依据 21 U.S.C. 356C(b)你可能必须报告你们药品中止或中断的义务，让 FDA 尽快考虑是否需要采取何种措施来避免短缺，保护依赖于你们药品的患者健康。

Until you correct all deviations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new drug applications or supplements listing your firm as a drug manufacturer.

在贵公司未能完成所有偏差纠正并且由我们确认你们符合 CGMP 之前，FDA 可能会搁置所有将你公司列为药品生产商的新申报和增补申报的批准。

Failure to correct these deviations may also result in the FDA refusing admission of articles manufactured at Signa S.A. de C.V. at Avenida Industria Automotriz No. 301, Fracc. Delegación Santa Ana Tlapaltitlan,Toluca, Toluca De Lerdo, Mexico, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Articles under this authority may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

未能纠正这些偏差可能还会导致 FDA 依据 FDCA 第 801(a)(3)条和 21 U.S.C. 381(a)(3)拒绝接受在上述地址生产的产品进入美国。

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your deviations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

在收到此函后，请在 15 个工作日内回复至本办公室。在回复中说明自从检查后，你们做了哪些工作来纠正你们的偏差，防止其再次发生。如果不能在 15 个工作日内完成纠正措施，说明延迟的原因以及完成计划。

PharmLink 简介

PharmLink 总部位于加拿大，聚集了一群孜孜以求、医药行业经验丰富的“制药人”，他们曾服务于北美地区的多家世界 500 强企业，面对传统模式无法满足医药专业市场需求的现状及运营模式无法优化的供给矛盾，专注为医药行业在中国和北美之间的技术交流搭建链接的桥梁。

PharmLink 现提供医药行业专业翻译和《Pharmlink 国际制药动态》期刊出版等服务。遵循欧盟、北美制药行业法规和指南不断变化的要求，将推动中国医药企业更快、更好的进入国际市场。

《Pharmlink 国际制药动态》介绍

中文版《Pharmlink 国际制药动态》期刊每月以电子和纸质两种方式发行，内容涵盖上个月内监管机构和其它组织发布的更新信息，并对此进行归纳与整理，通过以下七个栏目展现医药行业最新情报：

栏目		制药知识库
1	指南与技术标准	必备的战术性武器，日常工作中重要的参考资料
2	产业政策与法规	战略型的考虑，帮助药企更好地理解监管当局的监管思路，有助于公司确立目标区域市场的战略布局
3	药物研发与批准	对药物研发与批准现状与历史进行概述，帮助药企预测监管机构的期望和要求，提高获批的可能性和速度
4	召回、退市与安全信息	帮助药企及时评估产品安全风险，包括已经上市产品以及在研发与申报过程中的产品
5	警告信和违规通告	帮助药企从监管者的角度了解如何有效建立和运行制药质量体系
6	医药资讯	关注医药最新资讯类，帮助药企了解行业最新新闻动态
7	制药评论	关注行业内相关评论信息，帮助药企获得多维度的视角

联系方式

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