Guidance for Industry

Changes to an Approved
NDA or ANDA

已批准申请的新药变更指南

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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I. INTRODUCTION AND BACKGROUND

This guidance provides recommendations to holders of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) who intend to make post approval changes in accordance with section 506A of the Federal Food, Drug, and Cosmetic Act (the Act) and § 314.70 (21 CFR 314.70). The guidance covers recommended reporting categories for postapproval changes for drugs other than specified biotechnology and specified synthetic biological products. It supersedes the guidance of the same title published November 1999. Recommendations are provided for postapproval changes in (1) components and composition, (2) manufacturing sites, (3) manufacturing process, (4) specifications, (5) container closure system, and (6) labeling, as well as (7) miscellaneous changes and (8) multiple related changes.

本指南给打算将已批准变更的新药上市申请和新药报审简表申请的持有者提供建议，使其按照联邦食品、药品、化妆品法案的 506A 部分和§ 314.70 (21 CFR 314.70)。该指南包括建议对药品除了其他指定的生物技术和特定的合成生物制品的已批准变更进行报告类别。它取代了发表于 1999 年 11 月同一标题的指导原则。为以下已批准的变更提供建议（1）成分和组成 （2）厂址 （3）生产工艺 （4）质量标准 （5）包装 （6）标签 （7）其它变更 （8）复杂相关变更

Recommendations on reporting categories for changes relating to specified biotechnology and specified synthetic biological products regulated by CDER are found in the guidance for industry
建议由药品评价和研究中心规定对有关指定生物技术和特定的合成生物制品的变更进行报告类别，出现在企业的指南中 。

Paperwork Reduction Act Public Burden Statement: This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3520). The collection(s) of information in this guidance were approved under OMB Control No. 0910-0538 (until August 31, 2005). 文书工作减少法案：本指南包含资料的收集贮藏受到管理和预算办公室（OMB）的审查，根据 1995 年的文书工作减少方案(44 U.S.C. 3501-3520)。在此指南下，收集的资料依据管理和预算办公室控制的第 0910-0538 获得批准（直到 2005 年 8 月 31 日）。

On November 21, 1997, the President signed the Food and Drug Administration Modernization Act of 1997 (the Modernization Act).3 Section 116 of the Modernization Act amended the the Act by adding section

506A, which provides requirements for making and reporting manufacturing changes to an approved application and for distributing a drug product made with such changes. The FDA has revised its regulations on supplements and other changes to an approved application (21 CFR 314.70) to conform to section 506A of the Act.
1997 年 11 月 21 日，总统签署了美国食品和药物管理局 1997 现代化法案（现代化法案）。 第 116 条现代化法修正法案，增加了第 506A 条，要求对已批准申请的任何变更以及销售变更后产品的行为必须报告。对一个获批准的申请(21 CFR 314.70)，FDA 已经在补充和变更内容上修订规章，以符合法案第 506A 条。

This guidance does not provide recommendations on the specific information that should be developed by an applicant to assess the effect of the change on the identity, strength (e.g., assay, content uniformity), quality (e.g., physical, chemical, and biological properties), purity (e.g., impurities and degradation products), or potency (e.g., biological activity, bioavailability, bioequivalence) of a drug product as these factors may relate to the safety or effectiveness of the drug product. An applicant should consider all relevant CDER guidance documents for recommendations on the information that should be submitted to support a given change.4
作为可能关系到药品安全性和有效性的以下因素，药品的特征、剂量（例如含量测定、含量均一性）、质量（例如，物理、化学和生物学特性） 、纯度（例如，杂质和降解产物） ，或药效（例如，生物活性、生物利用度、生物等效性），申请人评估以上因素变更效果的具体信息，本指南不提供建议。申请者应该考虑所有相关的药品评价和研究中心的指导文件，建议资料应该提交以支持某一特定的变更。
CDER has published guidances, including the SUPAC (scale-up and postapproval changes) guidances, that provide recommendations on reporting categories. To the extent that the recommendations on reporting categories in this guidance are found to be inconsistent with guidances published before this guidance was finalized, the recommended reporting categories in such previously published guidances are superseded by this guidance. This guidance does not provide extensive recommendations on reporting categories for components and composition changes (see section V). Therefore, recommended reporting categories for components and composition changes provided in previously published guidances, such as the SUPAC guidances, still apply. Section 506A of the Act and § 314.70(c) provide for two types of changes-being¬effected supplements (see section II), while previously there was only one type. It is important for applicants to use this guidance to determine which type of changes-being-effected supplement is recommended. CDER intends to update the previously published guidances to make them consistent with this guidance.
CDER 已公布指南，包括 SUPAC（扩大和批准后的变更）指南，对报告类别提供了建议。发现在本指南中报告类别的建议范围和以前已定案公布的指南不一致，推荐本指南的报告类别取代先前公布的。对成分和组成变更（查看第 V 条）的报告类别，本指南不提供广泛建议。因此，推荐先前公布的指南提供的成分和组成变更的报告类别，例如 SUPAC 指南，目前还适用。法案的第 506A 和§ 314.70(c)提供了“有待生效的补充文件”的两种类型（查看第 II），然而先前的只有一种类型。对于申请者，运用本指南来决定用哪个 “有待生效的补充文件”是很重要的。CDER 打算更新先前公布的指南使其和本指南一致。

If guidance for either recommended reporting categories or information that should be submitted to support a particular change is not available, the appropriate CDER chemistry or microbiology review staff can be consulted for advice.

如果本指南中推荐的报告类别或者支持具体变更所提交的资料没有效，可以向合适的 CDER 化学或微生物检查人员征询意见。

FDA's guidance documents, in general, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidances means that something is suggested or recommended, but not required. Insofar as this guidance adjusts reporting categories pursuant to section 506A of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70, it does have binding effect. If you have any questions about the effect of any portion of this guidance, contact the Office of Pharmaceutical Science, Center for Drug Evaluation and Research (HFD-003), Food and Drug Association, 5600 Fishers Lane, Rockville, MD 20857.

FDA 的指导文件，大体上没有建立依法强制执行的责任。相反，指南叙述该机构目前正在考虑的话题且仅作为建议，除非特定的法令要求被引用。词的使用在机构的指南应该意味着一些建议或推荐，但不是要求。在本指导的范围内调整报告类别，依据联邦食品、药品和化妆品法第 506A 和 21 CFR 314.70 ，它确实有约束力。如果你有关于本指导任一部份作用的任何问题，联络医药科学办公室、药物评价和研究中心（ HFD-003 ） 、美国食品和药物管理局、5600 渔民巷，美国马里兰州罗克维尔市 20857。

II. REPORTING CATEGORIES 报告类别

Section 506A of the Act and § 314.70 provide for four reporting categories that are distinguished in the following paragraphs.

法案的第 506A 和§ 314.70 提供了在以下各段落中有区分的 4 个报告类别。

A major change is a change that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product. A major change requires the submission of a supplement and approval by FDA prior to distribution of the drug product made using the change. This type of supplement is called, and should be clearly labeled, a Prior Approval Supplement (§ 314.70(b)). An applicant may ask FDA to expedite its review of a prior approval supplement for public health reasons (e.g., drug shortage) or if a delay in making the change described in it would impose an extraordinary hardship on the applicant. This type of supplement is called, and should be clearly labeled, a Prior Approval Supplement - Expedited Review Requested (§ 314.70(b)(4)).5 FDA is most likely to grant requests for expedited review based on extraordinary hardship for manufacturing changes made necessary by catastrophic events (e.g., fire) or by events that could not be reasonably foreseen and for which the applicant could not plan.

大变更指对药品特征、剂量、质量、纯度或药效有重大潜在不良影响、与药品的安全性和有效性相关的变更。大变更后生产的产品需要提交补充申请，经 FDA 批准后方可销售。这类补充申请应有明显标识，称作“批准前变更申请”（314.70）。申请人可以以公众健康为由（如药品短缺）要求 FDA 加速批准前变更的审核，如果变更延迟会给申请人造成极大的困难，可以要求加速审批。这类变更称为“要求加速审批的批准前变更”（314.70(b)(4)）。由于灾难性事故或不可预见的事故造成生产变更，并对申报人造成极大的困难的情况，FDA 最有可能加速审批。

A moderate change is a change that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. There are two types of moderate change. One type of moderate change requires the submission of a supplement to FDA at least 30 days before the distribution of the drug product made using the change. This type of supplement is called, and should be clearly labeled, a Supplement -

Changes Being Effected in 30 Days (§ 314.70(c)(3)). The drug product made using a moderate change cannot be distributed if FDA informs the applicant within 30 days of receipt of the supplement that a prior approval supplement is required (§ 314.70(c)(5)(i)). For each change, the supplement must contain information determined by FDA to be appropriate and must include the information developed by the applicant in assessing the effects of the change (§ 314.70(a)(2) and (c)(4)). If FDA informs the applicant within 30 days of receipt of the supplement that information is missing, distribution must be delayed until the supplement has been amended to provide the missing information (§ 314.70(c)(5)(ii)).
中等变更指对药品特征、剂量、质量、纯度或药效有中等程度的潜在不良影响、可能与药品的安全性和有效性相关的变更。有两种中等变更，一种要求变更后生产的产品销售前至少 30 天提交补充申请，这类补充申请应有明显标识，称作“30 天后变更生效的补充文件”（314.70(c)(3)）。如果 FDA 收到补充申请的 30 天内要求提交“批准前变更申请”（314.70(c)(5)(i)），则变更后生产的产品不能销售。任何一种变更都必须包括 FDA 接受的信息，必须包括变更影响评估的信息（314.70(a)(2)和(c)(4)）。如果 FDA 在接收到补充申请后的 30 天内通知申请人信息不全，则必须延迟销售直到补充申请加入缺失的信息（314.70(c)(5)(ii)）。

FDA may identify certain moderate changes for which distribution can occur when FDA receives the supplement (§ 314.70(c)(6)). This type of supplement is called, and should be clearly labeled, a Supplement - Changes Being Effected. If, after review, FDA disapproves a changes-being-effected-in-30-days supplement or changes-being-effected supplement, FDA may order the manufacturer to cease distribution of the drug products made using the disapproved change (§314.70(c)(7)).
FDA 可能规定某些中等变更 FDA 接收到补充申请时产品可以销售，这类补充申请应有明显标识，称作“已完成变更的补充申请”。如果评审结束后，FDA 不批准“30 天后生效的变更补充文件”或“已生效的变更补充文件”，FDA 可以要求生产厂家停止销售变更后生产的产品 (§314.70(c)(7))。

A minor change is a change that has minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. The applicant must describe minor changes in its next Annual Report (§ 314.70(d)).
小变更指对药品特征、剂量、质量、纯度或药效有最小的潜在不良影响、可能与药品的安全性和有效性相关的变更。申请人必须在下一次年度报告中描述小变更(§ 314.70(d))。

Under § 314.70(e), an applicant can submit one or more protocols (i.e., comparability protocols) describing tests, studies, and acceptance criteria to be achieved to demonstrate the absence of an adverse effect from specified types of changes. A comparability protocol can be used to reduce the reporting category for specified changes. A proposed comparability protocol that was not approved as part of the original application must be submitted as a prior approval supplement (314.70(e)). On February 25, 2003, FDA issued a draft guidance on comparability protocols entitled Comparability protocols - Chemistry, Manufacturing, and Controls Information.
根据 314.70(e)，申请人可以提交 1 个或多个方案（如相比性方案），描述检测、研究、可接受标准，以证明特定的变更不会有不良影响。相比性方案可减少特定变更的报告范围。提交的相比性方案在原始申报资料中没有包括，必须作为“批准前变更申请”提交。见 Comparability protocols - Chemistry, Manufacturing, and Controls Information。

III. GENERAL REQUIREMENTS 常规要求

Other than for editorial changes in previously submitted information (e.g., correction of spelling or typographical errors, reformatting of batch records), an applicant must notify FDA about each change in

each condition established in an approved application beyond the variations already provided for in the application (§ 314.70(a)(1)).
除编辑上的改动，在以往提交的资料（如更正拼写或打字错误，重新格式化的一批纪录），申请人必须通知 FDA 了解在每个确立的情况、获批准的申请的各个改变，超出了变更在申请中应用(§ 314.70(a)(1))。

A supplement or annual report must include a list of all changes contained in the supplement or annual report. On the list, FDA recommends that the applicant describe each change in enough detail to allow FDA to quickly determine whether the appropriate reporting category has been used. For supplements, this list must be provided in the cover letter (§ 314.70(a)(6)). In annual reports, the list should be included in the summary section (§ 314.81(b)(2)(i)). The applicant must describe each change fully in the supplement or annual report (§ 314.70(a)(1)).
增补或年报必须包括一列所有变更，载于增补或年报。在目录上，FDA 建议申请者对每个变更叙述详尽，使 FDA 迅速决定是否合适的报告范围已被使用。对于增刊，此目录必须在信封面上(§ 314.70(a)(6))。在年报里，目录应包括在简节中(§ 314.81(b)(2)(i))。申请者必须说明每个变更都在增刊和年报里。

An applicant making a change to an approved application under section 506A of the Act must also conform to other applicable laws and regulations, including current good manufacturing practice (CGMP) requirements of the Act (21 U.S.C. 351(a)(2)(B)) and applicable regulations in Title 21 of the Code of Federal Regulations (e.g., 21 CFR parts 210, 211, 314). For example, manufacturers must comply with relevant CGMP validation and recordkeeping requirements and ensure that relevant records are readily available for examination by authorized FDA personnel during an inspection.
申请者依据法案的第 506A 部分对已批准的申请作出变更，必须同时符合其它适用的法律和规章，包括现行的药品生产管理规范（CGMP）要求的法案(21 U.S.C. 351(a)(2)(B))和美国联邦行政法规(e.g., 21 CFR parts 210, 211, 314)的 21 部中适用的规章。例如，生产厂家必须服从相关 CGMP 验证和保留记录的要求，确保有关的记录在检查期间随时可供获授权的 FDA 工作人员检查。

A changes-being-effected supplement providing for labeling changes under § 314.70(c)(6)(iii) must include 12 copies of the final printed labeling (§ 314.70(c)(1)). In accordance with § 314.70(a)(4), an applicant also must promptly revise all promotional labeling and drug advertising to make it consistent with any labeling change implemented in accordance with § 314.70(b) or (c).

“已生效的变更补充”提供了标签变更，依据§ 314.70(c)(6)(iii)必须包括 12 份最后打印的标签(§ 314.70(c)(1))。按照§ 314.70(a)(4),申请者还必须及时修改所有宣传标识和药品广告，使之符合任何标签变更，应按照 § 314.70(b) or (c)实施。

Except for supplements providing only for a change in labeling, an applicant must include in each supplement and amendment to a supplement a statement certifying that a field copy has been provided in accordance with 21 CFR 314.440(a)(4)6 (§ 314.70(a)(5)).
除了在标签中只补充一个变更，申请者必须包括有每个补充和修改的资料来补充说明，证明副本已按照 21 CFR 314.440(a)(4)6 (§ 314.70(a)(5))提供。

IV. ASSESSING THE EFFECT OF MANUFACTURING CHANGES 对生产变更的评估
A. Assessment of the Effects of the Change 评估变更效果

The holder of an approved application under section 505 of the Act must assess the effects of the change before distributing a drug product made with a manufacturing change (§ 314.70(a)(2)).7 For each change, the supplement or annual report must contain information determined by FDA to be appropriate and must include the information developed by the applicant in assessing the effects of the change (section 506A(b), (c)(1), (d)(2)(A), and (d)(3)(A) of the Act). The type of information that must be included in a supplemental application or an annual report is specified in § 314.70(b)(3), (c)(4), and (d)(3).
按照法案第 505 条，在发行有生产变更的药品前(§ 314.70(a)(2))，已批准申请的持有人必须评估变更效果。对每个变更，增刊或年报必须包含由 FDA 确定的合适的资料和申请者在评估变更效果所取得的资料(section 506A(b), (c)(1), (d)(2)(A), and (d)(3)(A) of the Act)。该类型的资料必须包括在补充申请或年报里，特别是在§ 314.70(b)(3), (c)(4), and (d)(3)中。

1. Conformance to Specifications
An assessment of the effects of a change on the identity, strength, quality, purity, and potency of the drug product should include a determination that the drug substance intermediates, drug substance, in-process materials, and/or drug product affected by the change conform to the approved specifications.8 A specification is a quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a drug substance or drug product. Acceptance criteria are numerical limits, ranges, or other criteria for the tests described (§ 314.3(b)). Conformance to a specification means that the material, when tested according to the analytical procedures listed in the specification, will meet the listed acceptance criteria.

对药品的特征、剂量、质量、纯度和药效变更效果进行评估，应该包括原料药中间体、原料药、中控物料和/或被符合已批准质量标准变更影响的制剂。规格是一个（例如，试验、分析步骤、可接受标准）在已批准的申请里提供证实原料药、成品、中间体、原材料、反应物、成分、中控物料、包装，和原料药或制剂生产过程中使用的其它物质的质量标准。可接受标准是个描述测试的数值界限，范围，或其他的标准(§ 314.3(b))。符合质量标准的意思是，当物料根据质量标准中所列出的分析步骤检验，将符合所列出的可接受标准。

2. Additional Testing 附加试验
In addition to confirming that the material affected by manufacturing changes continues to meet its specification, we recommend that the applicant perform additional testing, when appropriate, to assess whether the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product have been or will be affected. The assessment should include, as appropriate, evaluation of any changes in the chemical, physical, microbiological, biological, bioavailability, and/or stability profiles. This additional assessment could involve testing of the postchange drug product itself or, if appropriate, the material directly affected by the change. The type of additional testing that an applicant should perform would depend on the type of manufacturing change, the type of drug substance and/or drug product, and the effect of the change on the quality of the drug product. For example:

除了证实被生产变更影响的物料仍然符合它的质量标准，我们建议申请者实行附加试验，适当的时候评估可能关系到药品安全性和有效性的特征、剂量、质量、纯度或药效是否已经或将被影响 。评估

应该适当包括化学的、物理的、微生物的、生物的、生物利用度和/或稳定性的任何变化。这个附加评估包含变更后药品自身的试验或受变更直接影响的物料。申请者实行该类型的附加试验，取决于该类型的生产变更、该类型药用物质和/或成品，和在高质量药品的变更效果。例如：

Evaluation of changes in the impurity or degradant profile could first involve profiling using appropriate chromatographic techniques and then, depending on the observed changes in the impurity profile, toxicology tests to qualify a new impurity or degradant or to qualify an impurity that is above a previously qualified level.9

对于变更对杂质或降解物档案的评估，首先必须包括使用合适的色谱技术进行分析，然后根据观测到的杂质归档变更状况，对新的杂质或是降解物进行毒理试验确认，或是在确认杂质在一个先前确认的水平之上。

Evaluation of the hardness or friability of a tablet after certain changes.

在一些变更后必须考虑对片剂的硬度或脆度进行评估。

Assessment of the effect of a change on bioequivalence when required under 21 CFR part 320 could include, for example, multipoint and/or multimedia dissolution profiling and/or an in vivo bioequivalence study.

根据 21CFR320 条款的要求，评估变更对于生物等效性的影响。例如，进行多因素和/或多介质溶解性试验，或是体外生物等效性研究。

Evaluation of extractables from new packaging components or moisture permeability of a new container closure system. 对新包装组分通透性或新的容器密封系统的水份渗透性进行评估测试。

An applicant should refer to all relevant CDER guidance documents for recommendations on the information that should be submitted to support a given change. If guidance for information that should be submitted to support a particular change is not available, applicants can consult the appropriate CDER chemistry or microbiology review staff for advice.

申请者应该参考所有相关的 CDER 指导文件，建议为支持给定的变更提交资料。如果在本指南中，为支持一个特定的变更所提交的资料没有效，申请者可以向合适的 CDER 化学或微生物检查人员征询意见。

B. Equivalence 等价

When testing is performed, the applicant should usually assess the extent to which the manufacturing change has affected the identity, strength, quality, purity, and potency of the drug product. Typically this is accomplished by comparing test results from pre- and postchange material and determining if the test results are equivalent. Simply stated: Is the drug product made after the change equivalent to the drug product made before the change?

实行检测后，申请者应该经常评估哪个生产变更范围会影响到药品的特征、剂量、质量、纯度和药效。通常这是通过比较变更前和变更后物料的检验结果来完成的，确定检验结果是否等价。简单说明：药品是在药品变更前后等价的情况下生产的吗？

An exception to this general approach is that when bioequivalence is redocumented for certain ANDA postapproval changes, FDA recommends that the comparator be the reference listed drug. Equivalence

comparisons frequently have a criterion for comparison with calculation of confidence intervals relative to a predetermined equivalence interval.

这方面的例外情况是，如果要对某个已批准的 ADDA 进行变更，要求重新进行生物等效性研究， FDA 建议该参考对照物必须是参考的药物。在相对一个预定的等价区间里，等价比较经常有一个标准作为比较置信区间的计算结果。

For this, as well as for other reasons, equivalent does not necessarily mean identical. Equivalence may also relate to maintenance of a quality characteristic (e.g., stability) rather than a single performance of a test.

对此，和其它原因一样，等价并不是意味着相等。等价还可能关系到质量特征的维持（例如，稳定性）而不是简单的一项测试行为。

C. Adverse Effect 不良作用

Some manufacturing changes have an adverse effect on the identity, strength, quality, purity, or potency of the drug product. In many cases, the applicant chooses not to implement these manufacturing changes, but sometimes the applicant wishes to do so. If an assessment indicates that a change has adversely affected the identity, strength, quality, purity, or potency of the drug product, FDA recommends that the change be submitted in a prior approval supplement regardless of the recommended reporting category for the change. For example, a process change recommended for a changes-being-effected-in-30¬days supplement could cause the formation of a new degradant that requires qualification and/or identification.10 The applicant's degradation qualification procedures may indicate that there are no safety concerns relating to the new degradant. Even so, we recommend that the applicant submit this change in a prior approval supplement with appropriate information to support the continued safety and effectiveness of the drug product. During the review of the prior approval supplement, the FDA will assess the impact of any adverse effect on the drug product as this change may relate to the safety or effectiveness of the drug product.

一些生产变更对药品的特征、剂量、质量、纯度或药效有不良作用。在许多情况下，申请者选择不去实行这些生产变更，但有时申请者希望那样做。如果评估表明变更对药品的特征、剂量、质量、纯度或药效有不良影响，FDA 建议这种变更将提交在批准前变更申请里而不管变更报告范围的建议。例如，一个工序的变更，能引起新降解产物的生成，要求其合格和/或能识别，建议 30 天后进行变更补充申请。申请者的降解合格操作可能表明没有关于新降解产物的安全隐患。即使如此，我们建议申请者在批准前变更申请中提交此变更，以适当的资料支持药品持续的安全性和有效性。

Applicants are encouraged to consult with the appropriate CDER chemistry or microbiology review staff if there are any questions on whether a change in a characteristic would be viewed by CDER as adversely affecting the identity, strength, quality, purity, or potency of the drug product.

不论药品的特征是否改变，CDER 人员将当作影响药品特性、浓度、质量、纯度或药效的不利方面来检查，如果有任何问题，鼓励申请者咨询合适的 CDER 化学或微生物检查人员。

V. COMPONENTS AND COMPOSITION 成分和组成

Changes in the qualitative or quantitative formulation, including inactive ingredients, as provided in the approved application, are considered major changes requiring a prior approval supplement, unless exempted by regulation or guidance (§ 314.70(b)(2)(i)). The deletion or reduction of an ingredient intended to affect only the color of the drug product may be reported in an annual report (§ 314.70(d)(2)(ii)). Guidance on changes in components and composition that may be submitted in a changes-being-effected supplement or annual report is not included in this document because of the complexity of the recommendations, but may

be covered in one or more guidance documents describing post-approval changes (e.g., SUPAC documents).
处方质量或数量改变，包括非活性成分，认为是大变更，要求提交“批准前变更申请”，除非有法规或指南豁免(§ 314.70(b)(2)(i))。只是影响药品颜色的某种成分的取消或减少可以在年度报告中报告(§314.70(d)(2)(ii))。本指南不包括在“有待生效的变更补充文件”或年度报告中提交的变更。

VI. MANUFACTURING SITES11 厂址

A. General Considerations

CDER must be notified when a manufacturer changes to a manufacturing site that is different from those specified in the approved application (314.70(a)). Sites can include those used by an applicant to (1) manufacture or process drug products,12 in-process materials, drug substances, or drug substance intermediates, (2) package drug products, (3) label drug products, and (4) test components, drug product containers, closures, packaging materials, in-process materials, or drug products. Sites include those owned by the applicant or contract sites used by an applicant. Testing sites include those performing physical, chemical, biological, and microbiological testing to monitor, accept, or reject materials, as well as those performing stability testing. Sites used to label drug products are considered those that perform labeling of the drug product's primary or secondary packaging components. Sites performing operations that place identifying information on the dosage form itself (e.g., ink imprint on a filled capsule) are considered to be facilities that manufacture or process the drug product. FDA recommends that the supplement or annual report identify whether the proposed manufacturing site is an alternative to or replacement for the site or sites provided for in the approved application.

当变更生产地址时，如果变更的地点不包括在批准的申请中，必须通知 CDER(314.70(a))。生产地址变更的包括申请人用于制造或处理制剂药品、中控物料、原料药、原料药中间体，包装药品、贴标签，检测成分、药品容器、密封材料、包材、中控物料或药品的场所的地址变更厂址包括申请人所有的或合同场所。检测厂址包括物理、化学、生物学、微生物检测场所，用于物料控制、接收、拒收，以及稳定性检测。贴标签场所指对产品内包装和外包装贴标签的场所。FDA 建议在增补或年度报告中必须说明提交的生产地址是否时原来已批准的地址的替代选择，还是完全替代地址。

FDA recommends that a move to a different manufacturing site, when it is a type of site routinely subject to FDA inspection, be submitted as a prior approval supplement if the site does not have a satisfactory CGMP inspection13 for the type of operation14 being moved (see sections VI.B.1 and 2).

搬迁后的另一个生产厂址如果只需进行常规检查，尚未通过 GMP 检查，FDA 建议提交“批准前的变更申请”。

For labeling, secondary packaging, and testing site changes, the potential for adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product is considered to be independent of the type of drug product dosage form or specific type of operation being performed. Therefore, the recommended reporting category for any one of these manufacturing site changes will be the same for all types of drug products and operations. For manufacturing sites used to (1) manufacture or process drug products, in-process materials, drug substances, or drug substance intermediates or (2) perform primary packaging operations, the potential for adverse effect depends on factors such as the type of drug substance or drug product and operation being performed. Therefore, recommended reporting categories may differ depending on the type of drug product and operations.

对于贴标签、外包装和检测地点的变更，对关系到药品安全性或有效性的特性、剂量、质量、纯度或药效有不良作用的潜在因素，被认为独立于药品剂型或正在执行的具体操作。因此，建议这些生产场所任一变更的报告范围要和所有类型的制剂和操作一样。对于生产场所用于（1）生产药品、中控物

料、原料药、原料药中间体（2）实行内包装的操作，潜在的不良反应，取决于该类型的原料药或药品和正在执行的操作。因此。建议报告类别可以不同于依赖该类制剂和操作。

Except for the situations described in sections VI.B.4, VI.C.1.b, and VI.D.5, construction activities at a manufacturing site or moving production operations within a building or between buildings at the same manufacturing site do not have to be reported to CDER.
除了描述 VI.B.4, VI.C.1.b, and VI.D.5 的情况，在生产场所或活动的生产操作里、在相同生产场所、一个建筑物或两个建筑物之间的建筑活动不需要报告给 CDER 。

We recommend that a move to a manufacturing site that involves other changes (e.g., process, equipment) be evaluated as a multiple related change (see section XII) to determine the appropriate reporting category.
我们建议生产场所的移动牵涉到被看作是复杂的相关其他变更（例如，工序、设备），再决定合适的报告范围。

B. Major Changes (Prior Approval Supplement) 大变更
The following are examples of changes considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.
下面的例子是对药品特征、剂量、质量、纯度或药效有重大的潜在不良影响，可能与药品的安全性和有效性相关的变更。
1 A move to a different manufacturing site, except one used to manufacture or process a drug substance intermediate, when the new manufacturing site has never been inspected by FDA for the type of operation that is being moved or the move results in a restart at the new manufacturing site of a type of operation that has been discontinued for more than two years.
进行该项操作的新厂址从未接受过 FDA 现场检查，或该厂址的该项操作已中止 2 年以上，生产原料药中间体的厂址除外。

2 A move to a different manufacturing site, except one used to manufacture or process a drug substance intermediate, when the new manufacturing site does not have a satisfactory CGMP inspection for the type of operation being moved.
进行该项操作的新厂址 GMP 检查不合格，生产原料药中间体的厂址除外。

3 A move to a different manufacturing site for (1) the manufacture, processing, or primary packaging of drug products when the primary packaging components control the dose delivered to the patient or the formulation modifies the rate or extent of availability of the drug, or (2) the manufacture or processing of in-process materials with modified-release characteristics. Examples of these types of drug products include modified-release solid oral dosage forms,15 transdermal systems, liposomal drug products, depot drug products, oral and nasal metered-dose inhalers (MDIs), dry powder inhalers (DPIs), and nasal spray pumps.
新厂址（1）进行生产、加工、内包装，内包装控制患者的给药剂量或处方改变了药物吸收的速度或程度，（2）生产或加工具有缓释特性的中控物料，包括控释口服固体制剂，透皮吸收制剂，脂质体制剂、缓释制剂、MDIs、DPIs 和鼻喷雾泵。

4 Transfer of the manufacture of an aseptically processed sterile drug substance or aseptically processed sterile drug product to (1) a newly constructed or refurbished aseptic processing facility or area or (2) an existing aseptic processing facility or area that does not manufacture similar (including container types and

sizes) approved drug products. An example would be transferring the manufacture of a lyophilized drug product to an existing aseptic process area where no approved lyophilized drug products are manufactured or where the approved lyophilized drug products being manufactured have different container types and/or sizes than the container of the drug product being transferred. See section VI.C.1.b for recommendations for other manufacturing site changes relating to aseptically processed sterile drug substance or aseptically processed sterile drug product.
无菌原料药或无菌制剂转移到（1）新建的或改造的无菌厂房或厂区（2）现有的无菌加工厂房或厂区，但是未生产过类似的产品（包括包装类型和规格）。例如冻干粉剂转移到现有的未生产冻干粉剂的无菌生产区，或生产的产品的包装类型和规格与批准的产品不相符。其他无菌工艺相关的原料药或制剂的生产厂址变更见 sectionVI.C.1.b

5. Transfer of the manufacture of a finished drug product sterilized by terminal processes to a newly constructed facility at a different manufacturing site. Once this change has been approved, subsequent site changes to the facility for similar drug product types and processes may be submitted as a changes-being-effected-in-30-days supplement (see section VI.C.1.a).
使用终端灭菌工艺生产的制剂产品转移至不同厂址的新建厂房。一旦此变更被批准，后来的相似药品类型和工艺的场所变更可以作为“30 天后进行的变更补充申请”提交。

C. Moderate Changes (Supplement - Changes Being Effected) 中等变更（即将进行的变更的补充申请）
The following are examples of changes considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product. If the new site does not have a satisfactory CGMP inspection for the type of operation being moved (see sections VI.B.1 and 2), then FDA recommends that the changes listed below (excluding changes relating to drug substance intermediate manufacturing sites) be submitted in a prior approval supplement.
下面的例子是对药品特征、剂量、质量、纯度或药效有中等的潜在不良影响，可能与药品的安全性和有效性相关的变更。如果对正在被移动的该类型操作(see sections VI.B.1 and 2)，其新地点没有令人满意的 CGMP 检查，FDA 建议变更清单（包括有关原料药中间体的变更）提交在“批准前变更补充申请”。

1. Supplement - Changes Being Effected in 30 Days 补充文件-30 后变更生效
a. A move to a different manufacturing site for the manufacture or processing of any drug product, in-process material, or drug substance that is not otherwise provided for in this guidance.
本指南未提及的生产或加工制剂、中控物料、原料药的新厂址

b. For aseptically processed sterile drug substance or aseptically processed sterile drug product, a move to an aseptic processing facility or area at the same or different manufacturing site except as provided for in section VI.B.4.
无菌原料药或制剂搬迁至相同或不同厂址的无菌加工厂房或加工区域，section VI.B.4 除外

c. A move to a different manufacturing site for the primary packaging of (1) any drug product that is not otherwise listed as a major change and (2) modified-release solid oral dosage form drug products.
内包装搬迁至不同的厂址（1）不属于大变更的范畴（2）控制口服固体制剂

d. A move to a different manufacturing site for testing if (1) the test procedures approved in the application or procedures that have been implemented via an annual report are used, (2) all postapproval commitments

made by the applicant relating to the test procedures have been fulfilled (e.g., providing methods validation samples), and (3) the new testing facility has the capability to perform the intended testing.
搬迁至不同的检测厂址（1）使用申请中或年度报告中批准的检测规程（2）所有检测规程相关的批准后承诺都已完成（如提供方法验证样品），（3）新的检测场所有足够的检测能力。

2. Supplement - Changes Being Effected 补充文件-变更已生效
A move to a different manufacturing site for the manufacture or processing of the final intermediate.
搬迁至不同的厂址生产或加工最终中间体

D. Minor Changes (Annual Report) 小变更（年度报告）
The following are examples of changes considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product. If the new site does not have a satisfactory CGMP inspection for the type of operation being moved, then FDA recommends that the changes listed below (excluding changes relating to drug substance intermediate manufacturing sites) be submitted in a prior approval supplement (see sections VI.B.1 and 2).
下面的例子是对药品特征、剂量、质量、纯度或药效有最小的潜在不良影响、可能与药品的安全性和有效性相关的变更。如果新厂址针对搬迁的操作没有通过 GMP 检查，FDA 建议以下的情况提交“批准前的补充申请”，不包括原料药中间体的生产厂址。

1 A move to a different manufacturing site for secondary packaging.
不同的外包装厂址
2 A move to a different manufacturing site for labeling.
不同的贴标签厂址
3 A move to a different manufacturing site for the manufacture or processing of drug substance intermediates other than the final intermediate.
不同的原料药中间体生产加工厂址，不包括最终中间体
4 A change in the contract sterilization site for packaging components when the process is not materially different from that provided for in the approved application
包材的合同灭菌场所与申请中批准的不同
5 A transfer of the manufacture of a finished product sterilized by terminal processes to a newly constructed building or existing building at the same manufacturing site.
采用终端灭菌工艺生产的制剂产品转移至新建厂房或同一厂址的现有厂房
6 A move to a different manufacturing site for the ink imprinting of solid oral dosage form drug products.
口服固体制剂喷墨厂址改变

VII. MANUFACTURING PROCESS 生产工艺
A. General Considerations
The potential for adverse effects on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product depends on the type of manufacturing process and the changes being instituted for the drug substance or drug product. In some cases, there may be a substantial potential for adverse effect regardless of direct testing of the drug substance or drug product for conformance with the approved specification. When there is a substantial potential for adverse effects, a change must be submitted in a prior approval supplement (section 506A(c) of the Act).
可能对药品的安全性和有效性有关的特征、剂量、质量、纯度或药效的潜在不良影响，对于原料药或

制剂，取决于该类型生产工艺和正在开始的改变。在某些情况下，可能有重大的潜在不良影响不管原料药或制剂的直接检测和已批准的质量标准一致。当有重大潜在不良影响时，变更必须提交在“批准前变更补充申请” (section 506A(c) of the Act)。

B. Major Changes (Prior Approval Supplement) 大变更

The following are examples of changes considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

下面的例子是对药品特征、剂量、质量、纯度或药效有重大的潜在不良影响，可能与药品的安全性和有效性相关的变更

1 Changes that may affect the controlled (or modified) release, metering or other characteristics (e.g., particle size) of the dose delivered to the patient, including the addition or deletion of a code imprint by embossing, debossing, or engraving on a modified-release solid oral dosage form.

可能改变控释、定量给药或其他给药特性的变更，包括加入或取消刻字

2. Changes that may affect drug product sterility assurance including, where appropriate, process changes for sterile drug substances and sterile packaging components. These include:

可能影响产品无菌保证的变更，包括无菌原料药和无菌包材的工艺变更，包括

Changes in the sterilization method (e.g., gas, dry heat, irradiation). These include changes from sterile filtered or aseptic processing to terminal sterilization, or vice versa.

无菌方法变更（如汽、干热、放射），包括无菌过滤或无菌工艺改为终端灭菌

Addition, deletion, or substitution of sterilization steps or procedures for handling sterile materials in an aseptic processing operation.

无菌步骤或规程的增加、减少或替代

Replacing sterilizers that operate by one set of principles with sterilizers that operate by another principle (e.g., substituting a gravity displacement steam process with a process using superheated water spray).

灭菌原理改变

Addition to an aseptic processing line of new equipment made of different materials (e.g., stainless steel versus glass, changes between plastics) that will come in contact with sterilized bulk solution or sterile drug components, or deletion of equipment from an aseptic processing line.

加入不同材料制造的新设备的无菌工艺线，与无菌溶液或药品成分直接接触，或从无菌生产线上取消设备

Replacing a Class 100 aseptic fill area with a barrier system or isolator for aseptic filling. Once this change has been approved, subsequent process changes for similar product types in the same barrier system or isolator may be submitted as a changes-being-effected-in-30-days supplement.

用隔离系统或无菌灌装代替 100 级无菌灌装区，后续工艺变更可提交“30 天后进行的变更的补充申请”。

Replacement or addition of lyophilization equipment of a different size that uses different operating parameters or lengthens the overall process time.

不同规格、不同冻干参数、或延长工艺总时间的冻干设备的替换或添加

Changes from bioburden-based terminal sterilization to the use of an overkill process, and vice versa.

使用生物灭菌柜的终端灭菌方法改为使用过度杀伤工艺，反之亦然

Changes to aseptic processing methods, including scale, that extend the total processing, including bulk storage time, by more than 50 percent beyond the validated limits in the approved application.

改为无菌工艺方法，包括工艺能力放大，包括贮存时间超过申报资料的验证限度 50％以上

Changes in sterilizer load configurations that are outside the range of previously validated loads.

灭菌器负荷超过预先验证的限度

Changes in materials or pore size rating of filters used in aseptic processing.

无菌工艺中物料或过滤器的孔径规格改变

3. The following changes for a natural product

下述产品变更

Changes in the virus or adventitious agent removal or inactivation methods.

病毒或外源性物质或去活方法的改变

This applies to any material where such procedures are necessary, including drug substance, drug product, reagents, and excipients.

适用于任何物料，包括原料药、制剂、试剂、辅料

For drug substance and drug product, changes in the source material (e.g., microorganism, plant) or cell line.

对于原料药和制剂，来源（如微生物、培养）或细胞链改变

For drug substance and drug product, establishment of a new master cell bank or seed.

对于原料药和制剂，建立新的细胞库或种子

4. Any fundamental change in the manufacturing process or technology from that currently used by the applicant. For example:

现行生产工艺或技术的基本变更，例如：

a. Drug product 制剂

Dry to wet granulation or vice versa. 干法改为湿法或反之

Change from one type of drying process to another (e.g., oven tray, fluid bed, microwave).

由一种干燥工艺改为另一种（如烘箱、流化床、微波炉）

b. Drug substance 原料药

Filtration to centrifugation or vice versa. 过滤改为离心或反之

Change in the route of synthesis of a drug substance 原料药合成途径改变

5. The following changes for drug substance 原料药下述变更

Any process change made after the final intermediate processing step in drug substance manufacture.

原料药生产过程中，最终中间体以后的工艺步骤的任何变更

Changes in the synthesis or manufacture of the drug substance that may affect its impurity profile and/or the physical, chemical, or biological properties.

可能影响原料药杂质和/或物理、化学或生物学特性的合成或生产的变更

6. Addition of an ink code imprint or change to or in the ink used for an existing imprint code for a solid oral dosage form drug product when the ink as changed is not currently used on CDER-approved drug products.17

加入或改变喷墨，如果当前使用的喷墨已不用于 CDER 批准的产品

7. Establishing a new procedure for reprocessing a batch of drug substance or drug product that fails to meet the approved specification.

制定不合格原料药或制剂的新的再加工规程

C. Moderate Changes (Supplement - Changes Being Effected) 中等变更

The following are examples of changes considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

下面的例子是对药品特征、剂量、质量、纯度或药效有中等的潜在不良影响，可能与药品的安全性和有效性相关的变更

1. Supplement - Changes Being Effected in 30 Days 30 天后进行的变更补充申请

a. For drug products, any change in the process, process parameters, and/or equipment except as otherwise provided for in this guidance.

本指南未提及的制剂产品的所有工艺、工艺参数和/或设备变更

b. For drug substances, any change in process and/or process parameters except as otherwise provided for in this guidance.

本指南未提及的原料药的工艺和/或工艺参数变更

c. For natural protein drug substances and natural protein drug products:

蛋白质原料药和制剂

Any change in the process, process parameters, and/or equipment except as otherwise provided for in this guidance (e.g., section VII.B.5, VII.D.7).

本指南未提及的任何工艺、工艺参数和/或设备变更

An increase or decrease in production scale during finishing steps that involves different equipment.

涉及不同设备的生产结束步骤的增加或减少

Replacement of equipment with equipment of different design that does not affect the process methodology or process operating parameters.

不同设计的设备变更，不影响工艺方法和工艺参数

d. For sterile drug products, drug substances, and components, as appropriate:

对于无菌制剂、原料药、成分

Changes in dry heat depyrogenation processes for glass container systems for drug substances and drug products that are produced by terminal sterilization processes or aseptic processing.

终端灭菌或无菌工艺生产的原料药或制剂的玻璃容器的干热除热原工艺的变更

Changes to filtration parameters for aseptic processing (including flow rate, pressure, time, or volume, but not filter materials or pore size rating) when additional validation studies for the new parameters should be performed.

无菌工艺（包括流速、压力、时间、体积、不包括过滤器材料或孔径）过滤参数的变更，新参数需进行额外验证

Filtration process changes that provide for a change from single to dual sterilizing filters in series, or for repeated filtration of a bulk.

过滤工艺变更，从单一过滤器变为双重过滤器或重复过滤

Changes from one qualified sterilization chamber to another for in-process or terminal sterilization that result in changes to validated operating parameters (time, temperature, F0, and others).

一个验证过的灭菌柜改为另一个中控或终端灭菌，导致验证参数改变（时间、温度、F0、其他）

Changes in scale of manufacturing for terminally sterilized drug products that increase the bulk solution storage time by more than 50 percent beyond the validated limits in the approved application when bioburden limits are unchanged.

终端灭菌产品的生产规模改变，导致原液贮存时间增加 50％以上，在生物负荷限度不变的情况下超

过申报资料中的验证限度

e. For drug substances, redefinition of an intermediate, excluding the final intermediate, as a starting material.
对于原料药、中间体再定义、不包括最终中间体，作为起始物料

2. Supplement - Changes Being Effected 已进行的变更补充申请

a. A change in methods or controls that provides increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess.
方法或控制变更，提高原料药或制剂成分、剂量、质量、纯度、药效的保证

b. For sterile drug products, elimination of in-process filtration performed as part of the manufacture of a terminally sterilized drug product.
无菌制剂，取消终端灭菌生产的中控过滤步骤

D. Minor Changes (Annual Report) 小变更（年报）

The following are examples of changes considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.
下面的例子是对药品特征、剂量、质量、纯度或药效有最小的潜在不良影响，可能与药品的安全性和有效性相关的变更。

1 For drug products, changes to equipment of the same design and operating principle and/or changes in scale except as otherwise provided for in this guidance (e.g., section VII.C.1.c, VII.D.7).
本指南未涉及的制剂产品设备设计和操作原理和/或规模变更

2 A minor change in an existing code imprint for a dosage form. For example, changing from a numeric to alphanumeric code.
制剂刻字喷墨的变更，如由数字改为文字数字

3 Addition of an ink code imprint or a change in the ink used in an existing code imprint for a solid oral dosage form drug product when the ink is currently used on CDER-approved drug products.
加入喷墨或改变喷墨

4 Addition or deletion of a code imprint by embossing, debossing, or engraving on a solid dosage form drug product other than a modified-release dosage form.
非控制制剂的口服固体制剂加入或取消刻字代码

5 A change in the order of addition of ingredients for solution dosage forms or solutions used in unit operations (e.g., granulation solutions).
单剂量使用的液体制剂或溶液剂成分加入次序改变

1 Changes in scale of manufacturing for terminally sterilized drug products that increase the bulk solution storage time by no more than 50 percent beyond the validated limits in the approved application when bioburden limits are unchanged.
终端灭菌的制剂产品生产规模改变，延长原液贮存时间 50％以上，在生物负荷限度不变的情况下超过申报资料中的验证限度

7. For natural protein drug products and natural protein drug substances:
对于蛋白质制品和天然蛋白质原料药

An increase or decrease in production scale during finishing steps that does not involve an equipment change.
生产末期增加或降低生产规模，没有设备变更

Replacement of equipment with equipment of the same design, operating principle, and capacity with no change in production scale.
设备变更，变更前后的设备的设计、操作原理、产能、生产规模相同

VIII. SPECIFICATIONS 质量标准

A. General Considerations

All changes in specifications from those in the approved application must be submitted in a prior approval supplement unless otherwise exempted by regulation or guidance (§ 314.70(b)(2)(i)). Specifications (i.e., tests, analytical procedures, and acceptance criteria) are the quality standards provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a drug substance or drug product. For the purpose of defining specifications, acceptance criteria are numerical limits, ranges, or other criteria for the tests described. Examples of a test, an analytical procedure, and an acceptance criterion are, respectively, an assay, a specific, fully described high pressure liquid chromatography (HPLC) procedure, and a range of 98.0–102.0 percent. The recommendations in this section also apply to specifications associated with sterility assurance that are included in NDA and ANDA submissions.18

从那些已批准申请的质量标准里的所有变更必须提交在“批准前变更补充申请”，除非另有被规章或指导原则豁免的(§ 314.70(b)(2)(i))。规程（例如，检测、分析步骤、可接受标准）是在已批准的申请里提供证实原料药、制剂、中间体、原材料、反应物、成分、中控物料、包装，和原料药或制剂生产过程中使用的其它物质的质量标准。质量标准和可接受标准的目的是明确数值界限，范围，或为检验所描述的其他标准。实例检验，一个分析规程和一个可接受标准为各自检测、完全特定的高效液相步骤、范围 98.0%-102.0%。本条中的建议也适用于和无菌保证有联系的质量标准，包括在 NDA 和 ANDA。

A regulatory analytical procedure is the procedure in the approved application that is designated for use in evaluating a defined characteristic of the drug substance or drug product. Section 501(b) of the Act recognizes the analytical procedures in the U.S. Pharmacopeia/National Formulary (USP/NF) as the regulatory analytical procedures for compendial items. Tests and associated acceptance criteria and regulatory analytical procedures in addition to those specified in the USP/NF may be required for approving compendial items (section 505 of the Act).

获批准的法定分析规程是能被指定用于评估原料药或制剂的确定性质的规程。美国药典/国家处方集的法定分析规程是根据法案的第 501(b)确定的分析规程。对正在批准的简明条款除了那些在 USP/NF 中详细说明的，还有检测和有联系的可接受标准，法定分析规程，可能都被要求在其中。(section 505 of the Act)

The applicant may include in its application alternatives to the approved regulatory analytical procedures for testing the drug substance and drug product. However, for purposes of determining compliance with the Act, regulatory analytical procedures are used.

申请人可以在其申请书中包括其可实施的用于检验原料药和制剂的不同于法定分析规程的替代方法。不过，为了和法案相一致，使用法定分析规程来判断决定。

In sections B through D below, the use of the term analytical procedure without a qualifier such as regulatory or alternative refers to an analytical procedure used to test materials other than the drug substance or drug product.

在 B 部分到以下 D，没有限定分析规程的使用范围，例如法定或可替代的指的是被用于检测物料而不是原料药或制剂的分析规程。

B. Major Changes (Prior Approval Supplement) 大变更

The following are examples of changes in specifications considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

下面的例子是对药品特征、剂量、质量、纯度或药效重大的潜在不良影响，可能与药品的安全性和有效性相关的变更。

1 Relaxing an acceptance criterion except as otherwise provided for in this guidance (e.g., section VIII.C.1.b, VIII.C.1.e).

本指南未提及的可接受限度变宽

2 Deleting any part of a specification except as otherwise provided for in this guidance (e.g., section VIII.D.2).

本指南未提及的质量标准项目的删除

3 Establishing a new regulatory analytical procedure including designation of an alternative analytical procedure as a regulatory procedure.

制定新的法定分析规程，包括替代规程

4 A change in a regulatory analytical procedure that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the regulatory analytical procedure described in the approved application.

对申报资料中的法定分析规程的变更，但是不能等效或更好地保证被测物的特征、剂量、质量、纯度或药效

5 A change in an analytical procedure used for testing components, packaging components, the final intermediate, in-process materials after the final intermediate, or starting materials introduced after the final intermediate that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application except as otherwise noted. For example, a change from an HPLC procedure that distinguishes impurities to (1) an HPLC procedure that does not, (2) another type of analytical procedure (e.g., titrimetric) that does not, or (3) an HPLC procedure that distinguishes impurities but the limit of detection and/or limit of quantitation is higher.

检测成分、包材、最终中间体、最终中间体后的中控物料、或最终中间体之后引入的起始物料的分析规程的变更，但是不能等效或更好地保证被测物的特征、剂量、质量、纯度或药效。例如将可以分辨杂质的 HPLC 方法改为不能分辨杂质的 HPLC 方法或另一种分析方法（如滴定），或可以分辨杂质但是检测限和/或定量限更高的 HPLC 方法。

6 Relating to testing of raw materials for viruses or adventitious agents:19

原料病毒或外源物相关的检测

(1) relaxing an acceptance criterion, (2) deleting a test, or (3) a change in the analytical procedure that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.

放宽可接受标准，取消某项检测，对申报资料种的分析规程变更且不能提供等效或更好的质量保证

C. Moderate Changes (Supplement - Changes Being Effected) 中等变更

The following are examples of changes in specifications considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

下面的例子是对药品特征、剂量、质量、纯度或药效有中等的潜在不良影响，可能与药品的安全性和

有效性相关的变更。

1. Supplement - Changes Being Effected in 30 Days 增补-变更 30 天后生效

a. Any change in a regulatory analytical procedure other than those identified as major changes or editorial changes.

大变更以外的其他法定分析规程的变更

b. Relaxing an acceptance criterion or deleting a test for raw materials used in drug substance manufacturing, in-process materials prior to the final intermediate, starting materials introduced prior to the final drug substance intermediate, or drug substance intermediates (excluding final intermediate) except as provided for in section VIII.B.6.

放宽质量标准或取消某项检测，用于检验原料药的原料、中控物料、起始物料、中间体等

c. A change in an analytical procedure used for testing raw materials used in drug substance manufacturing, in-process materials prior to the intermediate, starting materials introduced prior to the final drug substance intermediate, or drug substance intermediates (excluding final intermediate) that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application except as provided for in section VIII.B.6.

分析规程变更，用于检测原料药生产中的原料、中间体前的中控物料、最终原料药中间体前引入的起始物料、原料药中间体（不包括最终中间体），没有提供和原先批准的分析规程等效或更好的保证，来确保被测物的特征、含量、质量、纯度、药效，第 VII.B.6.的部分除外

d. Relaxing an in-process acceptance criterion associated with microbiological monitoring of the production environment, materials, and components that are included in NDA and ANDA submissions. For example, increasing the microbiological alert or action limits for critical processing environments in an aseptic fill facility or increasing the acceptance limit for bioburden in bulk solution intended for filtration and aseptic filling.

放宽 NDA 或 ANDA 申报中声明的生产环境、物料、成分微生物监控的中控可接受标准。例如，增加无菌装量厂房关键工艺环境的微生物警戒或行动限度，或增加即将过滤或无菌装量的原液的生物负荷的可接受限度

e. Relaxing an acceptance criterion or deleting a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements (§ 314.70(c)(2)(iii)).

放宽可接受标准或减少某项检测，以满足药典要求、FDA 法规要求

2. Supplement - Changes Being Effected

a. An addition to a specification that provides increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess. For example, adding a new test and associated analytical procedure and acceptance criterion.

质量标准中加入项目以加强质量保证，例如，新的检测项目及其相关的分析规程、可接受标准

b. A change in an analytical procedure used for testing components, packaging components, the final intermediate, in-process materials after the final intermediate, or starting materials introduced after the final intermediate that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.

分析规程变更，用于检测成分、包材、中间体、中控物料、起始物料

D. Minor Changes (Annual Report) 小变更

The following are examples of changes in specifications considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may

relate to the safety or effectiveness of the drug product.
下面的例子是对药品特征、剂量、质量、纯度或药效有最小的潜在不良影响，可能与药品的安全性和有效性相关的变更。
1 Any change in a specification made to comply with an official compendium, except the changes described in section VIII.C.1.e, that is consistent with FDA statutory and regulatory requirements (§ 314.70(d)(2)(i)).
质量标准的变更，以符合药典要求，section VIII.C.1.e 提到的除外
2 For drug substance and drug product, the addition or revision of an alternative analytical procedure that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application or deletion of an alternative analytical procedure.
对于原料药和制剂，替代分析规程的增加或修订，以提供相同或更好的质量控制
3 Tightening of acceptance criteria 质量标准变严
4 A change in an analytical procedure used for testing raw materials used in drug substance synthesis, starting materials introduced prior to the final drug substance intermediate, in-process materials prior to the final intermediate, or drug substance intermediates (excluding final intermediate) that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.

用于检测原料药使用的原材料、最终原料药前引入的起始物料、最终中间体前引入的中控物料、中间体、原料药中间体（包括最后中间体）的分析规程的变更，能更好地保证被测物的特征、剂量、质量、纯度或药效，作为分析规程被描述在已批准的申请里。

IX. CONTAINER CLOSURE SYSTEM 4 包装
A. General Considerations
The potential for adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product when making a change to or in the container closure system is generally dependent on the route of administration of the drug product, performance of the container closure system, and the likelihood of interaction between the packaging component and the dosage form. In some cases there may be a substantial potential for adverse effect, regardless of direct drug product testing for conformance with the approved specification.
包装密封系统的变更可能给关系到药品的安全性和有效性的因素，药品的特征、剂量、质量、纯度或药效带来潜在不良影响，给药途径、包装的功效、包装成分和剂型间可能的相互作用将决定这种不良反应的大小。即使药品直接检测结果符合已批准的质量标准，在某些情况下包装系统的变更可能有重大的潜在不良影响。

A change to or in a packaging component will often result in a new or revised specification for the packaging component. This situation does not have to be considered a multiple related change. Only the reporting category for the packaging change needs to be considered.

在包装组分的变更经常将导致新的或者重新修改的质量标准。这种情况没有考虑复杂的相关变更。只需要考虑包装变更的报告类别。

B. Major Changes (Prior Approval Supplement) 大变更
The following are examples of changes considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety

or effectiveness of the drug product.
下面的例子是对药品特性、剂量、质量、纯度或药效有重大的潜在不良影响，可能与药品的安全性和有效性相关的变更。
1 For liquid (e.g., solution, suspension, elixir) and semisolid (e.g., creams, ointments) dosage forms, a change to or in polymeric materials (e.g., plastic, rubber) of primary packaging components, when the composition of the component as changed has never been used in a CDER-approved drug product of the same dosage form and same route of administration. For example, a polymeric material that has been used in a CDER-approved topical ointment would not be considered CDER-approved for an ophthalmic ointment.
对于液体剂型，内包装聚合物材料的变更（如塑料、橡胶），该成分从未在 CDER 批准的相同剂型和给药途径的产品上使用过。例如，CDER 批准的外用软膏使用的聚合物材料不能认为同样可以用于眼用软膏。

2 For liquid (e.g., solution, suspension, elixir) and semisolid (e.g., creams, ointments) dosage forms in permeable or semipermeable container closure systems, a change from an ink and/or adhesive used on the permeable or semipermeable packaging component to an ink or adhesive that has never been used in a CDER-approved drug product of the same dosage form and same route of administration and with the same type of permeable or semipermeable packaging component (e.g., low density polyethylene, polyvinyl chloride).
对于使用渗透性或半渗透性容器的液体和半固体制剂，墨水和/或粘合剂的变更为从未经 CDER 批准的同一剂型给药途径包装系统的药品使用过另一种墨水或粘合剂。

3 A change in the primary packaging components for any drug product when the primary packaging components control20 the dose delivered to the patient (e.g., the valve or actuator of a metered-dose inhaler).
制剂内包装材料改变，该内包装可控制给药剂量
4 For sterile drug products, any change that may affect drug product sterility assurance, such as:21
无菌制剂，任何可能影响产品无菌保证的变更，例如：
A change from a glass ampule to a glass vial with an elastomeric closure.
从玻璃安瓿改为带胶塞的玻璃小瓶
A change to a flexible container system (bag) from another container system.
从一种包装改为另一种灵活性包装
A change to a prefilled syringe dosage form from another container system.
从一种包装改为另一种预填充的注射器剂型
A change from a single unit dose container to a multiple dose container system.
从单剂量容器改为多剂量容器
Changes that add or delete silicone treatments to container closure systems (such as elastomeric closures or syringe barrels).
包装系统加入或取消硅化
Changes in the size and/or shape of a container for a sterile drug product.
无菌制剂容器的规格和/或形状改变

1 Deletion of a secondary packaging component intended to provide additional protection to the drug product (e.g., carton to protect from light, overwrap to limit transmission of moisture or gases) or a change in the composition of, or the addition of, a secondary packaging component that may affect the impurity profile of the drug product.
取消起到额外保护作用的外包装材料，或改变成分，或加入可能影响杂质情况的外包装

2 A change to a new container closure system if the new container closure system does not provide the same or better protective properties than the approved container closure system.
改为新的包装系统，如果新的包装系统与批准的系统比较不能提供相同或更好的保护作用

C. Moderate Changes (Supplement - Changes Being Effected) 中等变更
The following are examples of changes considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.
下面的例子是对药品特征、剂量、质量、纯度或药效有中等的潜在不良影响，可能与药品的安全性和有效性相关的变更。
1. Supplement - Changes Being Effected in 30 Days 增补-变更 30 天后生效
a. A change to or in a container closure system, except as otherwise provided for in this guidance, that does not affect the quality of the drug product.
本指南未提及的不影响产品质量的包装系统变更
b. Changes in the size or shape of a container for a sterile drug substance.
无菌原料药包装规格或形状的变更
c. A change in the number of units (e.g., tablets, capsules) or labeled amount (e.g., grams, milliliters) of a nonsterile drug product in a unit-of-use container.22
单剂量包装的非无菌制剂的数量或标示量改变

2. Supplement - Changes Being Effected
a. A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms (see section IX.D.2), without a change from one container closure system to another (§ 314.70(c)(6)(ii)).
非无菌制剂包装规格和/或形状变更，固体制剂除外，包装系统不改变
b. A change in the labeled amount (e.g., grams, milliliters) of drug product for a nonsterile drug product in a multiple-unit container,23 except for solid dosage forms (see section IX.D.3) .
多剂量包装的非无菌制剂的标示量改变，固体制剂除外
c. A change in or addition or deletion of a desiccant.
加入或除去干燥剂

D. Minor Changes (Annual Report) 小变更
The following are examples of changes considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.
下面的例子是对药品特征、剂量、质量、纯度或药效有最小的潜在不良影响，可能与药品的安全性和有效性相关的变更。
1 A change in the container closure system for a nonsterile drug product, based on a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium (§ 314.70(d)(2)(v)).
非无菌制剂包装系统的变更，可以依据申报中批准或官方出版的方案出具等效性证明，
2 A change in the size and/or shape of a container for a nonsterile solid dosage form (§ 314.70(d)(2)(iv)).
非无菌制剂包装规格和/或形状的变更
3 A change in the number of units (e.g., tablets, capsules) or labeled amount (e.g., grams) of nonsterile solid dosage form in a multiple-unit container.

多剂量包装的非无菌制剂的包装数目或标示量的改变

4 The following changes in the container closure system of solid oral dosage form drug products as long as the new package provides the same or better protective properties (e.g., light, moisture) and any new primary packaging component materials have been used in and been in contact with CDER-approved solid oral dosage form drug products:24

口服固体制剂的下述变更只要能提供相同或更好的保护作用，并且新的内包装材料已被 CDER 批准的药品使用过：

Adding or changing a child-resistant closure, changing from a metal to plastic screw cap, or changing from a plastic to metal screw cap.

加入或改变儿童锁，将金属盖改为塑料盖，或塑料盖改为金属盖

Changing from one plastic container to another of the same type of plastic (e.g., high density polyethylene (HDPE) container to another HDPE container).

从一种塑料包装改为另一种塑料包装，如从一种 HDPE 改为另一种 HDPE

Changes in packaging materials used to control odor (e.g., charcoal packets).

改变包装以控制气味

Changes in bottle filler (e.g., change in weight of cotton or amount used) without changes in the type of filler (e.g., cotton to rayon).

改变填充剂（如改变棉团重量或数量），但是不改变填充剂性质（如棉团改为人造纤维）

Increasing the wall thickness of the container.

增加容器壁的厚度

A change in or addition of a cap liner.

改变或加入瓶盖垫片

A change in or addition of a seal (e.g., heat induction seal).

改变或加入封口膜

A change in an antioxidant, colorant, stabilizer, or mold releasing agent for production of the container and/or closure to one that is used at similar levels in the packaging of CDER-approved solid oral dosage form drug products.

改变包材生产过程中使用的抗氧化剂、着色剂、稳定剂、模释放剂，使用另外一种与 CDER 批准的固体制剂类似水平的物质

A change to a new container closure system when the container closure system is already approved in the NDA or ANDA for other strengths of the drug product.

使用新的包装系统，该系统已批准用于该制剂产品其他的剂量

5. The following changes in the container closure system of nonsterile liquid drug products as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved liquid drug products with the same route of administration (i.e., the material in contact with a liquid topical should already have been used with other CDER-approved liquid topical drug products):

非无菌液体制剂的下述变更只要能提供相同或更好的保护作用，并且新的内包装材料已被 CDER 批准的药品使用过：

Adding or changing a child-resistant closure, changing from a metal to plastic screw cap, or changing from a plastic to metal screw cap.

加入或改变儿童锁，将金属盖改为塑料盖，或塑料盖改为金属盖

Increasing the wall thickness of the container.

增加容器壁的厚度
A change in or addition of a cap liner.
改变或加入瓶盖垫片
A change in or addition of a seal (e.g., heat induction seal).
改变或加入封口膜

1 A change in the container closure system of unit dose packaging (e.g., blister packs) for nonsterile solid dosage form drug products as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved drug products of the same type (e.g., solid oral dosage form, rectal suppository).
单剂量包装的非无菌固体制剂的下述变更只要能提供相同或更好的保护作用，并且新的内包装材料已被 CDER 批准的药品使用过：

2 The following changes in the container closure system of nonsterile semisolid drug products as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved semisolid drug products:
非无菌液体制剂的下述变更只要能提供相同或更好的保护作用，并且新的内包装材料已被 CDER 批准的药品使用过：

Changes in the closure or cap. 封口或盖的改变
Increasing the wall thickness of the container. 增加容器壁的厚度
A change in or addition of a cap liner. 改变或加入瓶盖垫片
A change in or addition of a seal. 改变或加入封口膜
A change in the crimp sealant. 改变密封剂

8. A change in the flip seal cap color as long as the cap color is consistent with any established color coding system for that class of drug products.
改变弹跳盖的颜色，该颜色符合该类产品已制定的颜色编号系统

X. LABELING 标签
A. General Considerations 基本情况
A drug product labeling change includes changes in the package insert, package labeling, or container label. In accordance with § 314.70(a)(4), an applicant must promptly revise all promotional labeling and drug advertising to make it consistent with any labeling change implemented in accordance with paragraphs (b) or (c) of § 314.70. All labeling changes for ANDA drug products must be consistent with section 505(j) of the Act.
药品的标签变更包括说明书、包装标签、容器标签的改变。按照§ 314.70(a)(4)，申请者必须迅速重新修正所有增加的标签和药品广告来保持核变更标签的一致性，按照§ 314.70 的(b) or (c)段执行。对于新药的所有标签变更必须符合法案第 505(j)。

B. Major Changes (Prior Approval Supplement) 大变更
Any proposed change in the labeling, except changes designated as moderate or minor by regulation or guidance, must be submitted as a prior approval supplement (§ 314.70(b)(2)(v)(A)). If applicable, any change to a Medication Guide required under 21 CFR part 208, except for changes in the information specified in § 208.20(b)(8)(iii) and (b)(8)(iv), must be submitted in a prior approval supplement (§

314.70(b)(v)(B)). The following list contains some examples of changes currently considered by CDER to fall into this reporting category.
任何打算在标签上的变更，除了由规章或指南制定的中等或较小的变更，必须作为批准前的变更补充提交(§ 314.70(b)(2)(v)(A))。依据 21 CFR part 208，任何用药指南要求的变更，除了在§ 208.20(b)(8)(iii)和 (b)(8)(iv)指定资料的变更，必须提交在批准前变更补充申请里(§ 314.70(b)(v)(B))。以下项目包含当前被 CDER 考虑为变更的一些例子，属于这个报告范围。

1 Changes based on postmarketing study results, including, but not limited to, labeling changes associated with new indications and usage.
依据上市后研究结果进行的变更，包括但不仅限于，新适应症和用法
2 Change in, or addition of, pharmacoeconomic claims based on clinical studies.
根据临床研究改变或加入药品声明
3 Changes to the clinical pharmacology or the clinical study section reflecting new or modified data.
改变临床药理学或临床研究部分，反映出新的或修订过的数据
4 Changes based on data from preclinical studies. 根据临床前研究数据进行的变更
1 Revision (expansion or contraction) of population based on data. 人数修订
2 Claims of superiority to another drug product. 相对另外一种药品优越性的声明
3 Change in the labeled storage conditions, unless exempted by regulation or guidance.
改变标签的贮存条件，除非有法规豁免

C. Moderate Changes (Supplement - Changes Being Effected) 中等变更
Under § 314.70(c)(6)(iii), a changes-being-effected supplement must be submitted for any labeling change that (1) adds or strengthens a contraindication, warning, precaution, or adverse reaction, (2) adds or strengthens a statement about drug abuse, dependence, psychological effect, or overdosage, (3) adds or strengthens an instruction about dosage and administration that is intended to increase the safe use of the drug product, (4) deletes false, misleading, or unsupported indications for use or claims for effectiveness, or (5) normally requires a supplement submission and approval prior to distribution of the drug product that FDA specifically requests be submitted under this provision. A changes-being-effected supplement that provides for a labeling change under §§ 314.70(c)(6)(iii) must include 12 copies of final printed labeling (§ 314.70(c)(1)). The following list includes some examples of changes currently considered by CDER to fall into this reporting category.

依据§ 314.70(c)(6)(iii)，对以下任一标签的变更，必须提交已生效的变更补充申请（1）增加或加强了禁忌症，警告和防范措施，或不良反应（2）增加或增强了关于药物滥用，依赖性，心理作用，或过量用药的申明（3）有意增加药物安全性相关的药品剂量和用法的指令（4）删除虚假，误导，或无支持的适应症或对功效的申明（5）正常要求补充提交和批准前药品的分发，依据这个提交 FDA 具体的要求。依据§§ 314.70(c)，已完成的变更补充申请提供了标签的变更（6）必须提交 12 份最终打印的标签(§ 314.70(c)(1))。以下项目包含当前被 CDER 考虑为变更的一些例子，属于这个报告范围。

Addition of an adverse event due to information reported to the applicant or Agency. /依据报告至申请者或代理机构的信息添加一个副反应事件。
Addition of a precaution arising out of a postmarketing study/添加一个产生于上市后研究中的用药警戒。
Clarification of the administration statement to ensure proper administration of the drug product./用药指南澄清声明，以确保药物产品的正确用药。

D. Minor Changes (Annual Report) 小变更（年度报告）

Labeling with editorial or similar minor changes or with a change in the information concerning the description of the drug product or information about how the drug is supplied that does not involve a change in the dosage strength or dosage form should be described in an annual report (§ 314.70(d)(2)(ix) and (d)((2)(x)) . The following list includes some examples currently considered by CDER to fall into this reporting category.
编辑的或相似的较小变更，关于药品描述变更的信息或不包括在剂量强度或剂型的变更，应该叙述在年报里(§ 314.70(d)(2)(ix) and (d)((2)(x))。以下项目包含当前被 CDER 考虑为变更的一些例子，属于这个报告范围。

1 Changes in the layout of the package or container label that are consistent with FDA regulations (e.g., 21 CFR part 201) without a change in the content of the labeling. /包装或容器标签版式改变，符合 FDA 法规要求，并且不改变标签内容。
2 Editorial changes, such as adding a distributor's name. /编辑信息改变，例如添加一个经销商名称。
3 Foreign language versions of the labeling if no change is made to the content of the approved labeling and a certified translation is included. /标签添加外语版本，内容对比已经批准的标签无任何改变，并且翻译内容经过确证。
4 Labeling changes made to comply with an official compendium. /改变标签使其符合官方文件。

XI. MISCELLANEOUS CHANGES /其它变更
A. Major Changes (Prior Approval Supplement) 大变更（批准前的增补）
The following are examples of changes considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.
下面的例子是对药品特征、剂量、质量、纯度或药效有重大的潜在不良影响，可能与药品的安全性和有效性相关的变更。
1 Changes requiring completion of studies in accordance with 21 CFR part 320 to demonstrate equivalence of the drug product to the drug product as manufactured without the change or to the reference listed drug (§ 314.70(b)(2)(ii)). /依据 21 CFR 320 部分，需要完成变更后产品与变更前产品或标准对照药品之间的生物等效性研究来证明其等效的变更。
2 Addition of a stability protocol or comparability protocol. /添加稳定性研究方案或可比性方案。
3 Changes to an approved stability protocol or comparability protocol unless otherwise provided for in this guidance (e.g., VIII.C, VIII.D, XI.C.2). /对已核准的稳定性研究方案或可比性方案进行变更，在本指南中有特殊规定的除外（例如：III.C, VIII.D, XI.C.2）
4 An extension of an expiration dating period based on (1) data obtained under a new or revised stability testing protocol that has not been approved in the application or (2) full shelf life data on pilot scale batches using an approved protocol. /有效期延长，基于（1）数据来自于一个新的或修订后的未经申请批准的稳定性方案，或（2）关键批次规模的使用已批准方案进行的完整的贮存期限数据。
5 Changes to a drug product under an application that is subject to a validity assessment because of significant questions regarding the integrity of the data supporting that application (§ 314.70(b)(2)(viii)). /药物产品变更，该产品基于一个由于显著的支持数据完整性问题存在而被要求进行有效性评估的申请。(§ 314.70(b)(2)(viii))

B. Moderate Changes (Supplement - Changes Being Effected) 中等变更（增补-变更已生效）

The following are examples of changes considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

下面的例子是对药品特征、剂量、质量、纯度或药效有中等的潜在不良影响，可能与药品的安全性和有效性相关的变更。

1. Supplement - Changes Being Effected in 30 Days / 增补-变更 30 天后生效

Reduction of an expiration dating period to provide increased assurance of the identity, strength, quality, purity, or potency of the drug product. Extension of an expiration date that has previously been reduced under this provision should be submitted in a changes-being-effected-in-30-days supplement even if the extension is based on data obtained under a protocol approved in the application. /为了加强保证提高药物产品的特性、剂量、质量、纯度、或药效，缩短失效期。由于以上原因而缩短的有效期，对其进行延长应递交“30 天后生效的变更补充申请”，同样适用于数据来源为经批准的申请中的方案。

2. Supplement - Changes Being Effected/增补-变更已生效

No changes have been identified. 此类未定义任何变更。

C. Minor Changes (Annual Report) 轻微变更（年度报告）

The following are examples of changes considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

下面的例子是对药品特性、剂量、质量、纯度或药效有最小的潜在不良影响，可能与药品的安全性和有效性相关的变更。

1. An extension of an expiration dating period based on full shelf life data on production batches obtained under a protocol approved in the application (§ 314.70(d)(2)(vi)). /有效期延长，数据基于生产批次规模的使用已批准方案进行的完整的贮存期限数据

1 Addition of time points to the stability protocol or deletion of time points beyond the approved expiration dating period. /在已批准的有效期外添加或删除稳定性方案中的时间点。

2 A change from previously approved stability storage conditions to storage conditions recommended in International Conference on Harmonisation (ICH) guidances. /贮存条件由已经批准的稳定性贮存条件改变至 ICH 指南推荐的条件。

4. Non-USP reference standards: /在没有 USP 对照品：

Replacement of an in-house reference standard or reference panel (or panel member) according to procedures in an approved application. /依据经批准的申请中的方法，替代内部对照品或标准对照组

Tightening of acceptance criteria for existing reference standards to provide greater assurance of drug product purity and potency. /减小已有标准对照品的可接受范围，以提高药物产品纯度和效力的可信性。

XII. MULTIPLE RELATED CHANGES 复杂变更

Multiple related changes involve various combinations of individual changes. For example, a site change may also involve equipment and manufacturing process changes or a components and composition change may necessitate a change in a specification. For multiple related changes where the recommended reporting categories for the individual changes differ, CDER recommends that the submission be in accordance with the most restrictive of the categories recommended for the individual changes. When the multiple related changes all have the same recommended reporting category, CDER recommends that the submission be in accordance with the reporting category for the individual changes.

复杂相关的变更包括不同的单个变更的组合。例如，地点的变更还可能包括设备和生产工艺的改变，或成分和组成的改变，可能有必要变更质量标准。对于复杂相关的变更，为个别变更的不同建议报告范围，CDER 推荐按照对单个变更限制最严的申报类别来申报。当复杂相关变更都有相同的申报类别，CDER 推荐按照各自变更的申报类别进行申报。

ATTACHMENT A: MANUFACTURING SITES 附录 A：生产地点

All owners or operators of all drug establishments (not exempt by regulation) that engage in the manufacture, preparation, propagation, compounding, or processing of a drug or drugs are required to register with the FDA (21 CFR 207.20). An establishment means a place of business under one management at one general physical location (§ 207.3(a)(7)). A general physical location is reasonably construed to include separate buildings within the same city if the activities in the buildings are closely related to the same business enterprise, are under the supervision of the same local management, and are all inspected at the same time (ORA Field Management Directive No. 132).

从事生产、制备、繁殖、配料或药物加工的所有药物工厂的拥有者或经营者（不能被法规免除），或药物需登记在 FDA(21 CFR 207.20)。公司意味着在一个普通物理位置管理下的营业地点(§ 207.3(a)(7))。一般的物理位置合理解释为包括在同一城市里单独的建筑物，如果建筑物里的活动与相同的企业有密切的关系，则由当地相同的管理部门监督，在同一时间接受检查 。

For the purposes of determining the reporting category for moves between buildings, the terms same manufacturing site and different manufacturing site mean: 对建筑物间的移动，为确定报告范围，相同生产地点和不同生产地点的意思是：

Domestic Establishments 国内企业

Same manufacturing site: 相同的生产地点

• The new and old buildings are included under the same drug establishment registration number25 相同注册地址的新旧建筑物。

and

• The same FDA district office is responsible for inspecting the operations in both the new and old buildings.

相同地区的 FDA 办公室负责新旧建筑物的审查。

Different manufacturing site: 不同生产地点

• The new and old buildings have different drug establishment registration numbers 新旧建筑物有不同的注册地址。

or

• Different FDA district offices are responsible for inspecting operations in the new and old buildings. 不同地区的 FDA 办公室负责新旧建筑物的审查

For domestic establishments, the terms same manufacturing site and different manufacturing site supersede the terms contiguous campus, same campus, and different campus as used in the SUPAC guidances.

Foreign Establishments 国外企业

25 The registration number is the number assigned to the establishment as part of the registration process (e.g., ORA Field Management Directive No. 92).

Foreign establishments are not currently required to register with the FDA. On May 14, 1999, FDA published a proposed rule to require registration of foreign establishments (64 FR 26330). Until registration of foreign establishments is required, same and different manufacturing sites mean:

当前外国企业不要求登记在 FDA。1999 年 5 月 14 日，FDA 出版了拟议的条例来要求外国企业的登记(64 FR 26330).直到外国企业要求登记，相同和不同生产地点的意思为：

Same manufacturing site: 相同生产地点

A contiguous or unbroken site or a set of buildings in adjacent city blocks. 邻近或连续的地点，或相邻城市街区的一套建筑物 □

Different manufacturing site: 不同生产地点

• The new and old buildings are not on a contiguous site or not in adjacent city blocks.不是在邻近地点或相邻城市街区的建筑物

ATTACHMENT B: TYPE OF OPERATION AND CGMP INSPECTIONS

附件 2：运营类别和 CGMP 检查

Section VI states that a change to a different manufacturing site should be submitted in a prior approval supplement when (1) the new manufacturing site has never been inspected by FDA for the type of operation being moved, (2) the move results in a restart at the new manufacturing site of a type of operation that has been discontinued for more than two years, or (3) the new manufacturing site does not have a satisfactory current good manufacturing practice (CGMP) inspection for the type of operation being moved.

第 VI 部分说到不同生产场所的改变应该提交在批准前补充申请中，当（1）对于已在被移动的操作，新的生产场所从来没有被 FDA 检查（2）移动导致在新的生产场所重新开始中断 2 年以上的此类操作（3）对于此类正在被移动的操作，新生产场所的没有满意的 CGMP 检查结果。

A profile class system is used by FDA to assist in (1) managing the CGMP inspection process, (2) evaluating the findings and the compliance follow-up needed, and (3) communicating the results of inspections. A profile class can relate to the manufacture of a particular dosage form (e.g., large volume parenterals, oral liquids), type of drug substance (e.g., sterile bulk by chemical synthesis), or specific function performed at a site (e.g., control testing laboratory). There are profile class codes for major categories of drug substance processes, dosage forms, and manufacturing functions (see table below). However, the system is not comprehensive for all operations performed in the pharmaceutical industry (see not elsewhere classified (NEC) profile class code).

FDA 用？？/协助（1）管理 CGMP 检查过程（2）评估检查所见结果和随访所需的顺从性（3）交流检查结果。A profile class 关系到特殊剂型（例如，大容量注射用药物，口服液体制剂）、此类原料药（例如，化学合成的无菌包装药）或在一个场所用特殊功能完成的（例如，实验室控制）生产。对于原料药的加工、剂型和生产功能（看下表）的主要分类，有档案分类代码。然而，该系统不包含所有在制药工业完成的操作。

The term type of operation refers to the specialized or even unique conditions and practices that are employed to manufacture a class or category of drug substance or drug product or to perform a limited segment of the manufacturing process. These conditions and practices exist and are performed within the framework of CGMPs, along with general conditions and practices that contribute to the manufacture of all drug products at a given manufacturing site. The conditions and practices, both general and specific, are inspected to evaluate the CGMP acceptability of a manufacturing site. A wide variety of classes or categories of drug substances and drug products may be produced at a manufacturing site, or the manufacturing site may only produce a single class of drug substance and/or drug product or perform a limited segment of a manufacturing process. Each type of operation is represented by a profile class code.

Generally, a satisfactory CGMP status for a profile class code is used to communicate a satisfactory CGMP clearance for all of the products and for all of the operations included within the category that code represents. Thus the profile class code for a particular dosage form or type of drug substance is used to communicate the CGMP status for all aspects of manufacturing, processing, packing, or holding that are performed at the specific manufacturing site relating to that particular dosage form or type of drug substance, including packaging and labeling operations, testing, and quality control. The profile class code for a particular dosage form or type of drug substance is also used to communicate the CGMP status for manufacturing sites that produce in-process material (e.g., controlled-release beads), package drug products, or label drug products, even if these are stand-alone (e.g., contractor) operations.

A few profile class codes that describe certain types of operations (see items in boldface in table) are provided to report the CGMP status for contractor firms whose only function in the manufacturing process is to perform this operation. If one of these operations (e.g., steam sterilization process) is performed at the manufacturing site involved in producing the drug product/drug substance, the CGMP status for that operation is reported as part of the profile class code for the particular dosage form or type of drug substance. For example, a manufacturing site

* Insofar as this guidance adjusts reporting categories pursuant to section 506A of the Federal Food, Drug, and Cosmetic Act

and 21 CFR 314.70, it does have binding effect. 31

producing a terminally sterilized small volume parenteral drug product would be reported with the profile class code for the dosage form (SVT), not by the profile code for the sterilization process (SSP).

Certain inspections may be required by program priorities even if the rating for a profile class code indicates an acceptable CGMP status. The current profile codes/classes for human drugs are:

ADM Aerosol dispensed medication
气溶胶配药服药

NEC Not elsewhere classified (when using this class, specific drug products are noted) 未分类的（当用这个分类记录特异性药物）

CBI Biotechnology crude drug 生物技术原料药 OIN Ointment, nonsterile (includes cream, jelly, paste) 有菌软膏（包括膏状物、胶状物、糊状物）

CEX Plant/animal extraction crude drug 植物/动物 提取的原料药 POW Powders (includes oral and topical) 粉末（包括口服和局部）

CFS Sterile bulk by fermentation crude drug RAD Radiopharmaceutical 放射性药品

CFN Nonsterile bulk by fermentation crude drug RSP Radiation sterilization process 辐射灭菌工序

CHG Capsule, prompt release 瞬间释放胶囊 SNI Sterile noninjectable 非注射用的灭菌

CRU Crude bulk drugs-nonsynthesized SOP Soap

CSG Capsules, soft gelatin 软胶囊 SSP Steam sterilization process 蒸气灭菌法工序

CSN Nonsterile bulk by chemical synthesis SUP Suppositories 栓剂

CSP Chemical sterilization process 化学灭菌法工序 SVL Small volume parenterals (lyophilized) 小容量注射剂（冻干粉末的）

CSS Sterile bulk by chemical synthesis SVS Sterile-filled small volume parenterals 小容量注射剂的无菌填充

CTL Control testing laboratories 实验室控制 SVT Terminally sterilized small volume parenteral 小容量注射剂末端灭菌

CTR Capsules, modified-release 缓释胶囊 TCM Tablets, prompt-release 迅速释放片

GAS Medical gas (includes liquid oxygen and other) 医用气体（包括液态氧和其他） TCT Tablets,

delayed-release 缓释片
GSP Gas sterilization process 气体灭菌法工序 TDP Transdermal patches 透皮贴剂
HSP Dry heat sterilization process 干热灭菌法工序 TSP Fractional (tyndallization) sterilization process 间歇灭菌法
LIQ Liquid (includes solutions, suspension, elixirs, and tinctures)液体（包括溶液、混悬液、酏剂、酊剂） TTR Tablets, extended-release 延长释放片
LVP Large volume parenterals 大容量注射剂 WSP Water sterilization process 水灭菌工序

CGMP inspectional status, based on the profile class, is available through FDA's Freedom of Information (FOI) Office. (See Glossary under Satisfactory Current Good Manufacturing Practice (CGMP) Inspection for more information regarding FOI requests.)
Examples of postapproval manufacturing site changes and recommended reporting categories: 举例批准后生产场所的变更和推荐的报告类别
An applicant wants to move the manufacture of an immediate-release tablet (TCM) to a different manufacturing site that currently manufactures, and has satisfactory CGMP status for, capsules (CHG) and powders for oral solution (POW). This manufacturing site change should be submitted in a prior approval supplement because the new manufacturing site does not have a satisfactory CGMP inspection for immediate-release tablets.
申请者想要把 TCM 的生产转移到不同于当前的生产地点，对于 CHG 和 POW 都能满足 CGMP 的要求。这个生产地点的变更应该提交在批准前补充申请里，因为对于 TCM，新的生产地点没有令人满意的 CGMP 检查。

An applicant wants to contract out packaging operations for immediate-release tablets (TCM) and capsules (CHG) and modified-release capsules (CTR). The potential contract packager has a satisfactory CGMP status for immediate-release and modified-release capsules but has never packaged immediate-release tablets. The packaging site change for the immediate-release tablet drug products should be submitted in a prior approval supplement. The packaging site change for the capsule drug products should be submitted as recommended in section VI of this guidance for packaging sites with a satisfactory CGMP inspection.

申请者想要承办 TCM、CHG、CTR 的包装操作。对于有 CHG 和 CTR 没有 TCM，可能的合法包装者，要有令人满意的 CGMP 状况。对 TCM 药品包装场所的改变应该提交在批准前补充文件里。对胶囊制剂包装地点的改变应该提交。

An applicant wishes to consolidate product testing to a single analytical laboratory at a manufacturing site. This manufacturing site produces various solid oral dosage form drug products, has an operational analytical laboratory currently at the site, and satisfactory CGMP inspections for the manufacturing occurring at the facility. Some of the drug products that will be tested at the analytical laboratory when the consolidation occurs are not solid oral dosage form products. Unlike most other production operations, testing laboratories (and other operations in boldface in the table) are not inspected on a dosage form /type of drug substance specific basis. The satisfactory CGMP inspection of the analytical laboratory, which was performed as part of the CGMP inspection for manufacture of the solid oral dosage form drug products, is considered to apply to all dosage forms, including those not actually produced at the site. The consolidation can be submitted in a

changes-being-effected-in-30-days supplement if the change is consistent with the recommendations in section VI.C.1.d.

在生产地点的单一分析实验室，申请者希望加强产品的检测。该生产地点生产不同的固体口服制剂药品，在当前生产地点要有一个能运作的分析实验室，对生产中出现的设备要有令人满意的 CGMP 检查。在分析实验室将要检测的一些药品，当？？？？。和许多其他生产操作不同，试验室（和在表格中黑体字的操作）没有检测原料药剂型的特定主药。对于固体口服制剂药品的生产，分析检验室令人满意的 CGMP 检查就是完成了 CGMP 检查的一部份， 考虑应用到所有剂型，包括那些实际上没在生产地点生产的。如果变更和 VI.C.1.d. 部分建议的一致，The consolidation 提交在“30 天后生效的变更补充文件”。

ATTACHMENT C: CDER-APPROVED DRUG PRODUCTS 附件 C：CDER 已批准的药品

In several places throughout the guidance, different reporting categories are proposed for changes to or the addition of certain components based on whether the component/material has been used in and has been in contact with CDER-approved drug products. Different reporting categories are recommended once CDER has reviewed certain components/materials in association with a drug product approval because similar subsequent changes then have a reduced potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product. For example, certain changes in the container closure systems of solid oral dosage form drug products may be included in an annual report as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved solid oral dosage form drug products (see section IX.D.4). If the new primary packaging component material has not been used in or has not been in contact with CDER-approved solid oral dosage form drug products, then submission of the change in an annual report is not recommended.

在一些地方，通过本指南，对变更，或附加确定组分，其是基于组分/物料是否用于和 CDER 已批准药品接触，提出了不同的报告类别。一旦 CDER 审查某个和已批准药品有联系的组分/物料，建议使用不同的报告类别，因为相同结果的变更能减少药品的特征、含量、质量、纯度、药效的潜在不良影响，以上这些因素可能关系到药品的安全性和有效性。例如，在固体口服制剂的容器密封系统，某个变更可能包括在年度报告中，只要新的包装提供了形同或更好的保护特性和任何新的内包装组分/物料被用于和 CDER 已批准的固体口服制剂接触。如果新的内包装组分/物料没有被用于 CDER 已批准的固体口服制剂的接触，不建议在年度报告中提交变更。

CDER-approved drug products are considered those drug products subject to an approved NDA or ANDA. Some information on which components/materials are used in CDER-approved products is available from the Agency (e.g., FDA, CDER, Inactive Ingredient Guide, 1996, Division of Drug Information Resources). When information is not available, an applicant should use reliable sources of information to determine that the component or material has been used in and has been in contact with a CDER-approved drug product of the same dosage form and route of administration, as appropriate. The applicant should identify in the supplement or annual report the basis for the conclusion that the component or material is used in a CDER-approved drug product.

CDER 批准的药品是那些已批准 NDA 或 ANDA 的药品。从此机构获得用于 CDER 已批准药品的组分

/物料的一些资料是有效的（例如，FDA、CDER、非活性成分指南）当资料无效，申请者应该利用可靠的资料来源决定，用于直接接触 CDER 已批准的相同剂型和给药途径的药品的组分或物料。申请者应该辨别在增补文件或年报里对用于 CDER 已批准药品的组分或物料的结论。

If an applicant cannot confirm that a component or material has been used in and has been in contact with a CDER-approved drug product of the same dosage form and route of administration, the applicant has the option of submitting the change for a single NDA or ANDA using the higher recommended reporting category and, after approval, submitting similar changes for other NDAs and ANDAs using the lower recommended reporting category. 如果申请者不能确定用于接触 CDER 已批准的相同剂型和给药方式的药品的组分或物料，申请者对提交的变更有选择，对于单一的 NDA or ANDA 用较高的报告类别；批准后，提交相同的变更，对其他 NDAs and ANDAs 使用较低的报告类别

GLOSSARY 词汇表

Acceptance Criteria: Numerical limits, ranges, or other criteria for the tests described (21 CFR 314.3(b)).

可接受标准：所述测试的数字限制、范围或其他标准。

Active Ingredient/Drug Substance: Any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of a disease, or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient. The term includes those components that may undergo chemical change in the manufacture of the drug product and are present in the drug product in a modified form intended to furnish the specified activity or effect (21 CFR 210.3(b)(7) and 314.3(b)).

活性药物成分（APIs）（或药物）：任何要用于药物（医疗）产品及用于药物生产的物质或混合物，即药物产品的活性成分。这样的物质是用于修饰药物活性或在诊断、治疗、缓解症状或防止疾病或影响机体结构和功能中起直接作用的。但不包括被用于此成分合成中的中间体。本术语包括那些能承受药品生产中的化学变化和为了保证其指定的活性或作用以一种经调整的形式存在于药品中的组分。

Assess the Effects of the Change: To evaluate the effects of a manufacturing change on the identity, strength, quality, purity, and potency of a drug product as these factors may relate to the safety or effectiveness of the drug product (21 CFR 314.3(b)).

评估变更效果：评估生产中的变更对药品特征、含量、质量、纯度和药效的影响，这些因素有可能关系到药品的安全性和有效性。

Container Closure System: The sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components if the latter are intended to provide additional protection to the drug product.

容器密封系统：

Component: Any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product (21 CFR 210.3(b)(3)).

组分：指用于药品生产的所有成份，包括那些未在药品中出现的成份。

Drug Product: A finished dosage form, for example, tablet, capsule, or solution, that contains an active ingredient generally, but not necessarily, in association with inactive ingredients (21 CFR 210.3(b)(4)).

药品：指成品制剂(如：片剂、胶囊剂、口服液等)，通常含有一种活性成份并伴有非活性成份(但不是必需的)。本术语也包括不含有活性成份但作为安慰剂使用的成品制剂。

Final Intermediate: The last compound synthesized before the reaction that produces the drug substance. The final step forming the drug substance involves covalent bond formation or breakage; ionic bond formation (i.e., making the salt of a compound) does not qualify. Consequently, when the drug substance is a salt, the precursors to the organic acid or base, rather than the acid or base itself, should be considered the final intermediate.
最终中间体：生产原料药反应前合成的最后化合物。形成原料药的最后一步包括共价键的形成或断裂；离子键的形成（例如，制成一种化合物的盐）不在此列。为此，当原料药是盐时，有机酸或碱的前体，而不是有机酸或碱本身，应被当作最终中间体。
Inactive Ingredient: Any intended component of the drug product other than an active ingredient.
非活性成分：指不同于“活性成份”的其他组分
In-process Material: Any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the drug product (21 CFR 210.3(b)(9)). For drug substance, in-process materials are considered those materials that are undergoing change (e.g., molecular, physical).
中间产品：是指所有经制备、复合、混合或由化学反应得到的用于药品生产或制备的物料。对于原料药，中间产品指那些不停经受改变的物质（例如，分子的，物理的）

Intermediate: A material that is produced during steps of the synthesis of a drug substance and undergoes further molecular change before it becomes a drug substance.
中间体： 在原料药合成步骤中产生的，在成为原料药之前还会经历进一步的分子变化的一种物质。

* Insofar as this guidance adjusts reporting categories pursuant to section 506A of the Federal Food, Drug, and Cosmetic Act
and 21 CFR 314.70, it does have binding effect. 35
本指南的报告类别的范围根据美国食品药品管理法和化妆品法第 506A、21 CFR 314.70 来制定的

Package: The container closure system and labeling, associated components (e.g., dosing cups, droppers, spoons), and external packaging (e.g., cartons, shrink wrap).
包装：包装密封系统和标签，有关组分（例如，定量杯、滴管、匙）和外部的包装（例如，纸箱、收缩包装）.
Packaging Component: Any single part of a container closure system.
包装组分：包装密封系统的任一部分。
Primary Packaging Component: A packaging component that is or may be in direct contact with the dosage form.
内包装组分：可能或和剂型直接接触的包装组分。
Reference Listed Drug: The listed drug identified by FDA as the drug product on which an applicant relies in seeking approval of its abbreviated application (21 CFR 314.3(b)).
对照药：
Satisfactory Current Good Manufacturing Practice (CGMP) Inspection: A satisfactory CGMP inspection is an FDA inspection during which (1) no objectionable conditions or practices were found (No Action Indicated (NAI)) or (2) objectionable conditions were found, but voluntary corrective action is left to the firm and the objectionable conditions will not be the subject of further administrative or regulatory actions (Voluntary Action Indicated (VAI)).
满意的 CGMP 检查：指在 FDA 在 CGMP 检查中没有发现不好的操作或恶劣的生产环境；或者发现了恶劣的生产环境，但是该环境由公司进行整改。

Information about the CGMP status of a firm may be obtained by requesting a copy of the Quality Assurance Profile (QAP) from the FDA's Freedom of Information (FOI) Office. The QAP contains information on the CGMP compliance status of firms that manufacture, package, assemble, repack, relabel, or test human drugs, devices, biologics, and veterinary drugs. All FOI requests must be in writing (21 CFR 20.40(a)) and should be prepared following the instructions found in the reference entitled A Handbook for Requesting Information and Records from FDA. An electronic version of this reference is available on the Internet at http://www.fda.gov/opacom/backgrounders/foiahand.html.

Secondary Packaging Component: A packaging component that is not and will not be in direct contact with the dosage form.

外包装组分：没有和剂型直接接触的包装组分。

Specification: The quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a drug substance or drug product (21 CFR 314.3(b)).

规格：在已批准的申请里的质量标准（例如，检测、分析规程、可接受标准），能确定原料药、制剂、中间体、原材料、反应物、组分、中控物料、包装，和原料药或制剂生产中用到的其他物料的质量。