Tools to Ensure Safe Medicines: New Monograph Tests in *USP-NF*.

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ABSTRACT

This paper describes *USP-NF* compendial updates to six 'high-priority'' excipient monographs: Glycerin, Propylene Glycol, Sorbitol Solution, Sorbitol Sorbitan Solution, Noncrystallizing Sorbitol Solution and Maltitol Solution. The *USP-NF* revisions arose from the Food and Drug Administration's (FDA's) requests to include, as part of each monograph's Identification test, a limit test to detect the presence of Diethylene Glycol (DEG), a toxic adulterant. These revisions align with the 2007 FDA Guidance for Industry: Testing of Glycerin for Diethylene Glycol (1), that drug product manufacturers perform a specific identity test for DEG on all containers of all lots of glycerin before glycerin is used in the manufacture and preparation of drug products. This paper describes several risk factors due to a complex global excipient supply chain, nonspecific specifications, inadequate supply chain qualification, and poor understanding of regulations. Strengthening and conformance to compendial specifications is one of the tools necessary to mitigate risk and help prevent the next DEG adulteration that is part of USP's efforts to ensure safe medicines.

KEY WORDS: *USP-NF*, "high-priority" monograph, diethylene glycol (DEG), ethylene glycol (EG), FD&C Act, CGMPs, Identity, Identification, Supply chain

INTRODUCTION

The globalization of excipient supply chains has become the norm for the 21st century pharmaceutical and consumer health-care products industries (2). Global sourcing has grown so rapidly that it has challenged the current regulatory and industry control strategies that maintain product quality and safety The growing global supply chain from emerging markets over the past decade provides the advantage of lower cost pharmaceutical excipients. However, regulatory agencies, pharmaceutical and consumer health products companies find it more difficult to control quality in a global supply chain setting.

Excipients constitute a large portion of most prescription and over-the-counter (OTC) drug

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products and have traditionally been considered a low-risk aspect of the product's safety. The evidence from recent tragedies and loss of life surrounding DEG-contaminated excipients illustrates that excipients can no longer be considered low-risk. When an excipient is procured from multiple sources (manufacturers, distributors, repackagers, traders, brokers, and vendors), the level of control can vary tremendously from lot-to-lot and supplier-to-supplier. Factoring in the global sourcing of multi-sourced excipients creates an even greater challenge for the user.

Sourcing of excipients, as we now realize, because of perennial episodes with DEG-adulterated excipients, can lead to disastrous consequences for public health and safety. Therefore, in addition to distribution and supply-chain control, an approach to establish specific compendia tests is especially useful and effective for the detection of DEG adulteration. The use of compendial testing methodologies, especially specific identification testing, provides added safety assurance for the excipient, as it is tracked through the supply chain that ultimately qualifies the excipient for its intended use. Establishing a specific and required compendial identification test for DEG in glycerin helps in the detection of this adulterant and does not allow companies to accept a result from a certificate of analysis (COA).

Their designation as Identification (ID) tests makes them compulsory which will be discussed in more detail later in this paper, in the section describing the Role of Identification Testing in a *USP-NF* Monograph. Specific identification tests can thus be relied upon by FDA for enforcement purposes under section 501(b) of the Federal Food Drug and Cosmetic Act, (FFD&C Act), Sec. 501 [21 USC §351] Adulterated Drugs and Devices (3). Conformance ensures the excipient has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess. The previous USP Glycerin (4) monograph included a Gas Chromatographic (GC) procedure for the "Limit of diethylene glycol and related compounds" in which the limit of DEG was 0.1%. This impurities test was added to the Glycerin monograph in 1997 as a result of the 1995-1996 DEG-related deaths in Haiti (5). The revised USP Glycerin monograph (6), official from May 1, 2009, includes a revised GC procedure added to the identification section to determine the "Limit of Diethylene Glycol and Ethylene Glycol", each at 0.10%.

HISTORY OF DEG ADULTERATION IN GLYCERIN

The first episode of DEG in Glycerin occurred in 1937 in the United States and resulted in the death of 107 children. The "Elixir of Sulfanilamide" was compounded using diethylene glycol as the solvent to liquefy the sulfur drug. This tragedy resulted in drastic changes to how drugs would be regulated in the U.S., the first of which was passage of the FFD&C Act of 1938, the first amendment to the Pure Food and Drugs Act of 1906. Prior to 1938, no statutory mechanism existed for premarket approval of drugs. The 1906 Act only regulated adulteration and misbranding of drugs on a post-marketing basis. However, since the passage of the FD&C Act amendment of 1938, over 500 additional deaths have occurred throughout the world as a direct result of DEG-contaminated glycerin shown in Table 1.

Table 1 Diethylene Glycol History of Adulteration

Country	Year	Incident
USA	1937	Sulfanilamide Elixir – 107 deaths Resulted in Implementation of the FD&C Act in 1938
South Africa	1969	Sedative formulated with DEG – 7 deaths
Italy	1985	DEG in wines from Austria – no known deaths
India	1986	Medicinal glycerin laced with DEG – 14 deaths Industrial grade used
Nigeria	1990	Acetaminophen syrup containing DEG – 40 deaths (some sources say 200 deaths)
Bangladesh	1990-2	Acetaminophen syrup containing DEG – 339 deaths
Haiti	1995/6	Cough medicine containing DEG – 85 deaths
Panama	2006	Cough and anti-allergy syrup containing DEG – 46 deaths (116 or 365 according to other sources)
USA	2006/7	Toothpaste containing DEG – no deaths
Panama	2007	Toothpaste containing DEG – no deaths reported
Nigeria	2008/9	Teething formula contaminated with DEG from propylene glycol – 84 deaths
Bangladesh	2009	Paracetamol syrup for children adulterated with diethylene glycol. Twenty-four children have died.

The 2006 Panama (7) incident involved DEG-contaminated glycerin used in cough syrups resulting in over 100 deaths, the Nigeria (8) incident between 2008 and 2009 where more than 50 children died after ingesting contaminated teething syrup, and in Bangladesh (9) where 24 children died in July 2009 from DEG adulterated Paracetamol syrup.

According to the FDA/CDER Guidance for Industry, Testing of Glycerin for Diethylene Glycol, the cases reveal the following similarities and, as a result of these practices, DEG-contaminated glycerin entered the pharmaceutical supply chain.

The pharmaceutical manufacturers of the syrups that contained contaminated glycerin did not perform full identity testing on the glycerin raw material, and did not quantify the amount of DEG present or verify the purity of the glycerin received.

1. The pharmaceutical manufacturers of the syrups containing contaminated glycerin relied on the COA provided by the supplier.

2. The origin of the glycerin was not easily apparent from the COA. The COA obtained by the pharmaceutical manufacturers of the syrups was often a copy of a COA on the letterhead of the distributor and not the COA provided by the manufacturer of the glycerin.

3. The chain of custody or distribution history of the glycerin was not readily known because the glycerin may have been sold several times between its manufacture and its use in medicinal syrup or other drug product.

According to the guidance, FDA recommends that the drug product manufacturers perform a specific identity test that includes a limit test for DEG on all containers of all lots of glycerin before the glycerin is used in the preparation of drug products because of the serious hazard associated with DEG contamination. This reiterates 21 C.F.R. §211.84(d)(2) (10) requirement for specific ID testing in the absence of full USP compendial testing. Validated alternative procedures that demonstrate equivalent identification and sensitivity for DEG can be used. A thin-layer chromatographic (TLC) method published in the Journal of AOAC International (11) was presented as an example of an alternative method with a sensitivity of 0.05% for DEG. In addition, since DEG contamination presents a serious hazard, the Agency recommends that the representative sample collected for testing is from each container of each lot, and the testing has to be capable of detecting DEG. This applies to all recipients of Glycerin USP, and is not limited to those who only formulate or compound. The guidance also recommends intimate knowledge of the members of the supply chain to assure the excipients traceability.

USP METHOD DEVELOPMENT FOR 'HIGH- PRIORITY' MONOGRAPHS

In addition to the FDA request to revise the Glycerin monograph, FDA provided a list of *USP-NF* monographs evaluated for risk of DEG adulteration. Monographs on the list were prioritized as high (H), medium (M), and low (L). A total of five excipient monographs were categorized as 'high-priority'(12): Propylene Glycol, Sorbitol Solution, Sorbitol Sorbitan Solution, Noncrystallizing Sorbitol Solution, and Maltitol Solution (Table 2). USP held 3 public web meetings, announced through the USP website's Hot Topics page, to call for methods (13).

As part of the method development and revision process for determination of DEG adulteration, USP laboratory evaluated the TLC method for Glycerin from the FDA guidance in parallel with development of a capillary gas chromatographic method with flame ionization detection (GCFID) for the detection of EG and DEG in glycerin (14). Compared to the

Table 2 *USP-NF* Articles Identified as 'High-Priority' for Adulteration with DEG and EG

Maltitol Solution (1) (H)
Sorbitol Solution (1) (H)
Sorbitol sorbitan solution (1) (H)
Noncrystallizing sorbitol solution (1) (H)
Propylene glycol (2) (H)
Propylene glycol dilaurate (4) (M)
Polyethylene glycol (3) (M)
Lactitol (1) (L)
Maltitol (1) (L)
Sorbitol (1) (L)
Polyethylene glycol monomethyl ether (4) (L)
Diethylene glycol monoethyl ether (4) (L)
Diethylene glycol stearates (4) (L)

Notes:

(1) Sugar alcohols, (2)Propane diols and triols (3) Polyols (polyethylene glycol), (4)Derivatives of categories 1-3

The risk levels for undetectable contamination are categorized as (H) – high, (M) – medium, (L) - low

TLC method, the GCFID method showed greater sensitivity and specificity. The GC method was robust and sensitive enough to unambiguously quantitate 0.025% (w/w) DEG and EG in glycerin compared to the TLC method which was capable of detecting only 0.1% of the analytes. Also, the accuracy of the TLC test depended greatly on an analyst's techniques as the transitory nature of the spot development process may give false negative results. The GC procedure has the additional advantage in that it can be used for the assessment of identity and content of DEG and EG in glycerin as well as in glycerin-containing products such as toothpaste, while the TLC method has problems with complex matrices due to interference. The USP GCFID method for glycerin showed satisfactory validation data for all validation parameters.

USP sought feedback from major sugar alcohol manufacturers and trade organizations on the capability and suitability of the TLC method referenced in the 2007 FDA Glycerin Guidance document. The feedback indicated that TLC was outdated and no longer relevant for complex materials. In addition, discussions with the Agency regarding the potential presence of trace levels of ethylene glycol (EG), which may be produced during the hydrogenation process used to manufacture sugar alcohols, lead to an agreement that one procedure should monitor the presence of both DEG and EG resulting either from adulteration or from the manufacturing process. Even though EG was not mentioned in the FDA guidance, USP added this compound to the list of potential adulterants of 'high-priority' excipients because of its high toxicity and its similar physical and chemical properties to DEG. EG is a poisonous, inexpensive chemical used in the same types of industrial products as DEG, and in fact is more toxic than DEG (15).

During method development, the USP laboratory studied the feasibility of using the existing High Performance Liquid Chromatography (HPLC) method measuring the content of sorbitol under the Assay section of the current Sorbitol Solution monograph to test for DEG and EG. However, this HPLC test procedure for Sorbitol Solution was not suitable due to interference from the sample matrix. A gas chromatographic (GC) method submitted by industry was modified by USP and finally proposed via Revision Bulletin (16) as the USP method to measure DEG and EG in sugar alcohols. The modified method prepared samples by precipitation with an acetone:water mixture (96:4, v/v) yielding adequate DEG and EG recoveries and results. With this modification, a limit of 0.10% can be readily met with sufficient precision to preclude use of inferior methodologies prone to producing false-negative results. In conclusion, the GC test procedure for DEG and EG in sugar alcohols is simple and easy-to-operate, employing a basic GC instrument with direct injection. The GC run time is short, sample preparation is quick and easy, and no internal standard is required for Sorbitol Solutions.

The European Pharmacopoeia recently proposed a test to detect DEG at 0.1% in the impurities section of the Propylene glycol monograph. This monograph is currently at stage 4 in the harmonization process within the Pharmacopeial Discussion Group (17). The USP laboratory determined that this method, while suitable for DEG, is not suitable for EG detection as the method did not separate EG

from propylene glycol. Changing the instrument conditions did not improve the separation. The USP laboratory determined that the GC method developed for detection of DEG and EG in glycerin was suitable for detection of these analytes in propylene glycol. Due to DEG and EG exhibiting higher responses in the presence of propylene glycol, an internal standard was used to avoid false positives. The method was satisfactorily validated for specificity, accuracy, method precision, and LOD.

SUPPLY CHAIN CONTROL

Currently, both quality control and supply chain integrity of globally sourced excipients vary significantly primarily because excipient supply chains are getting longer and more complex due to global sourcing practices. The use of on-site audits and quality agreements establishes a clear communication between the supplier/ manufacturer and the pharmaceutical user or through third party certification, and ultimately protects the safety of the patient. Unfortunately, in reality, disparate practices exist throughout the globe and have resulted in the supply chain tragedies, as in the case of DEG contaminated glycerin. If these practices continue, regulatory agencies and pharmaceutical companies will have to devote more resources to anticipate potential supply chain risks and implement preventive measures. Harmonized, globally-enforced standards provide assurance of excipient quality control and supply chain integrity. Conformance to strong compendial specifications is one of the tools necessary to help prevent the next DEG adulteration. In response to increasing concerns about the quality of pharmaceutical ingredients, the USP Verification program verifies drug substances and excipients used to make OTC and prescription pharmaceuticals (18).

THE ROLE OF IDENTIFICATION TESTING IN A *USP-NF* MONOGRAPH

An inactive ingredient or "other component" of a drug product is defined as a drug under section 201(g)(1) of the FDCA (21 U.S.C. §321(g)(1)) (19). Section 501(a)(2)(B) of the of the FD&C Act, Sec. 501 [21 U.S.C. §351] Adulterated Drugs and Devices Act requires that the methods used in, or the facilities or controls used for, a drug's manufacture, processing, packing, or holding to conform to CGMP. Testing bulk or repackaged glycerin for DEG content is consistent with good manufacturing practice required under the Act.

From a US regulatory standpoint, it makes a difference whether the detection and quantification of an adulterant such as DEG in Glycerin or other 'high-priority' excipients is considered part of the Identification test or is considered solely a standard for strength, quality, purity or impurity testing. While including a test for the absence of a substance is an unusual paradigm for an Identification test, it was deemed crucial to include DEG testing as part of the Identification test, as opposed to simple inclusion as an ordinary impurities test for the following reasons. If DEG detection and quantification is part of the Identification test, the CGMP regulations at 21 C.F.R. § 211.84(d)(l) require that manufacturers of drug products quantify any DEG present both at the time of manufacture and upon receipt at the point of transfer to another party. In contrast, if DEG quantification is solely part of a purity (impurity) test, a manufacturer need not quantify DEG in the glycerin or other high priority polyols (identity is the only test required to accept the material). Furthermore, manufacturers could not deviate from the DEG limit since this would be an aspect of identity. This is a fundamental difference as, according to Section 501(b) of the Act, if a USP compendial monograph exists, a manufacturer could deviate from the official compendial standard's impurity requirements by labeling the product to indicate that it deviates from the USP test requirements in this regard, yet

continue to sell the product as pharmaceutical-grade glycerin.

Furthermore, one of the most difficult challenges is to establish practical requirements for demonstrating "absence" of a substance that should not be present. Determining "absence" is dependent on the capabilities of the analytical instrument chosen. Any analytical technique has a limit of detection below which the analyte of interest will not be observed. USP worked closely, with stakeholders and FDA, through a collaborative study to establish a limit that would provide adequate protection from adulteration while providing the industry with a compendial standard that could be met with common analytical technology.

CONCLUSION

DEG-contaminated Glycerin tragedies represent one of the difficulties facing pharmaceutical manufacturers as excipient supply chains get longer and more complex due to the increase in global sourcing practices. Often, no formal tracking process exists of the shipment of an excipient from its manufacture to its use in the production of a drug or OTC drug product. The tragedy surrounding DEG-contaminated glycerin also highlights a problem of no clear indication of the intended use of the excipient from its Label or the COA. Products shipped as "chemicals" sometimes end up being used as starting materials in pharmaceutical applications which may not have been the intended use. Possible alteration of documents throughout the supply chain makes it more critical to employ appropriate compendial testing and verification of content sourced through a global supply chain. In summary, a test for Identity/Identification of DEG and EG in sugar alcohols and propylene glycol provides a more robust standard, both in terms of the compendial standard itself (including FDA enforcement under FD&CA 501(b)), and FDA CGMPs (enforced by FDA under FD&CA 501(a)). Strengthening and conformance to compendial specifications is part of USP's efforts to ensure safe medicines, and is one of the tools necessary to help mitigate risk and help prevent the next DEG adulteration.

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