Testing of Glycerin, Propylene Glycol, Maltitol Solution, Hydrogenated Starch Hydrolysate, Sorbitol Solution, and other High-Risk Drug Components for Diethylene Glycol and Ethylene Glycol

Guidance for Industry

行业指南

甘油、丙二醇、麦芽糖醇溶液、氢化淀粉水解产物、山梨醇溶液和其他的高风险药物成分中二甘醇和乙二醇的测试

This guidance is for immediate implementation.

本指南发布即刻实施

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(2). Comments may be submitted at any time for Agency consideration. Submit electronic comments to https:// Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.www.regulations.gov.

For questions regarding this document, contact (CDER) Office of Compliance, 301-796-3400.

U.S. Department of Health and Human Services

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Center for Drug Evaluation and Research (CDER)

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Immediately in Effect Guidance for Industry[1]

立即生效

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I. INTRODUCTION 简介

This guidance is intended to alert pharmaceutical manufacturers, compounders, repackers, and suppliers to the potential public health hazard of glycerin and other high-risk drug components contaminated with diethylene glycol (DEG) or ethylene glycol (EG)[2] [3], FDA has received and continues to receive (most recently in early 2023) reports about fatal poisonings of consumers who ingested drug products in a liquid dosage form (such as cough, allergy, analgesic, and antiemetic drug products) that were manufactured with DEG- or EG-contaminated components[4].

本指南旨在提醒制药商、药房、重新包装商和供应商注意被二甘醇（DEG）或乙二醇

1 This guidance has been prepared by the Office of Compliance in the Center for Drug Evaluation and Research (CDER), Food and Drug Administration. 本指南由FDA药物评估与研究中心（CDER）合规办公室编制。

[2] For purposes of this guidance, "high-risk drug components" are components that, through historical experience, have been found to be at higher risk of DEG or EG contamination compared to other drug components. For brevity, the title of this guidance does not list all high-risk drug components. 在本指南中，“高风险药物成分”是指根据历史经验发现，与其他药物成分相比，DEG或EG污染风险更高的成分。为简洁起见，本指南的标题并未列出所有高风险药物成分。

[3] Many, but not all, high-risk drug components have a United States Pharmacopeia or National Formulary (USP-NF) monograph that includes testing for DEG and EG. USP-NF refers to the combination of two compendia, the United States Pharmacopeia (USP) and the National Formulary (NF). The USP-NF monographs establish identity testing for drugs listed therein, in addition to other tests and methods for determining the strength, quality, and purity of those products. The USP-NF monographs for the high-risk drug components listed by name in the title of this guidance include DEG and EG limit testing as part of the specific identification tests. There are additional high-risk drug components whose corresponding USP-NF monographs include testing for DEG and EG in either the identification test or the impurities tests, such as sorbitol sorbitan solution, noncrystallizing sorbitol solution, polyethylene glycol, and diethylene glycol stearates. FDA expects manufacturers to ensure they are referencing the current USP-NF when determining which testing is required to be performed. 许多但不是全部高风险药物成分都有美国药典或国家处方集（USP-NF）各论，其中包括DEG和EG的测试。USP-NF是指两种药典，美国药典（USP）和国家处方集（NF）的组合。USP-NF专著除了确定这些产品的强度，质量和纯度的其他测试和方法外，还为其中列出的药物建立了身份测试。本指南标题中按名称列出的高风险药物成分的USP-NF专论包括DEG和EG极限测试，作为特定鉴定测试的一部分。还有其他高风险药物成分，其相应的USP-NF专论包括在鉴定测试或杂质测试中测试DEG和EG，例如山梨醇-山梨醇酐溶液，非结晶山梨醇溶液，聚乙二醇和二甘醇硬脂酸酯。FDA希望生产商在确定需要进行哪些测试时，确保他们参考现行USP-NF。

[4] See, e.g., WHO urges action to protect children from contaminated medicines, World Health Organization, Jan 23, 2023, available at https://www.who.int/news/item/23-01-2023-who-urges-action-to-protect-children-from-contaminated-medicines. 例如，见世界卫生组织敦促采取行动保护儿童免受受污染药物的侵害，世界卫生组织，2023年1月23日

（EG）污染的甘油和其他高风险药物成分对公众健康的潜在危害。FDA已经收到并将继续收到（最近一次是在2023年初）关于消费者摄入由DEG或EG污染成分生产的液体剂型（如咳嗽，过敏，止痛药和止吐药）药品的致命中毒报告。

This guidance provides information on compliance with applicable regulatory requirements and recommendations to help pharmaceutical manufacturers, repackers, other suppliers of high-risk drug components, and compounders prevent the use of glycerin and other high-risk drug components that are contaminated with DEG or EG. These requirements and recommendations, along with other appropriate measures under current good manufacturing practice (CGMP), are vital to prevent further consumer poisonings.

本指南提供了有关遵守适用监管要求和建议的信息，以帮助制药商、重新包装商、其他高风险药物成分供应商和成分防止使用甘油和其他受DEG或EG污染的高风险药物成分。这些要求和建议，以及CGMP下的其他适当措施，对于防止进一步的消费者中毒至关重要。

In general, FDA's guidance documents 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.

一般来说，FDA的指导文件没有规定法律上可执行的责任。相反，指南描述了FDA目前对某一主题的想法，除非引用了具体的监管或法定要求，否则只能将其视为建议。在机构指南中使用should一词意味着有建议或推荐，但不是必需的。

II. BACKGROUND 背景

In 1937, an outbreak of DEG poisoning occurred in the United States, which resulted from people ingesting elixir of sulfanilamide that contained DEG as a solvent. A total of 107 people died, many of them children. This event led to the enactment of the Federal Food, Drug, and Cosmetic Act (FD&C Act or Act), which included a provision requiring that drugs be demonstrated to be safe before marketing. In late 1995 and early 1996, many children were admitted to hospitals in Port-au-Prince, Haiti, with sudden kidney failure, resulting in at least 80 fatalities. An investigation by Haitian health officials, the Centers for Disease Control (CDC), and FDA discovered that the cause was DEG-contaminated glycerin in acetaminophen syrup manufactured in Haiti. Between 1990 and 1998, similar incidents of DEG poisoning occurred in Argentina, Bangladesh, India, and Nigeria, and resulted in the deaths of hundreds of children[5]. In October 2006, an outbreak of DEG poisoning occurred in Panama, resulting in multiple cases of illness and death.

1937年，美国爆发了二甘醇中毒，这是由于人们摄入含有二甘醇作为溶剂的磺胺长生不老药所致。共有107人死亡，其中许多是儿童。这一事件导致了《联邦食品、药品和化妆品法案》（FD＆C法案或法案）的颁布，其中包括一项规定，要求在上市前证明药物是安全的。1995年末和1996年初，海地太子港的许多儿童因突然肾衰竭入院，导致至少80人死亡。海地卫生官员、疾病控制中心（CDC）和FDA的一项调查发现，原因是海地生产的对乙酰氨基酚糖浆中被二甘醇污染的甘油。1990年至1998年间，阿根廷、孟加拉国、印度和尼日利亚发生了类似的二甘醇中毒事件，导致数百名儿童死亡。2006年10月，巴拿马爆发了二甘醇中毒事件，导致多起疾病和死亡病例。

These cases reveal the following similarities:

这些案例揭示了以下相似之处：

[5] World Health Organization (WHO), Report of the Diethylene Glycol Contamination Prevention Workshop, 1997, p. xi.
世界卫生组织（WHO），《二甘醇污染预防研讨会报告》，1997年，p. xi

- The manufacturers of the liquid drug products that contained contaminated glycerin did not perform full identity testing on the glycerin raw material, including tests to quantify the amount of DEG present and to verify the purity of the glycerin received.
- 含有受污染甘油的液体药品的生产商没有对甘油原料进行完整的鉴别测试，包括DEG定量检测并验证所接收甘油纯度。
- The manufacturers of the liquid drug products containing contaminated glycerin relied on the certificate of analysis (COA) provided by the supplier of the glycerin.
- 含有受污染甘油的液体药品的生产商依赖甘油供应商提供的分析证书（COA）。
- The origin of the glycerin was not readily apparent from the COA. The COA obtained by the manufacturers of the liquid drug products was often a copy of a COA on the letterhead of the distributor from whom they had purchased the glycerin and not the COA provided by the original manufacturer of the glycerin. The chain of custody or distribution history of the glycerin was also not readily known, often because the glycerin might have been sold multiple times between its manufacture and its use in manufacturing the finished drug product.
- 从COA来看，甘油的来源并不明确。液体药品生产商获得的COA通常是他们购买甘油的分销商信台头的COA副本，而不是甘油原始生产商提供的COA。甘油的存储链或分销历史也不清楚，通常是因为甘油可能在生产之后到其用于制剂生产前已有多次转手

In 2022 and 2023, numerous countries reported incidents of oral liquid drug products, primarily indicated for children, with confirmed or suspected contamination with high levels of DEG and EG[6]. The cases of contamination, spanning at least seven different countries, were associated with more than 300 fatalities—mostly in children under the age of 5[7]. In October 2022, and as part of the investigation into these cases, the Indonesian health authorities identified the presence of DEG and EG in a propylene glycol excipient used in manufacturing oral liquid drug products[8]. At the time of

[6] See WHO urges action to protect children from contaminated medicines, World Health Organization, Jan 23, 2023, available at The WHO has issued global medical alerts addressing incidents in The Gambia (Oct 5, 2022), Indonesia (Nov 6, 2022), Uzbekistan (Jan 11, 2023), and the Marshall Islands and Micronesia (Apr 25, 2023). See Medical Product Alert N 6/2022: Substandard (contaminated) paediatric medicines, World Health Organization, Oct 5, 2022, available at Medical Product Alert N 7/2022: Substandard (contaminated) paediatric liquid dosage medicines, World Health Organization, Nov 2, 2022, available at Medical Product Alert N 1/2023: Substandard (contaminated) liquid dosage medicines, World Health Organization, Jan 11, 2023, available at ; and Medical Product Alert N 4/2023: Substandard (contaminated) syrup medicines, World Health Organization, Apr 25, 2023, available at https://www.who.int/news/item/23-01-2023-who-urges-action-to-protect-children-from-contaminated-medicines.https://www.who.int/news/item/05-10-2022-medical-product-alert-n-6-2022-substandard-(contaminated)-paediatric-medicines;https://www.who.int/news/item/02-11-2022-medical-product-alert-n-7-2022-substandard-(contaminated)-paediatric-liquid-dosage-medicines;https://www.who.int/news/item/11-01-2023-medical-product-alert-n-1-2023-substandard-(contaminated)-liquid-dosage-medicineshttps://www.who.int/news/item/25-04-2023-medical-product-alert-n-4-2023--substandard-(contaminated)-syrup-medicines. 见世卫组织敦促采取行动保护儿童免受受污染药物的侵害，世界卫生组织，2023年1月23日，可在世卫组织发布全球医疗警报，以应对冈比亚（2022年10月5日）、印度尼西亚（2022年11月6日）、乌兹别克斯坦（2023年1月11日）以及马绍尔群岛和密克罗尼西亚（2023年4月25日）的事件。参见第6/2022号医疗产品警报：不合格（受污染）儿科药物，世界卫生组织，2022年10月5日，可在第7/2022号医疗产品警报：不合格（受污染）儿科液体剂量药物，世界卫生组织，2022年11月2日，可在第1/2023号医疗产品警报：不合格（受污染）液体剂量药物，世界卫生组织，2023年1月11日，可在；2023年4月25日，世界卫生组织，2023年4月25日，第4/2023号医疗产品警报：不合格（受污染）糖浆药

[7] See WHO urges action to protect children from contaminated medicines, World Health Organization, Jan 23, 2023, available at https://www.who.int/news/item/23-01-2023-who-urges-action-to-protect-children-from-contaminated-medicines. 见世卫组织敦促采取行动保护儿童免受受污染药物的侵害，世界卫生组织，2023年1月23日

[8] See Indonesia revokes firms' fever syrup licences amid inquiry into 150 deaths, Reuters, Oct 31, 2022, available at https://www.reuters.com/world/asia-pacific/indonesia-revokes-firms-fever-syrup-licences-amid-probe-into-150-deaths-

issuance of this guidance, FDA had no indication that any contaminated products connected to the recent international incidents have entered the U.S. drug supply chain.

2022年和2023年，许多国家报告了口服液体药品事件，主要针对儿童，已确认或疑似高浓度DEG和EG污染。跨越至少七个不同国家的污染病例与300多人死亡有关，主要是5岁以下儿童。2022年10月，作为对这些病例调查的一部分，印度尼西亚卫生当局确定了用于生产口服液体药品的丙二醇辅料中存在DEG和EG。在发布本指南时，FDA没有迹象表明与最近的国际事件有关的任何受污染产品已进入美国药品供应链。

The 2022 outbreak resembles previous ones, as manufacturers of oral liquid drug products relied upon COAs provided by suppliers where the chain of custody or distribution history of the high-risk drug component was also not readily known or apparent from the COA. For example, in one instance, the appearance of the label and COA of propylene glycol, used as a component of a drug product, suggested the component container's content might differ from what the container label and COA stated. As a result of these practices, DEG- and EG-contaminated components, such as propylene glycol, entered the pharmaceutical raw material supply chain.

2022年的疫情类似于之前的疫情，因为口服液体药品生产商依赖供应商提供的COA，而高风险药物成分的监管链或分销历史也不容易从COA中得知或显见。例如，在一个例子中，用作药品成分的丙二醇标签和COA的外观表明，成分容器的含量可能与容器标签和COA所述不同。由于这些做法，二甘醇和乙二醇污染的成分，如丙二醇，进入了制药原料供应链。

III. REGULATORY REQUIREMENTS 法规要求

The FD&C Act and its implementing regulations contain many drug manufacturing requirements. This guidance highlights certain key provisions that are critical to ensuring the detection of DEG- and EG-contaminated drug components and avoiding additional poisoning incidents. However, this guidance is not intended to be an all-inclusive list of drug manufacturing requirements. Drug manufacturers are responsible for ensuring their drug products are manufactured in compliance with all applicable FDA laws and regulations.

FD&C法案及其实施条例包含许多药物生产要求。本指南强调了某些关键规定，这些规定对于确保检测DEG和EG污染的药物成分并避免更多的中毒事件至关重要。然而，本指南并不打算成为一份包罗万象的药物生产要求清单。药品生产商有责任确保其药品的生产符合所有适用的FDA法律法规。

Manufacturers (including outsourcing facilities) of drugs, as defined in section 201(g) of the FD&C Act, must ensure that the drugs they manufacture comply with drug CGMP under section 501(a)(2)(B) of the FD&C Act[9]. For purposes of section 501(a)(2)(B) of the FD&C Act, CGMP includes "oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the

2022-10-31/.见路透社2022年10月31日，在对150人死亡的调查中，印尼吊销了公司的发烧糖浆许可证

[9] Under section 201(g) of the FD&C Act, the term "drug" means "(A) articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C)." Thus, a high-risk component that is intended as an excipient or other component of a drug product is a drug as defined by section 201(g) of the FD&C Act. 根据FD&C法案第201（g）节，"药物"一词是指（A）美国官方药典、美国官方顺势疗法药典或官方国家处方集或其任何补充中认可的物品；（B）用于诊断、治疗、缓解、治疗或预防人类或其他动物疾病的物品；（C）物品（食品除外）意图影响人或其他动物身体的结构或任何功能；（D）作为第（a）、（B）或（C）条规定的任何物品的组成部分使用的物品。"因此，作为药品赋形剂或其他成分的高风险成分是FD&C法案第201（g）节定义的药物。

manufacturing of drugs, and finished drug products."[10] [11], Further, bulk or repackaged high-risk drug components intended as excipients or other components of a drug product are drugs as defined by section 201(g)(1)(D) of the FD&C Act. Testing bulk or repackaged high-risk components for DEG and EG content is consistent with the CGMP requirement under section 501(a)(2)(B) of the FD&C Act.

《FD＆C法案》第201(g)节定义的药物生产商（包括外包设施）必须确保他们生产的药物符合《FD＆C法案》第501(a)(2)(B)节规定的药物CGMP。就《食品和药品管理法》第501(a)(2)(B)节而言，CGMP包括"对药品生产的监督和控制，以确保质量，包括管理原材料、药品生产中使用的材料和成品的风险并建立其安全性。"作为赋形剂或药品其他成分的散装或重新包装的高风险药物成分是《FD＆C法案》第201(g)(1)(D)节定义的药物。测试散装或重新包装的高风险成分的DEG和EG含量与FD＆C法案第501(a)(2)(B)节规定的CGMP要求是一致的。

Manufacturers of finished drug products must also comply with the CGMP regulations codified in 21 CFR Parts 210 and 211[12]. To comply with FDA's CGMP regulations, identity testing must be conducted to verify each component of a drug product[13]. Specific identity tests, if they exist, must be used[14]. Identity testing confirms that the component is what it is labeled to be. A component's identity can be described as its chemical structure and its physical form (e.g., polymorph, solvate, and appearance) including, if appropriate, its stereochemistry or immunochemistry[15]. To comply with CGMP regulations, representative samples of each shipment of each lot of a component must undergo appropriate identity testing before use in drug product manufacturing[16]. These requirements apply irrespective of the route of administration or dosage form of the finished drug

[10] Section 501 of the FD&C Act, as amended in 2012. 2012年修订的《FD＆C法案》第501节。

[11] In accordance with section 501(a)(2)(B) of the FD&C Act, a drug is adulterated "if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess." 根据《FD＆C法案》第501（a）（2）（B）节，药物掺假"如果其生产、加工、包装或持有所使用的方法或所使用的设施或控制不符合或未按照现行良好生产规范进行操作或管理，以确保该药物符合本章的安全要求，具有特性和强度，并符合其所需的质量和纯度特征或被代表拥有。

[12] FDA intends to promulgate more specific CGMP regulations for outsourcing facilities. Until these final regulations are promulgated, outsourcing facilities are subject to the CGMP requirements in parts 210 and 211. 美国食品和药物管理局打算为外包设施颁布更具体的CGMP法规。在颁布这些最终法规之前，外包设施应遵守第210部分和第211部分中的CGMP要求。

[13] See 21 CFR 211.84(d)(1).

[14] *Id.同上*

[15] See FDA's website addressing Questions and Answers on Current Good Manufacturing Practice Requirements | Control of Components and Drug Product Containers and Closures, available at https://www.fda.gov/drugs/guidances-drugs/questions-and-answers-current-good-manufacturing-practice-requirements-control-components-and-drug. 参见FDA网站，解决当前良好生产规范要求的问题和答案

[16] Under 21 CFR 211.84(a), "[e]ach lot of components … shall be withheld from use until the lot has been … tested … as appropriate." Under 21 CFR 211.84(b), "[r]epresentative samples of each shipment of each lot shall be collected for testing or examination. The number of containers to be sampled, and the amount of material to be taken from each container, shall be based upon appropriate criteria such as statistical criteria for component variability, confidence levels, and degree of precision desired, the past quality history of the supplier, and the quantity needed for analysis and reserve where required by § 211.170." Because DEG and EG contamination presents a serious hazard and FDA has seen wide variability of DEG and EG contamination from container to container, the Agency recommends that the representative sample collected for testing is of each container of each lot of a high-risk component. See Police arrest two fugitives over kidney failure case, ANTARA Indonesian News Agency, Jan 30, 2023, available at https://en.antaranews.com/news/271113/police-arrest-two-fugitives-over-kidney-failure-case (noting that nine drum samples were found to contain a wide variability of DEG and EG over the safety limit.), 成分和药品容器和封口的控制，可在21 CFR 211.84（a）下的第16页获得，"[e]每批成分……应停止使用，直到该批次……经过……测试……视情况而定。"根据21 CFR 211.84（b），"[右]e应收集每批货物的代表性样品进行测试或检查。取样容器的数量和从每个容器中取出的材料量应基于适当的标准，例如部件可变性的统计标准、置信水平和所需精度、供应商过去的质量历史和所需数量。根据§211.170的要求进行分析和保存。"由于二甘醇和乙二醇污染具有严重危害，并且FDA发现不同容器的二甘醇和乙二醇污染差异很大，因此FDA建议收集用于测试的代表性样品是每批高风险成分的每个容器。参见《警方因肾衰竭案件逮捕两名逃犯》，印尼安塔拉通讯社，2023年1月30日，网址为（注意到发现九个桶样本中DEG和EG的变异性很大，超过了安全极限。）

product (e.g., topical[17]). Furthermore, manufacturers of finished drug products must have a quality unit that is responsible for approving or rejecting incoming lots of materials (including components) for use in manufacturing operations[18]. The quality unit must have written procedures and follow those written procedures in carrying out its responsibilities[19]. For example, any lot of a component that does not meet the appropriate written specifications must not be used in drug product manufacturing[20].

制剂生产商还必须遵守21 CFR第210和211部分中的CGMP法规。为了遵守FDA的CGMP规定，必须进行鉴别测试以验证药品的每个成分。必须使用特定的鉴别测试（如果存在）。鉴别测试证实了该成分是其标记的。成分的身份可以描述为其化学结构和物理形式（例如多晶型物，溶剂化物和外观），包括其立体化学或免疫化学（如果适用）。为了遵守CGMP法规，每批成分的每批装运的代表性样品在用于药品生产之前必须进行适当的鉴别测试。这些要求适用于任何给药途径或制剂的剂型（例如局部）。此外，制剂生产商必须有一个质量部门，负责批准或拒绝用于生产操作的散装物料（包括原料药）。质量部门必须有书面程序，并在履行其职责时遵循这些书面程序。例如，任何不符合适当书面规范的组分批次都不得用于药品生产。

In addition, a drug, including a drug component, with a name recognized in the United States Pharmacopeia-National Formulary (USP-NF) must comply with compendial identity standards or be deemed adulterated, misbranded, or both[21].

此外，具有美国药典国家处方集（USP-NF）中认可名称的药物（包括药物成分）必须符合药典鉴别项要求，否则将被视为掺假或错标或两者兼而有之。

We note that all drug component that is used to manufacture a drug must either conform to an applicable USP-NF monograph, including the DEG and EG limits if specified, or conform to appropriate acceptance criteria if a DEG and EG test or limit has not been established in an applicable USP-NF monograph[22]. Accordingly, any container sampled and tested by FDA must conform to these safety limits or will be deemed adulterated, misbranded, or both[23].

我们注意到，用于生产药物的所有药物成分必须符合适用的USP-NF专论，包括DEG和EG限度（如有规定），或者如果DEG和EG测试或限度尚未在适用的USP-NF专论中建立，则必须符合适当的验收标准。因此，FDA取样和测试的任何容器都必须符合这些安全限制，否则将被视为掺假、贴错标签或两者兼而有之。

Some USP-NF monographs include, as part of the applicable identity testing, a limit test for DEG and EG. The relevant safety limit for DEG and EG is not more than (NMT) 0.10%, as recognized by the applicable USP-NF monograph for each high-risk drug component identified in the title of

[17] 21 CFR 211.84. See also Schier, J.G., Barr, D.B., Li, Z. et al. Diethylene Glycol in Health Products Sold Over-the-Counter and Imported from Asian Countries. J. Med. Toxicol. 7, 33–38 (2011). (noting that DEG-contaminated topical products have caused toxicity).https://doi.org/10.1007/s13181-010-0111-9 21 CFR 211.84。另请参见Schier，J.G.，Barr，D.B.，Li，Z.等人在柜台销售并从亚洲国家进口的保健品中的二甘醇。J、 医学毒理学。7,33-38（2011）。（注意到DEG污染的局部产品已引起毒性）。

[18] See 21 CFR §211.22.

[19] See id.

[20] See 21 CFR 211.84(e).

[21] See section 501(b) and 502(a) of the FD&C Act; see also 21 CFR 299.5(a) and (b). 参见《FD&C法案》第501（b）和502（a）节；另见21 CFR 299.5（a）和（b）。

[22] See footnote 11. A drug, including an inactive ingredient, with a name recognized in USP-NF must comply with compendial standards or be deemed adulterated, unless the difference in strength, quality, or purity from such standard is plainly stated on its label. Note that such "differences" do not extend to the drug's identity. See section 501(b) of the FD&C Act. 见脚注11。具有USP-NF中认可名称的药物（包括非活性成分）必须符合药典标准或被视为掺假，除非其标签上明确说明了强度，质量或纯度与该标准的差异。请注意，这种"差异"并不延伸到药物的身份。参见《FD&C法案》第501（b）节。

[23] See sections 501(a)(2)(B) and 502(a) and (g) of the FD&C Act. 参见《FD&C法案》第501（a）（2）（B）节和第502（a）和（g）节。

this guidance[24]. Accordingly, when a limit test for DEG and EG is included in the identity testing of a component's applicable USP-NF monograph, a drug manufacturer must perform the DEG and EG limit test on representative samples of each shipment of each lot of the component and find that the component contains no more than 0.10% of DEG and EG before using that component in drug product manufacturing[25].[2425]

作为适用鉴别测试的一部分，一些USP-NF专论包括DEG和EG的限度测试。DEG和EG的相关安全极限不超过（NMT）0.10%，这是适用的USP-NF专论对本指南标题中确定的每种高风险药物成分的认可。因此，当成分的适用USP-NF专论的鉴别测试中包括DEG和EG的限度测试时，药物生产商必须对每批成分的每次装运的代表性样品进行DEG和EG限度测试，并发现该成分在使用该成分进行药品生产之前不超过DEG和EG的0.10%。

For example, the United States Pharmacopeia (USP) monograph for glycerin provides a three-part identity test, including test A using "Infrared Absorption" and test B using gas chromatography that references the "Limit of Diethylene Glycol and Ethylene Glycol[26]." Though the infrared absorption test (test A) identifies glycerin, it is not suitable for detection or quantitation of DEG or EG. Test B allows for quantitation of DEG and EG, if present, individually, down to the identified safety limit (NMT 0.10%[27]). Thus, representative samples of each shipment of each lot of glycerin intended to be used as a component in drug product manufacturing must be tested and found to meet the DEG and EG limit included in the identity testing in the USP Glycerin Monograph before use in drug product manufacturing.[2627]

例如，美国药典（USP）甘油专论提供了三部分鉴别测试，包括使用"红外吸收"的测试a和使用参考"二甘醇和乙二醇限量"的气相色谱的测试B。虽然红外吸收测试（测试a）识别甘油，但它不适合检测或定量检测DEG或EG。测试B允许单独定量DEG和EG（如果存在），直至确定的安全极限（NMT 0.10%）。因此，在用于药品生产之前，必须对每批拟用作药品生产成分的甘油的代表性样品进行测试，并发现其符合USP甘油专论中鉴别测试中包含的DEG和EG限值。

If any testing reveals that their distributed drug products contain DEG or EG levels in excess of the applicable safety limit, manufacturers of New and Abbreviated New Drug Application products must submit a Field Alert Report (FAR[28]). FDA's guidance for industry Field Alert Report Submission: Questions and Answers addresses how to submit a FAR[29].

如果任何测试显示其分销的药品含有DEG或EG水平超过适用的安全限值，则NDA和ANDA药品的生产商必须提交现场警报报告（FAR）。FDA的现场警报报告提交行业指南问答说明了如何提交FAR。

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[24] At the time of issuance of this guidance, USP identified 0.10% as the DEG and EG limit in the identification section of the USP-NF monographs for Glycerin, Propylene Glycol, Maltitol Solution, Hydrogenated Starch Hydrolysate, and Sorbitol Solution. 在本指南发布时，USP在USP-NF专著的甘油，丙二醇，麦芽糖醇溶液，氢化淀粉水解产物和山梨醇溶液的鉴定部分中确定了0.10%的DEG和EG限值。

[25] See section 501(b) and 502(a) of the FD&C Act; see also 21 CFR 299.5(a) and (b); see also 21 CFR 211.84(a) and (b). 参见《FD&C法案》第501（b）和502（a）节；另见21 CFR 299.5（a）和（b）；另见21 CFR 211.84（a）和（b）。

[26] Test C is an examination of the Test B chromatograms. 测试C是对测试B色谱图的检查。

[27] Although the USP test method is effective, there may be a potential for variability in the composition of products labeled as glycerin. Therefore, method modifications may be needed to the preparation of the Resolution, Standard, and Sample solutions and to the Chromatographic system to achieve suitable performance. Method modifications in analyses performed by FDA have included preparation of all solutions in methanol with appropriate modifications to the chromatographic system, as needed, such as temperature ramps and hold times. 虽然USP测试方法是有效的，但标记为甘油的产品的组成可能存在差异。因此，可能需要对分辨率，标准和样品溶液的制备以及色谱系统进行方法修改，以实现合适的性能。FDA进行的分析方法改进包括制备甲醇中的所有溶液，并根据需要对色谱系统进行适当修改，例如温度梯度和保持时间。

[28] 21 CFR 314.81(b)(1)(ii).

[29] For the most recent version of a guidance, check the FDA guidance web page at.https://www.fda.gov/regulatory-information/search-fda-guidance-documents. 有关指南的最新版本，请查看FDA指南网页

Pharmacies that compound drug products that meet the conditions under section 503A of the FD&C Act must compound drug products using bulk drug substances that comply with the standards of an applicable USP or NF monograph, if a monograph exists (section 503A(b)(1)(A)(i)(I)), and using ingredients (other than bulk drug substances) that comply with the standards of an applicable USP or NF monograph, if a monograph exists (section 503A(b)(1)(B)). This includes compliance with DEG and EG limits when specified in an applicable USP-NF monograph. Accordingly, any drug sampled and tested by FDA must conform to the applicable USP-NF safety limit for DEG and EG or will be deemed adulterated, misbranded, or both[30].

符合FD&C法案第503A节规定条件的复方药品的药店必须使用符合适用USP或NF专论标准的原料药（如果有专论）（第503A（b）（1）（a）（i）（i）节））并使用符合适用USP或NF专论标准的成分（原料药除外）来复方药品，如果有专论（第503A（b）（1）（b）节）。这包括符合适用USP-NF专论中规定的DEG和EG限值。因此，FDA采样和测试的任何药物都必须符合适用的USP-NF DEG和EG安全限值，否则将被视为掺假，错误标签或两者兼而有之。

IV. RECOMMENDATIONS TO SAFEGUARD THE QUALITY AND SAFETY OF MEDICINES FROM DEG AND EG CONTAMINATION 保障药品质量和安全免受二甘醇和乙二醇污染的建议

It is critical for safeguarding the quality and safety of medicines that all manufacturers and others using high-risk drug components to manufacture or prepare drug products be aware of the importance of preventing the use of DEG- and EG-contaminated components.

为了保障药品的质量和安全，所有生产商和其他使用高风险药物成分生产或制备药品的人都必须意识到防止使用DEG和EG污染成分的重要性。

In addition to the requirements listed above, in order to prevent the use of DEG- and EG-contaminated components, the Agency recommends:

除了上面列出的要求外，为了防止使用DEG和EG污染的成分，FDA建议：

1. Ensure the specific identity analysis for each lot, which includes a limit test for DEG and EG, incorporates testing of samples from **all containers of all lots** of a high-risk drug component before the high-risk drug component is used in the manufacture or preparation of drug products[31].

   在高风险药物成分用于生产或制备药品之前，确保每个批次的特定鉴别分析，包括DEG和EG的限度测试，包括对所有批次高风险药物成分的所有容器中的样品进行测试

2. For high-risk drug components where the DEG and EG tests are not included in the identification test of the USP-NF monograph for the component[32], a manufacturer uses a

[30] See sections 501(b) and 502(a) and (g) of the FD&C Act参见《FD&C法案》第501(b)和502(a)和(g)节。

[31] FDA's regulation at 21 CFR 211.84(a) requires testing of each lot of components; 21 CFR 211.84(b) requires that a representative sample of each shipment of each lot be collected for testing and describes that the number of containers to be sampled shall be based upon appropriate criteria. Because DEG contamination presents a serious hazard and FDA has seen wide variability of DEG and EG contamination from container to container, the Agency recommends that the representative sample collected for testing is of each container of each lot. FDA在21 CFR 211.84（a）中的规定要求对每批成分进行测试；21 CFR 211.84（b）要求收集每批货物的代表性样品进行测试，并说明要取样的集装箱数量应基于适当的标准。由于二甘醇（DEG）污染具有严重危害，且美国食品和药物管理局（FDA）发现不同容器之间的二甘醇（DEG）和乙二醇（EG）污染差异很大，因此FDA建议收集用于测试的代表性样品是每批容器的样品。

[32] At the time of publication of this guidance, some examples of such components include, but are not limited to, high-risk components for which the USP-NF monograph includes testing for DEG and EG in the impurities tests (rather than the identities tests) (e.g., Polyethylene Glycol (MW <1000 only), Diethylene Glycol Stearates, Polyethylene Glycol Monomethyl Ether 350/550 (MW <600 only), and Polyoxyl 35 Castor Oil), high-risk components that have USP-NF monographs and testing procedures described in a

suitable and equivalent procedure that includes a test to detect and quantify DEG and EG. The Agency recommends that any tests to detect and quantify DEG and EG use a safety limit for DEG and EG of NMT 0.10%.

对于高风险药物成分，其中DEG和EG测试不包括在USP-NF各论对该成分的鉴别测试中，生产商使用合适且等效的程序，包括检测和DEG和EG的定量测试。FDA建议任何检测和DEG和EG的定量测试都使用NMT 0.10%的DEG和EG安全限值。

3. Drug product manufacturers maintain current knowledge of their supply chain for high-risk drug components (i.e., the identity of the original manufacturer of the component and any subsequent repackers or distributors).

   药品生产商保持其高风险药物成分供应链的最新知识（即成分的原始生产商和任何后续重新包装或分销商的身份）。

4. All personnel in pharmaceutical manufacturing facilities (especially personnel directly responsible for receipt, testing, and release of components) be made aware of the importance of proper DEG and EG contamination testing, and the potential hazards if this testing is not done.

   药品生产设施中的所有人员（特别是直接负责接收，测试和释放成分的人员）都要意识到适当的DEG和EG污染测试的重要性，以及如果不进行此测试的潜在危害。

5. Repackers, and others who distribute and prepare high-risk components for use in drug products, test the high-risk components that are used, sold for use, or intended for use in drug products. Accurate and complete COAs that identify the original manufacturer of the components should be issued for each component lot shipment[33].

   重新包装者和其他分销和制备用于药品的高风险成分的人，测试用于、出售用于或计划用于药品的高风险成分。应为每批装运的部件发布准确完整的COA，以确定部件的原始生产商。

6. Pharmacies that compound drug products that meet the conditions under section 503A of the FD&C Act (21 U.S.C. 353a) and that use high-risk components in compounding those drug products either test each lot of each high-risk component for DEG and EG content, or ensure that such testing was properly done by a reliable supplier.

   符合FD&C法案（21 U.S.C.353a）第503A节规定条件并在配制这些药品时使用高风险成分的药品的药店要么测试每批高风险成分的DEG和EG含量，要么确保由可靠的供应商正确进行此类测试。

The foregoing recommendations are also important precautions when determining supplier and lot acceptability of other components (e.g., polyethylene glycol 40 castor oil) that may be at risk for DEG or EG contamination and are not specifically named in this guidance.

USP-NF General Chapter (e.g., Polysorbate 20/40/60/80, Polyoxyl 15 Hydroxystearate, Polyoxyl 20 Cetostearyl Ether, Polyoxyl 8 Stearate, Octoxynol 9, and Nonoxynol 9), and high-risk components that do not have USP-NF monographs at all. USP monographs and standards are periodically updated. FDA expects manufacturers to ensure they are referencing the current USP-NF when determining which testing to perform. 在本指南发布时，此类成分的一些例子包括但不限于USP-NF专论中包括在杂质测试（而不是身份测试）中测试DEG和EG的高风险成分（例如聚乙二醇（仅MW<1000），硬脂酸二甘醇酯，聚乙二醇单甲醚350/550（仅MW<600），和聚氧乙烯35蓖麻油），具有USP-NF专论和USP-NF一般章节中描述的测试程序的高风险成分（例如，聚山梨醇酯20/40/60/80，聚氧乙烯15-羟基硬脂酸酯，聚氧乙烯20-十六烷基醚，聚氧乙烯8-硬脂酸酯，辛氧醇9和壬氧醇9），以及根本没有USP-NF专论的高风险成分。USP专著和标准定期更新。FDA希望生产商在确定进行哪些测试时，确保他们参考当前的USP-NF。

[33] See, for example, section XI (11.4) and XVII (17.2 and 17.6) of FDA's guidance for industry, Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients. 例如，参见FDA行业指南第十一节（11.4）和第十七节（17.2和17.6），Q7活性药物成分良好生产规范指南。

在确定供应商和批次可接受的其他成分（例如聚乙二醇40蓖麻油）时，上述建议也是重要的预防措施，这些成分可能有DEG或EG污染的风险，并且在本指南中没有具体说明。

If any testing of any drug component identifies DEG or EG levels at or above the USP-NF monograph limit, the manufacturer should notify of the finding. Manufacturers should also contact the if any drug product batches made with components whose testing identifies DEG or EG levels at or above the USP-NF monograph limit are already in distribution, to discuss appropriate next steps, such as voluntary initiation of a recall.CDER-DEG-EG-Reporting@fda.hhs.govappropriate Division of Pharmaceutical QualityOperations

如果对任何药物成分的任何测试确定DEG或EG水平等于或高于USP-NF专论限值，生产商应通知其所发现的情况。生产商还应联系已经在分发的含有该成分的任何药品批次，这些成分的测试确定DEG或EG水平等于或高于USP-NF专论限值，以讨论适当的后续步骤，例如启动自愿召回。