International Pharmaceutical Excipients Council of the Americas

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Cc: Catherine Sheehan
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Re: Oleyl Oleate PF 47(1)

Dear Dr. Yarkala,

Members of the International Pharmaceutical Excipients Council of the Americas (IPEC- Americas) have reviewed the proposed revision to the Oleyl Oleate NF monograph as published in PF 47(1). IPEC-Americas appreciates the opportunity to provide comments for the proposed revision.

IPEC-Americas Background

IPEC-Americas represents more than 50 excipient manufacturers, distributors and pharmaceutical/biopharma companies to support the safe production and use of excipients. This letter represents the IPEC-Americas membership. A complete list of IPEC-Americas member companies can be found at: https://ipecamericas.org/what-ipec-americas/member-companies. IPEC-Americas is dedicated to working closely with regulatory authorities, industry organizations and scientific bodies (globally) to advance public health on matters relating to the quality, safety, manufacture, distribution, use and functionality of excipients. IPEC is the sole association representing excipients.

IPEC-Americas Comments

1. IPEC-Americas recognizes the efforts of the USP and other pharmacopeias to continually improve, harmonize, and modernize excipient monographs. IPEC-Americas has communicated the need for better understanding of excipient composition and supports the introduction of tests and limits for impurities and inherent concomitant components that are needed to define or assure the excipient quality and/or safety. However, IPEC-Americas is concerned that the USP monograph modernization efforts for excipients are not aligned with FDA and industry priorities and are trying to characterize excipients to a greater degree than is needed for a pharmacopeial monograph.

   Pharmacopeial monographs should focus on the key characteristics that are necessary to confirm the material is appropriate for pharmaceutical use and provide reasonable safety controls for components that may have significant potential to impact patient safety. Pharmaceutical monographs are public standards intended to provide the basic controls for excipients sourced from many different manufacturers. Therefore, it is not appropriate to try to fully define the excipient compositional in a pharmacopeial monograph. If a more detailed understanding of the excipient

composition is needed for a specific drug application, it should be discussed between the excipient maker and user of the excipient since this requirement would be drug product specific and therefore not needed in a public standard.

In a letter to the (then) USP CEO Roger Williams, dated October 12, 2010, the (then) FDA CDER Director Janet Woodcock wrote, "[…] we encourage USP to update all monographs that include non-specific assay or identification tests, and to re-evaluate antiquated methodologies in general. FDA strongly believes that monographs utilizing outdated analytical procedures are vulnerable to economically motivated adulteration (EMA), and current advancements in science and technology can help to fill the void." The letter from Dr. Woodcock went on to describe an FDA monograph modernization task force formed which "is responsible for developing a strategy to identify priority products for monograph modernization to provide requested FDA assistance to USP in your modernization efforts."

The FDA monograph modernization task force issued letters to the USP dated November 16, 2010 and October 7, 2016. In these letters, the task force stated the need to update the non-specific nitrogen assay test in the povidone, crospovidone, and copovidone monographs due to the risk for the EMA melamine and the need to update the talc monograph to increase assurance that asbestos is not present.

IPEC-America's interpretation of these letters is that the FDA has not specifically requested USP to add new chromatographic assay tests or to introduce limits for composition to all existing excipient monographs. FDA simply requested that USP consider updating their analytical methods used in monographs when appropriate, not create new limits for various components in existing excipients.

Are there any specific economically motivated adulterants (EMA) that the proposed GC test would be able to detect in oleyl oleate, if present?

2. The composition of oleyl oleate is controlled by the purity of the raw materials and manufacturing process used and could vary greatly among suppliers and grades. Knowledge of the compositional profile is important for appropriate selection of excipients during drug product formulation development and evaluation of significant changes, including alternate sources. However, control of all components via compendial limits is not usually necessary to demonstrate quality of each excipient batch manufactured and distributed.

   Setting compendial acceptance criteria for concomitant components should be avoided when no specific safety concerns exist. When included, composition-related quantitative or qualitative methods and specifications should be justified and should represent the full range of the current global excipient supply chain. Further, the impact of concomitant components on drug product performance differs from product to product; the criticality of concomitant components is not universal to all drug product applications. As described in ICH Q8, it is the responsibility of the drug product manufacturer to determine the criticality of the excipient composition to the quality of the drug product.

   IPEC-Americas seeks to understand the rationale for the new proposed GC test and limits for assay and related fatty alcohols, fatty acids and fatty esters.

   Is there a known safety and/or quality concern with any of the related fatty alcohol, fatty acid, or related fatty ester components of oleyl oleate?

   How has USP confirmed that the proposed limits reflect the full range of oleyl oleate in the current global excipient supply chain? Do the samples USP evaluated represent various manufacturing processes utilizing various raw materials, and do they represent the full range of expected variability for these processes?

3. The tests already included in the existing oleyl oleate monograph are sufficient to ensure the identification and purity of pharmaceutical oleyl oleate.

   Identification Test A <197>, Infrared Spectroscopy: 197F is a specific identification test. As stated in USP General Chapter <197>, "The NIR, IR, and Raman spectra, or X-ray diffraction pattern of a substance, compared with the spectrum or diffraction pattern obtained with the corresponding USP Reference Standard, provides perhaps the most conclusive evidence of the identity of the substance that can be realized from any single test." The proposed chromatographic Identification Test B is less specific and does not increase assurance of positive identification.

   The combination of the specific gravity, refractive index, acid value, hydroxyl value, iodine value, and saponification value tests, which are already included in the existing oleyl oleate monograph, define the composition of pharmaceutical oleyl oleate. Introduction of a chromatographic test to replace specific gravity, refractive index, iodine value and saponification value is problematic because, while the chromatographic test is more specific for the defined analytes, the proposed tests and limits apply to the discrete analytes only as opposed to the cumulative property (which may be important for excipient performance). For example, the specific gravity of any particular batch is determined by all of the components present, not just the nominal oleyl oleate and individual related fatty ester components.

   Further, the proposed limits for oleic acid (i.e. NMT 1.0%) and oleyl alcohol (i.e. NMT 3.0%) are not aligned with the limits for acid value and hydroxyl value, respectively. The current limit for acid value (i.e. NMT 3.0) correlates to an oleic acid content of about 1.5% and the current limit for hydroxyl value (i.e. NMT 10) correlates to about 4.8% oleyl alcohol content. Because the new limits proposed for oleic acid and oleyl alcohol represent a tightening of the requirements in the existing monograph, there is potential for some suppliers currently in the market to be adversely impacted. If their current supplier does meet the tighter requirements, drug product manufacturers would need to qualify new suppliers of oleyl oleate, which could potentially lead to disruptions in drug product manufacture or even drug product shortages. Therefore, existing monograph requirements should not be tightened unless there is a significant patient safety-related concern.

   Why are chromatographic methods for identification, assay, and related fatty acids, fatty alcohols, and fatty esters required for oleyl oleate?

   Why are the proposed limits for oleic acid and oleyl alcohol tighter than the corresponding limits for acid value and hydroxyl value?

In summary, IPEC-Americas respectfully requests that the USP postpone the implementation of the proposed revisions to the Oleyl Oleate NF monograph until such a time that the USP, FDA, and industry agree to a process and criteria to modernize this monograph that is consistent with the real risks associated for current uses in pharmaceutical products and not simply introduce additional characterization tests that are unnecessary for a public standard.

Respectfully yours,

Janeen Skutnik-Wilkinson
Chair, IPEC-Americas