USP Virtual Roundtable on Reporting Thresholds in Monographs
Tuesday, June 29, 2021

I. Overview

United States Pharmacopeia (USP) hosted a virtual roundtable on Tuesday, June 29, 2021 to review USP's proposed "user-determined" approach to address reporting thresholds within *United States Pharmacopeia–National Formulary* (*USP–NF*) documentary standards, collect stakeholder feedback, and discuss next steps.

The roundtable began with welcoming remarks from Ed Gump, USP Vice President, Small Molecules. Then, representatives from the Food and Drug Administration (FDA) and USP provided context setting presentations. FDA outlined its primary concerns with including reporting thresholds in monographs and examples of regulatory challenges it has created for the agency. USP described the stakeholder engagement efforts it has conducted on reporting thresholds since FDA raised its initial concerns in 2016 and outlined the current proposed approach for "user-determined" reporting thresholds. The roundtable moved to discussion among participants regarding the proposal.

II. Presentations

Opening Remarks from Food and Drug Administration
Jin Zhang, FDA Center for Drug Evaluation and Research / Compendial Operations and Standards Staff, shared an overview of why FDA broached the issue of reporting thresholds with USP, and stated their primary concerns and interests in reaching a solution. In particular, Dr. Zhang noted that misalignment between USP's standards and FDA's review processes can lead to adverse impacts on public health by impeding application approval, creating confusion for stakeholders, and potentially leading to enforcement actions despite conformance to USP standards. Dr. Zhang explained that FDA's current thinking on quality expectations aligns with the International Conference on Harmonization (ICH) guidelines (i.e., Q3A/B and M7). Additionally, ICH reporting thresholds are based on the clinical use of the product, rather than the capability of the analytical procedures.

Dr. Zhang provided an overview of factors that, from the agency's perspective, need to be considered in order to bring USP reporting thresholds into alignment with ICH standards, including the following key points:

- Drug substance monographs often cover, and some drug product monograph may cover, multiple products with different indications and maximum daily doses (MDDs).
- It is challenging to align USP reporting thresholds with ICH reporting thresholds when the USP-specified impurity limits are lower than ICH identification thresholds, thereby suggesting the need for reporting thresholds that are lower than the ICH default limits.
- A further complication is that impurity profiles in USP monographs are often based on one or very few sponsors, and they can lack key degradation products that may require lower specified impurity limits. Many USP monographs have been modernized with current analytical procedures, but others continue to lack appropriate impurity standards.
- USP has no access to approved applications' specifications unless the firms are willing to share them with USP. FDA has been unable to share this information with USP.
- USP reporting thresholds are often based on the analytical procedures from sponsors or are developed by USP labs. The method-specific reporting thresholds (analytical capability or LOQ

based) create confusion for monograph users, and this may result in discrepancy between USP and ICH reporting thresholds.
- Special accommodations for reporting thresholds may be necessary for non-ICH products, such as fermentation antibiotics. In addition, special routes of administration (including nasal sprays and ophthalmic products) may require tighter limits for unspecified impurities than ICH identification thresholds, due to high sensitivity of the affected organs.

Dr. Zhang reiterated the recommendation FDA made in its 2020 letter to USP (available here: https://www.fda.gov/media/141063/download) that reporting thresholds be described in a general chapter (e.g., proposed USP General Chapter <476>), rather than being established on an individual basis for each monograph. She added that FDA supports USP's proposal of adding sensitivity solutions in the system suitability tests into monographs without adding reporting thresholds. This use of a sensitivity solution should fulfill the need for checking sensitivity of chromatographic systems.

Overview of USP's Proposed Approach

Nicholas Garito, Principal Scientist, Science-Small Molecules, USP, provided an overview of USP's stakeholder engagement efforts on reporting thresholds since 2019, and described how USP's proposed approach is reflective of the stakeholder input received to date. Mr. Garito began with a brief history of the reporting thresholds within USP, noting that since 2016, FDA has expressed concerns about the inclusion of numeric limits for reporting thresholds in drug product monographs (and in drug substance monographs). In response, in August 2019 USP published a compendial notice proposing the removal of reporting thresholds in *USP-NF* monographs. In November 2020, USP hosted the first reporting thresholds roundtable at which it shared three potential approaches for addressing reporting thresholds in USP monographs for stakeholder feedback.

The roundtable had broad participation from a variety of stakeholders (including manufacturers, trade associations, and consulting firms), though unfortunately FDA was unable to provide comments in the roundtable through the virtual, asynchronous format. Based on the feedback received through the roundtable and in consultation with an advisory panel from USP's Council of Experts, USP decided to pursue a "hybrid" approach to reporting thresholds that would remove prescriptive numeric values for reporting thresholds from monographs and provide some additional guidance for non-applicant users in an informational note in the monographs, suggesting a reporting threshold that may be appropriate. This "hybrid" approach is the basis of USP's proposed "user-determined reporting thresholds" approach. Mr. Garito shared an overview of the key themes that emerged from feedback on the proposed hybrid approach, noting in particular 1) the need for a compromise to address concerns from different users (i.e., "testers" and "submitters"); 2) the need for exclusions for products with complex impurity profiles (e.g., fermentation products, semi-synthetic products); and 3) the need to produce detailed guidance for users to implement the complex (requiring user interpretation) approach.

Mr. Garito walked through an example "mockup" of how the proposed user-determined reporting thresholds would appear within a monograph, highlighting the guidance that will suggest numeric values that may be suitable based on product specific factors known to the user. Mr. Garito also reviewed key points that will be addressed in the General Notices, rather than the monographs, highlighting the following points:

- Rather than making the General Notice applicable across the entire compendium, it will only go into effect when called directly by the monograph.
- The General Notice will provide technical guidance for selecting user-determined reporting thresholds, taking into account the route of administration and the MDD.

- The General Notice will provide guidance for the rational selection of reporting thresholds based on other factors, such as acceptance criteria (e.g., unspecified limit) and the nature of specific impurities (e.g., highly toxic impurities).
- The General Notice will indicate that it is the responsibility of the user to verify the suitability of the analytical procedure used to the level of the "user-determined" reporting threshold. USP will have confirmed the validity of the method to the level of the suggested reporting threshold.

III. Stakeholder Discussion: Feedback on the Proposed Approach

Following the presentations by FDA and USP, participants were invited to share feedback stimulated by the presentations.

In particular, participants were invited to share their reflections on the following question: *Is the proposed strategy for user-determined reporting thresholds in monographs coherent and cohesive? Are there critical gaps? What else might be needed?*

Key points raised during the discussion include the following:

- The proposed approach should be reviewed by a broader group of stakeholders before final decisions are made. Industry stakeholders in particular are going to be interested in seeing the specific guidance included in the General Notices to better understand how USP's guidance relate to ICH guidelines.
- The "hybrid" approach is acceptable in the absence of other agreements, but there are still issues with respect to the variety of generics as well as products not within the scope of ICH Q3A/Q3B (e.g., fermentation products, semi-synthetic products).
- In order to ensure harmonization with ICH, USP should consider including in their General Notices the ICH table and note that different reporting thresholds are applicable for particularly toxic impurities. Additionally, USP should ensure that the General Notice is sufficiently visible.
- More information is needed on how to address mutagenic and potentially mutagenic impurities.
- Some participants expressed concern that two users following the same guidance from USP could ultimately determine two different reporting thresholds for the same product, which may cause issues for FDA reviewers. While there is a need for some flexibility with respect to product-specific factors, ultimately, USP guidance could be in alignment with ICH principles.
- USP General Notices should include guidance on controlling for impurities at low levels, but monographs are limited in the guidance they can provide and some compendial procedures may not be appropriate for detecting impurities at a low level. In some instances, private firms do not use compendial methods, but they still adopt the fixed reporting threshold from the monograph, which may not be appropriate. To avoid this issue, participants suggested some companies may need further education of the expectations for the market and/or a better understanding of ICH principles requiring an understanding of the impurity profile for a product before establishing impurity limits.
- For future discussion, it would be helpful to review sample language for reporting thresholds in the General Notice under the proposed approach.

Participants were then invited to share their reflections on the following question: *The Signal-to-noise ratio requirement in the monograph will continue to be qualified by USP based on a single Sensitivity solution concentration; the concentration may not be aligned with a user-determined reporting threshold. Does this cause concern, and if so, how might those concerns be addressed?*

Key points raised during the discussion include the following:

- Different drug product applications can have different impurity profiles or utilize alternative analytic methods, and monographs frequently miss key impurities. If an end user must utilize a different *Sensitivity solution* concentration (or method for verification) than the one specified by USP in the monograph, then there may be confusion as to whether that user is complying with the monograph. It is essential for end users to understand USP's initial reporting threshold and the level to which the method was validated, to understand how their methods may differ. The value of the sensitivity solution is diminished without the reporting threshold in the monograph.
- While some participants would prefer to keep reporting thresholds in USP monographs, the proposed hybrid approach could be a way forward. It will be important to continue to include reporting thresholds for complex products, such as fermentation products. One option may be to continue to include reporting thresholds in monographs and align them with the highest ICH guidelines for which they are validated, with a note (either in the monograph or general notices) that a tighter reporting threshold could apply for particular highly toxic impurities/higher MDDs.
- If monographs could cover all applications of the standard and all possible impurities, then the inclusion of reporting thresholds in the monograph would not be an issue.
- One path forward may be to continue to include reporting thresholds in monographs and include a caveat for especially toxic impurities.
- European Pharmacopoeia guidelines include general system suitability requirements, as does the related USP general chapter. These general chapters are nearing completion of the harmonization process. Does this jeopardize the monograph harmonization process as well? It would be easier for the end user to fulfill guidelines harmonized between USP and European Pharmacopoeia.
- In the context of ICH Q3A and Q3B guidelines, any harmonized excipient monographs may be out of scope of this application.
- The reporting threshold is not a standalone parameter and should be considered alongside the identification threshold and qualification threshold. Ideally, USP standards should follow the principles of ICH Q3A and Q3B to avoid issues of misalignment in acceptance criteria.
- Reporting thresholds should follow the principles of ICH Q3 and M7. The hybrid approach for reporting thresholds will effectively decouple this parameter from historically approved limits (or values in USP that are not aligned with ICH) and default to the ICH limits. Additional issues (misalignments) between other monograph parameters and their corresponding ICH thresholds may remain.
- It may be worth exploring how to develop guidelines that separate the concepts of sensitivity and reporting thresholds within the monograph, wherein the analytical method sensitivity (LOQ) would be used to establish the sensitivity requirement (a method characteristic) and the reporting threshold could be allowed to vary by product.
- Is it possible to develop four-layer acceptance criteria based on MDD addressing ICH identification and qualifications thresholds, as well?

Participants were also invited to share their reflections on the following question: *What challenges are anticipated with implementing user-determined reporting thresholds in a cGMP environment? How could those challenges be addressed?*

Key points raised during the discussion include the following:

- The user-determined reporting thresholds approach may not provide sufficient guidance for the compliance needs of the end user. For example, companies developing a new product may not

know the MDD. In addition, there may not be sufficient guidance on how to calculate total impurities to report.

- In response to a question on European Pharmacopoeia guidelines, participants explained that the general monograph addresses the requirement that all substances must follow ICH Q3A. In order to develop European Pharmacopoeia monographs, all drug manufacturers are contacted for the approved specifications and impurity profiles of their products, so all products on the European market are covered. Any user of the European Pharmacopoeia monographs has to demonstrate their methods are suitable for the finished product. This is different from the U.S. context. There are complex legal considerations related to the disclosure of proprietary information that inform USP's current approach.
- Some industry stakeholders felt that it would be simplest to keep reporting thresholds in monographs. In order to resolve this tension, USP could consider linking their guidance to the method used, including a "disregard limit" to exclude irrelevant impurities.
- The modernization effort underway at USP will likely address many issues outlined in the FDA's opening remarks, including where there is no alignment between reporting thresholds and the limit for unspecified impurities of degradation products.
- It would be clearer to keep the reporting threshold and the disregard limit (quantitation limit) separate by definition, expanding reportable values to link to analytical solutions and leaving the reporting threshold as a regulatory limit linked to MDD/ICH.

IV. Registered Participants

- Bachem AG
- EDQM, Council of Europe
- Eli Lilly and Company
- EMD Serono
- FDA
- Merck Healthcare
- Novartis
- Olsen Pharmaceutical Consulting
- Organon
- Pharmalytik
- PMcG Consulting
- Raaha LLC
- Sun Pharmaceutical Industries Ltd

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