European Pharmacopoeia Commission Secretariat

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USP - U.S. Pharmacopoeia the Standard of Quality
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RZ/PH/2019-04756L
CV/vn

Strasbourg, 11/10/2019

Subject: **EP Comment on USP Compendial Notices, General Announcement of 13 August 2019 "Reporting Threshold in USP-NF Monographs: Proposed Policy Change for Public Comment"**

Dear Dr MOORE,

In this document, USP proposes a "*policy change pertaining to the inclusion* (more precisely the omission) *of reporting thresholds in drug substance and drug product monographs in order to address the FDA's recommendation*".
EP does appreciate the public health and safety concerns expressed by FDA. However, the proposal to omit the reporting threshold in existing monographs on drug substances and drug products and no longer include it in new monographs in order to address these concerns is a critical deviation from the ICH Q3A and Q3B Guidelines:

1.- Risk of de-harmonisation

The EU as well as the Swiss competent authorities fully embrace the ICH recommendations and guidelines they have signed-off. In addition, ICH Q3A is rendered legally binding by the European Pharmacopoeia general monograph "Substances for pharmaceutical use". If the proposals made in the USP Compendial Notices are approved, the following consequences may result:

- No harmonisation of chapter G-20 Chromatography (currently under discussion in PDG): this would not be possible because the reporting threshold is an important general system suitability requirement in this draft chapter. Deleting this requirement from the general chapter would not be acceptable to EP.
- De-harmonisation of the related substances test in individual monographs on drug substances and/or drug products which have been harmonised between EP-USP (prospective harmonisation) – and no possible future harmonisation of such monographs.

2.- Risk of incorrect determination of the sum of impurities

Omitting the reporting threshold in monographs on drug substances and drug products may also potentially affect public health and safety since the user may find it difficult to determine the sum of impurities correctly as the sensitivity depends on the individual chromatographic system. The use of reporting thresholds is 2-fold

- Criterion for the user to decide whether a peak area or a corrected peak area of an impurity should be included in the total of impurities

- General system suitability criterion to determine whether the user's actual chromatographic system complies with the requirements of general chapter 2.2.46 (USP chapter 621) -> S/N ratio minimum 10 at the reporting threshold/disregard limit (LOQ should be equal or less than the reporting threshold).

Even though the above-mentioned article indicates that alternative sensitivity requirements might be provided in monographs, it is not clear which threshold the user should apply in order to decide which impurities are to be included in the total of impurities.

It is acknowledged that the reporting threshold described in the ICH Q3 A and B guidelines cannot be applied to determine particularly toxic impurities, e. g. DNA-reactive impurities. For such impurities, more sensitive methods and much lower acceptance criteria are required. This requirement is expressed in the ICH Guidelines e.g.:

"For impurities known to be unusually potent or to produce toxic or unexpected pharmacological effects, the quantitation/detection limit of the analytical procedures should be commensurate with the level at which the impurities should be controlled. " [Q3A R2] & *"For degradation products known to be unusually potent or to produce toxic or unexpected pharmacological effects, the quantitation/detection limit of the analytical procedures should be commensurate with the level at which the degradation products should be controlled."* [Q3B R2]

"Identification of impurities present at an apparent level of not more than (≤) the identification threshold is generally not considered necessary. However, analytical procedures should be developed for those potential impurities that are expected to be unusually potent, producing toxic or pharmacological effects at a level not more than (≤) the identification threshold." [Q3A R2] & *"(...), analytical procedures should be developed for those degradation products that are suspected to be unusually potent, producing toxic or significant pharmacological effects at levels not more than (≤) the identification threshold."* [Q3B R2]

To address the public health and safety concerns related to "toxic impurities", and in line with the considerations in the ICH guidelines, the Ph. Eur. Commission has decided to add the following requirement in general monograph 2034 "Substances for pharmaceutical use":

"Specific thresholds may be applied for impurities known to be unusually potent or to produce toxic or unexpected pharmacological effects".

Pro memoria, general monograph 2034 "Substances for pharmaceutical use" is legally binding for any organic or inorganic substances that are used as active substances or excipients for the production of medicinal products for human or veterinary use, whether they are obtained from natural sources or produced by extraction from raw materials, fermentation or synthesis and whether or not they are subject of an individual monograph in the Ph. Eur.

In conclusion, EP would strongly recommend addressing this issue at the level of the relevant ICH EWG rather than implementing the proposal made in the above-mentioned USP Compendial Notices, for the reasons mentioned above.

We hope you find these comments helpful.

Kind regards,

pp

Dr Susanne KEITEL
Director

Mrs Cathie VIELLE
Secretary to the European
Pharmacopoeia Commission

Association for Accessible Medicines

Your Generics & Biosimilars Industry

December 31, 2019

The Association for Accessible Medicines (AAM) acknowledges the efforts of USP on USP's proposal titled, ***Reporting Threshold in USP-NF Monographs: Proposed Policy Change for Public Comment to the USP.*** We would also like to thank you for the opportunity to share our thoughts on this important public health issue.

AAM represents the manufacturers and distributors of finished generic pharmaceutical products, manufacturers and distributors of bulk active pharmaceutical chemicals, and suppliers of other goods and services to the generic pharmaceutical industry. Our members manufacture more than 90% of all generic pharmaceuticals dispensed in the U.S., and their products are used in more than three billion prescriptions every year. Generics represent greater than 90% of all prescriptions dispensed in the U.S., but only 22% of expenditures on prescription drugs. AAM is the sole association representing America's generic pharmaceutical sector.

General Comments:

AAM recommends the continued use of Reporting Thresholds in related compounds methods in order to maintain a clear public standard. The reporting threshold is important in that it assures that industry will have a consistent methodology for incorporation of unknown impurities into the total impurities. This opinion is based upon:

- Need for clarity to generic pharmaceutical companies of data expectations in order to improve access to life saving medicines to the public;
- Assurance that method verification of the USP method by all firms achieve the necessary limit of quantitation;
- Creating a uniform expectation for the uniform reporting of unknown impurities based upon the ability of the methodology to differentiate that impurity from noise;
- The USP is a public standard that reflects the quality standards already approved by the FDA and should be relied upon by industry, physicians and patients.

Firms which develop generic pharmaceutical products need clarity of the requirements to meet the public standard. Analytical methods and specifications are directly related, in that it is important to assure that the method is developed and validated to achieve the accuracy and precision necessary to properly represent the true values. With respect to impurity analyses, it is critical that the method can determine the difference between impurities and noise within the analytical system. The incorporation of reporting thresholds which have been approved in monograph

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sponsors new drug or abbreviated new drug applications will assure that firms report down to a low enough level.

Consistent with ICH Q3A and Q3B low reporting thresholds may be required if impurities are extremely toxic and the USP monograph is a convenient publicly available quality standard to inform all stakeholders. Industry utilizes the USP/ICH reporting thresholds as a guide to identifying the Quantitation Limit (QL) of the method. Having the FDA approved reporting threshold in the USP monograph, provides industry with an indication of the expectations of the QL that FDA would consider acceptable for the method. Without the reporting threshold in the USP monograph, industry may submit a method with a QL that does not meet FDA's expectations. For example, an applicant submits a method with a QL of 0.03% and FDA may request the applicant to resubmit to establish the QL at 0.01%. In this case, it will require the applicant to revalidate the method and re-assess all the impurity data provided in the submission, including stability. It may also require the applicant to expend time and resources in identifying minor peaks. All of which would increase the cost of the drug, but more importantly, potentially delay the availability of generic medicines to the patient. Therefore, reporting thresholds, provides for a uniform expectation for firms to verify that their execution of the USP or house method can achieve the necessary limit of quantitation to accurately report both individual and total impurities.

AAM acknowledges that there will be instances where the public standard will need to be changed based upon new learnings or new drug products that will be introduced using the same drug substance. AAM encourages the use of the available procedures such as the pending monograph procedure so that the FDA can assure that as standards evolve and change, all stakeholders are able to participate and be included in the process. The Agency should utilize the USP, as it is a useful tool, to communicate public quality standards and expectations.

Lastly, AAM would like additional clarity to the impact, if any, to the following:

- For approved products where USP monographs are revised to remove the reporting threshold?
- Will industry need to re-evaluate the reporting threshold in the impurity methods that were already approved by FDA based on the previous version of the USP monograph?

In conclusion, AAM appreciates the opportunity to provide comments and looks forward to further dialogue with the USP on this topic.

Sincerely,

David R. Gaugh, R.Ph.
Senior Vice President for Sciences and Regulatory Affairs

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CHPA CONSUMER HEALTHCARE PRODUCTS ASSOCIATION
founded 1881

December 19, 2019

Elena Gonikberg, Ph.D.
Principal Scientific Liaison
US Pharmacopeia ("USP")
12601 Twinbrook Parkway
Rockville, MD 20852-1790

RE: **USP General Announcement: Reporting Threshold in USP-NF Monographs**

On behalf of the Consumer Healthcare Products Association (CHPA), a 138 year-old trade association representing the nation's leading over-the-counter (OTC) medicine and dietary supplement manufacturers, we submit these comments on the proposal to delete reporting thresholds in drug substance and drug product monographs without republishing the monographs for comment and to no longer include reporting thresholds in PF proposals for drug substances and drug products as part of the modernization of organic impurities testing. The OTC industry currently has a number of products that are, potentially, directly affected by this change.

We understand that the U.S. Food and Drug Administration (FDA) requested that reporting thresholds not be included in drug substance and product monographs because compendial monographs are not intended to identify every impurity and degradation product. FDA expressed concern that the inclusion of reporting thresholds could result in toxic impurities not being identified and/or reported.

We recognize that reporting thresholds for drug substances and products vary based on product-specific factors and could be addressed as an application assessment issue. It is understood that FDA uses ICH reporting thresholds as a guideline and deviates from them as needed based on application-specific considerations. However, expectations for establishing a reporting threshold for non-application products where the FDA is not reviewing and approving the impurity test limits are not addressed (or specifically excluded) in the USP General Announcement. For non-application products, individual companies manage the reporting threshold(s) for their drug substances and products (presumably to ICH limits). Yet, as described in the notice, there may be instances where an impurity needs to be controlled to levels lower than ICH.

We recommend that the USP maintain the practice of including reporting thresholds in monographs and follow the standard PF proposal and comment process for the proposed removal of reporting thresholds in order for the OTC industry to provide input, when needed. Additionally, we recommend that reporting thresholds for current monographs be maintained and specifically note within the USP-NF that for OTCs marketed without an ANDA, individual companies are required to manage the reporting threshold(s) for their drug substances and products when using a reporting threshold lower than stated in a monograph or for a monograph that does not contain a reporting threshold.

USP standards are continually in a state of revision with varied impact across the industry. As USP knows, CHPA supports improving compendial methods and establishing product standards which can provide an additional measure of safety for OTC products. However, the USP proposal to implement this change is not appropriate because of the scope and breadth of OTC monograph products impacted. Ideally the implementation would follow the normal time lines for the comment period and publication of final revision.

We are available to further discuss the substantial impact to the industry so that a process for implementation can be presented to the public as a recommended path forward.

Best regards,

John S. Punzi, Ph.D.
Senior Director Quality Assurance and Technical Affairs

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NJPQCA

New Jersey Pharmaceutical Quality Control Association

December 31, 2019

Elena Gonikberg, Ph.D., Principal Scientific Liaison
United States Pharmacopeial Convention
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E-mail: EG@usp.org.

Subject: Reporting Threshold in USP–NF Drug Product Monographs: Proposed Policy Change
Reference: USPNF Website: [General Announcement; Posting Date: 07-Nov-2019; Comment Deadline: 31-Dec-2019]

NJPQCA is an organization whose membership encompasses pharmaceutical industry professionals from four states in the New Jersey area, and some additional states, with a mission to encourage and stimulate dialogue among Quality Assurance/Control and Regulatory Compliance professionals by providing forums and networking opportunities for the exchange of views on technical topics and regulatory issues relevant to the pharmaceutical industry. The NJPQCA Compendial Discussion Group is comprised of about 50 professionals responsible for monitoring compendial changes at about 20 pharmaceutical companies. Most of the pharmaceutical companies represented are global companies.

NJPQCA would like to provide the following comments and recommendations regarding the proposed policy changes on reporting threshold from USP-NF monographs.

- NJPQCA appreciates the USPC's decision to post the draft policy for clear communication and stakeholder feedback. We recommend this as a best practice for future policy development activities.

- In general, NJPQCA supports the policy which simplifies monograph content, promotes international harmonization through ICH guidelines and allows industry flexibility to apply material/product specific knowledge to regulatory commitments. If implemented properly, this policy can reduce resources to maintain monographs and reduce conflicts between different Pharmacopoeial organizations.

- We would like to discuss the following recommendations to ensure appropriate USP implementation that supports monograph simplification and ICH harmonization. Additional recommendations to expand on the benefits of the prospective policy, including comments related to the introduction of 'sensitivity solutions' are also presented for USP consideration:

1. Policy Impact:
    a. If the limit for total impurities was based on the existing reporting threshold in the monograph and the policy results in adopting a lower reporting threshold, then the possible impact to the limit for total impurities needs to be considered with the deletion of reporting threshold from the USP monographs. For example, deletion of reporting thresholds may result in compliance issues, namely failures of APIs and/or drug products to meet USP monograph requirements. This may result in drug shortages, which could put more stress on the drug shortage situation in the United States.

    b. The elimination of reporting thresholds alone will not resolve FDA's concern. Even with flexibility in reporting thresholds, impurity assessments per ICH Q3A/B are still a critical aspect of an API/product impurity control strategy (e.g., consideration for an application to address identification thresholds, see sections 3.b. and 4.a. below for more details/recommendations).

    c. FDA has indicated that Reporting Threshold should be addressed as an application assessment issue; however, they have not indicated how they would address products that do not have applications (i.e., OTC-monograph products).

2. Revision:
    a. Public Review of Monograph Changes: The proposed policy changes have a potential to impact established materials/products and must go through public review to assure both the intended change is applied appropriately and secondary impact can be assessed. For example, a reduction in the reporting threshold may require a change in the acceptance criteria for Total Impurities. Additionally, the USP's plan for handling currently official monographs (with Reporting Threshold, including those with disregard limits or similar terminology) for marketed products and their respective API(s) could go on for years and may never be updated. We strongly recommend that any such changes to these monographs should go through the routine PF process to allow for public comment. A Compendial Notice of this magnitude may not have garnered enough attention for impacted manufacturers to comment. Publishing individual monograph revision proposals in PF would hopefully gain more attention.

    b. Sensitivity Solutions: USP plans to continue to include the sensitivity solution in monographs. It is not clear if the presentation of sensitivity solutions in USP monographs, as a system suitability requirement, will represent the "new" Reporting Threshold. Nonetheless, the suggested application of a specified sensitivity solution as thresholds will vary based on application. A solution presents itself with further harmonization of <621> Chromatography. Addition of a default system suitability criteria equivalent to Ph. Eur. 2.2.46 Chromatographic Separation Techniques would provide for confirmation of method sensitivity and continue to promote simplified monograph content.

Unless otherwise prescribed, in an organic impurity test, the limit of quantification (corresponding to a signal-to-noise ratio of 10) is equal to or less than the disregard limit (see general notices).

3. Implementation: General Notices application – With the simplification of the monograph content, clear directions/guidance needs to be added to the general notices.
    a. USP standards are minimal standards for compliance. If a company needs to control an impurity at a lower level than the Reporting Threshold, then this would constitute a higher standard than the USP monograph, which is an acceptable and expected practice. We recommend stronger language in the General Notices (e.g., in section 5.60.10), consistent with the Ph. Eur., to put the onus on the manufacturer to ensure that toxic impurities are controlled by the manufacturer even if not detected/controlled via the USP monograph.

    b. USP has not provided any plans for how this new strategy would be implemented within monograph modernization or with plans to revise <476>. ICH guidelines Q3A and Q3B contain general content on managing potential toxicity of organic impurities and thresholds. Analysis needs to be specific and the methodology is defined in the monographs and/or regulatory filings. As such, it is recommended that the proposed chapter <476> Control of Organic Impurities in Drug Substances and Drug Products is not adding any unique value over the established ICH guidelines and can be replaced by suitable application reference in general notices.

    c. We recommend the General Notices Project Team (GN PT) be engaged in the discussion and development of the appropriate language that captures the above-discussed implementation approach.

4. General:
    a. Broader Organization and Scope - There has already been a considerable amount of work performed on monograph modernization to date. While the USP is not suggesting modifying all monographs in one sweeping change with this policy, this does open further modifications for many monographs. We suggest USP consider expanding the policy to consider applications to identification thresholds as well. The broader scope will group similar threshold guidance content into monograph revision activities.

    b. Scope and timing – ICH Q3A and Q3B have very specific scope of materials and products. The application of a USP policy needs to match this application. Additionally, ICH is very specific about timing of application for the guidelines. Therefore, the current USP monograph reporting threshold may represent the appropriate and approved level. In addition to recognition of ICH, established regulatory commitments need to be acknowledged to allow for variance (higher and lower) established between the regulatory agency and specific regulatory filing.

c. Dual use excipients – Dual use excipients have the potential of being both in scope and out of scope of Q3A. For clarification purposes, we recommend the proposed policy to include discussion of a clear position on how dual use excipients will be managed.

d. Concerns were also raised at the October 24th Prescription/Nonprescription Stakeholder Forum with regard to process issues for how this change is being handled. Please refer to the slides and discussion during the P/NP for more details.

While the elimination of reporting thresholds from individual monographs addresses the FDA request, it is our belief that information must be added into the General Notices so the important use of reporting thresholds by those who follow the standards in USP are indicated, to ensure appropriate control of impurities in drug products and APIs. The absence of appropriate reporting thresholds puts at risk the release of materials that meet overall quality requirements, but may not meet the limits for total impurities. Not including this information in the General Notices also puts at risk disharmonizing those monographs that have been prospectively harmonized with other pharmacopoeias. The absence of information on reporting thresholds also risks misalignment with the ICH Q3A and Q3B guidance on impurities. The General Notices should clearly and consistently reflect the information on reporting thresholds that are provided in the ICH documents. To address safety concerns with highly toxic impurities, additional information could be added to the USP General Notices to indicate that lower limits for these particular impurities may be appropriate, depending on the risk of their presence in specific materials or products.

In summary, we understand that FDA is ultimately concerned with the safety of patients, and we share that concern, but we feel that the General Notices approach would put the responsibility for control of toxic impurities where it belongs – on the manufacturer. In addition to flexibility/simplification of monographs contents, the above approach and recommendations will help enhance clarity (applications/scope), promote international harmonization (i.e., ICH, compendial, etc.) and avoid potential compliance issues that may result to drug shortages in the United States.

NJPQCA appreciates the opportunity to comment on the proposed policy changes on reporting threshold from USP-NF monographs, and we hope that USP takes our comments and recommendations into consideration.

Sincerely

Hantz Tattegrain
Chair, NJPQCA Compendial Discussion Group

BPTF
Bulk Pharmaceuticals Task Force

Submitted electronically to eg@usp.org

December 12, 2019

Elena Gonikberg, Ph.D.
Principal Scientific Liaison
US Pharmacopoeial Convention
12601 Twinbrook Parkway
Rockville, MD 20852-1790

RE: Comments on Reporting Threshold in USP-NF Product Monographs: Proposed Policy Change

Dear Dr. Gonikberg,

The Bulk Pharmaceuticals Task Force (BPTF) is a U.S.-based association for manufacturers of active pharmaceutical ingredients, excipients, and pharmaceutical intermediates. Our primary objective is to seek clarification of the current regulatory requirements for our products and to interact with government agencies on emerging issues that may impact members. BPTF's membership includes manufacturers with foreign as well as domestic facilities, and both large and small business entities.

The members of the BPTF organization understand the concept of a complete and thorough impurities evaluation, based on the specific manufacturing process for the monograph product. And we acknowledge that the identification and reporting limits in ICH Q3A/B do not apply to compounds that are potentially genotoxic, as listed in ICH M7.

However, we are not certain that removal of listed reporting impurities threshold limits in drug substance monographs will accomplish the stated goal of a more thorough impurities evaluation. Additionally, we are concerned about some potential unintended consequences from this proposed change.

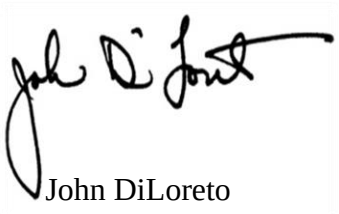
What will be the quality of a drug substance labeled as, "USP"? This may now be company specific. Some companies will continue to follow ICH Q3A/B guidance. However, there are now other allowed definitions, with the rationale that the limit is not defined until the drug product application. For example, the reporting threshold may be defined by the LOQ of the analytical method. For older products with older methods, or products without USP defined impurities methods, the lack of defined reporting threshold may in fact increase the allowed limits of impurities.

The stated request from the FDA was to encourage drug substance quality to be evaluated in a drug product application. This is ultimately true, even now, as the drug substance is not reviewed independent of a drug product application. Drug substance manufacturers may have many customers for a single product, and frequently do not have details of the formulation or dose. The inclusion of ICH Q3A/B reporting threshold provides a consistent quality of drug substance for USP labeled compounds. Additional specifications may be requested by customers, when needed for the specific formulation and dose.

The stated goal of the USP proposal is to address the FDA concern related to toxic impurities. An alternative method to ensure that toxic impurities are addressed, may be to consider instead of removing ICH Q3A/B reporting thresholds, a clear statement of the applicability of ICH M7 risk evaluation and controls.

BPTF would like to thank you for this opportunity to provide these comments. If you have questions or comments please feel free to contact me.

Sincerely,



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Elena Gonikberg

[redacted]

Subject: CPI PT Comments on Reporting Thresholds Process

Dear Dr. Gonikberg,

The Compendial Process Improvement Project Team (CPI PT) considers the USP query on reporting thresholds to be an important topic. To meet the requested timelines, the following comments are from the individual industry representatives participating in the direct CPI PT discussions.

We support the decision to post the draft policy for broad communication and stakeholder feedback, as was provided in the August and November Compendial Notices. We view this as a best practice for future policy development. Stakeholders need the opportunity to review the final content of a policy, therefore we support further compendial notices to complete the development process before implementation. Additionally, we encourage building in a measure of success to ensure the policy is adding the intended value to provide confirmation and ongoing improvement (e.g., USP Prospectus Process evaluation). For future consideration with any policy or proposal, in addition to core information (Intended Improvement, Proposed Policy, etc.) stakeholders look for practical application information to understand and respond appropriately (Intended application/specific scope, Supporting content documentation – General Notices, etc.).

Regarding the proposed policy, we strongly encourage USP to post each monograph revision associated with documentation of reporting thresholds in PF to ensure that it receives appropriate attention through the review process. This policy has a potential to impact established material/product requirements not only through the reporting threshold, but secondary impact to the acceptance criteria for Total Impurities also needs to be considered.

Finally, we support international harmonization through alignment with ICH guidelines in a manner that allows industry the flexibility to apply material/product-specific knowledge to regulatory commitments. A benefit of this approach is that it can reduce resources to maintain monographs and reduce conflicts/differences among the various Pharmacopoeial organizations.

The CPI PT is available to support further discussions with the USP on this policy.

Best Regards,
CPI PT

Reporting Threshold in USP-NF Monographs: Proposed Policy Change for Public Comment

General Announcement

The meaning of Reporting Thresholds in Monographs

With the introduction of the ICH Guidelines Q3A and Q3B a suitable approach for the reporting of organic impurities by experts in toxicology was introduced. The daily doses for drug products are already considered in Q3B.

The reporting thresholds are applicable for the determination and quantification of organic impurities in new drug substances and drug products as well in applications of pharmacopoeial monographs defined as the *reporting threshold* or a *disregard limit* and have well proved their practical virtues.

There are a number of distinct benefits of retaining reporting thresholds in monographs for establishing compliance with the pharmacopoeial standard;

1. In general, reporting thresholds are suitable for the verification of pharmacopoeial analytical procedures, e.g. for the preparation of system suitability solutions for ensuring that limits of quantitation and detection are met. It should be also noted that pharmacies or hospitals should be able to apply the monographs, e.g. for the preparation of drug products like infusion solutions. The reporting threshold is a suitable and important tool for the quantification of impurities

2. For impurities in monographs which don't fall under the conditions of the ICH Q3A and Q3B Guidelines, it is the responsibility of the manufacturer of an API or a medicinal product to justify suitable S/N ratios or even lower reporting thresholds for the respective impurities e.g. according to the current ICH M7 Guideline. In many cases analytical procedures with higher sensitivities may be necessary for the determination of e.g. class I or class II impurities. It is not the objective of monograph procedures for "Related substances" to control toxic or mutagenic impurities. Examples know from the past (e.g. bis-tryptophan or nitrosamines) would not have been detected by related substances methods.

3. Furthermore, the reporting threshold plays an increasingly important role with respect to the potential harmonisation of pharmacopoeial monographs (Ph. Eur. USP, JP etc.).

In conclusion, it is strongly recommended to maintain the reporting threshold for a clear definition of reporting impurities in pharmacopoeial monographs.

Elena Gonikberg

[redacted]

Subject: Reporting Threshold in USP-NF Monographs: Proposed Policy Change forPublic Comment
Attachments: reporting-threshold-proposed-chan.pdf

Hello Dr. Elena,

This is pertaining to General announcement for " Reporting Threshold in USP-NF Monographs: Proposed Policy Change for Public Comment ". We would like to informed that we have go thru the subjected Proposed Policy.

Proposal for removal of Reporting threshold from the monograph seems acceptable as it can be vary with product-specific factors as quoted in the proposed policy.

We have comment for USP proposal i.e. *" USP will continue including a sensitivity solution and signal-to-noise requirement in monographs, to ensure that the sensitivity of the equipment is sufficient to reliably integrate any impurities that are included for calculating the total impurities result."* We want to bring in to your notice that every applicant is establishing LOD-LOQ values based on Impurity specification limit, sensitivity of the method & equipment. Applicant use the same LOD-LOQ values during the calculation of impurities. In view of this, it is not require to include Sensitivity solution & signal-to-noise requirement in the USP monograph method.

Regards,
Jigesh

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We make healthy possible

|Jigesh Shah |General Manager-Analytical R & D|
|Amneal Pharmaceuticals Co. India Pvt. Ltd. |Oral Solid Dosage Unit |Plot No. 16 & 17, PHARMEZ Special Economic Zone|
[redacted]
|

Elena Gonikberg

[redacted]

Subject: RE: Compendial Notice Reporting Threshold

Dear Elena,

NTO-LI would like to provide comments related to the recently proposed policy change for reporting threshold in USP-NF. Our specific concerns are summarized in the following section:

Reporting Threshold:

- *Where will the reporting threshold expectations be defined, only ICH or in USP as well?*
- *How is the sensitivity solution defined if reporting threshold is less than sensitivity solution in monograph? Will there be multiple sensitivity solutions for different impurities based on toxicity levels?*
- *Are all peaks below LOQ and/or sensitivity solution expected to be reported in Total impurities?*
  - *This can have a major impact on Total impurities as well as prompt addition of impurities.*
- *We request an extended time to comply with this policy for method development and validation purposes (more than 6 months).*
- *If genotoxic impurities are controlled by manufacturer in API, are finished product manufacturers required to test for these impurities or is a justification sufficient?*
- *Are you planning to include genotoxic impurities (if any) in USP monographs?*

Kind Regards,

Desiree Hudson
Scientist II, AS&T

[redacted]

Novartis Technical Operations / Solids
60 Baylis Road
Melville, NY 11747-0103 USA

Elena Gonikberg

[redacted]

Subject: Comment on the PF Reporting Threshold in USP-NF Monographs: Proposed Policy Change for Public Comment.

Dear Dr. Gonikberg,

I would like to comment on the PF titled "Reporting Threshold in USP-NF Monographs: Proposed Policy Change for Public Comment".

The proposed policy addresses only partly the concern expressed by the FDA in the following statement:

"…, the FDA is concerned that the inclusion of reporting thresholds could result in very toxic impurities not being identified or reported."

Explanation:

The sensitivity solution will remain in the monograph and this is a definite and highly positive analytical requirement. This implies that the analytical chemist can only quantify imps at and above this level.

Therefore, we need to distinguish two possibilities:

a. A potential potent impurity happens to be at a level between the Sensitivity Level and the Reportable Level: in this case, the analytical chemist will report this potent impurity and possibly identify it. This answers the FDA concern.

b. A potential potent impurity happens to be at a level lower than the Sensitivity Level: in this case, the analytical chemist will, in the absence of a Reportable Level, have to report all imps that are at any level above the sensitivity level and the reporting of this toxic impurity will be missed. Here,

the FDA concern still remains since the Chemist cannot quantify reliably a level below the Sensitivity Level.

Kind regards!

Raphy

Raphael (Raphy) Bar, Ph.D.
BR Consulting

Elena Gonikberg

[redacted]

Subject: Reporting Threshold in USP-NF Monographs: Proposed Policy Change for Public Comment

Dear Elena,

AbbVie is submitting comments regarding the proposed policy change for reporting thresholds in USP-NF monographs.

AbbVie understands the reason for replacing the reporting threshold (disregard limit) from drug substance and drug product monographs with a sensitivity solution corresponding to the reporting threshold. The concentration of the sensitivity solution for disregarding purposes should be based on approved specifications, ICH reporting thresholds and the method quantitation limit.

Because of the differences in manufacturing processes, different impurity profiles can be obtained which result in different controls that may be needed. For this reason, there should be an allowance to adjust the concentration of the sensitivity solution in the monograph or information should be included in general chapter <621> Chromatography to allow for the proper controls to be used.

As stated in the USP General Announcement on 13-Aug-2019, the FDA is concerned that the inclusion of the reporting thresholds could result in very toxic impurities not being identified or reported and because the FDA uses ICH reporting thresholds as guidelines and deviates from them as needed based on application specific considerations, the allowance for an adjustment of the sensitivity solution concentration that is given in a specific monograph for a lower limit should be included. The sensitivity solution represents the minimum requirement based on the approved specifications that are included in the monograph.

As mentioned, some impurities may not be included in the monograph and may be unique to a manufacturer and require a lower specification limit. For this reason, a reference could be included in USP General Notices to allow for additional impurities that are detected by the method, which have lower specification requirements.

AbbVie supports the development of a new USP General Information Chapter that includes test methods for the detection of impurities e.g. nitrosamines, and other known toxic impurities, that require lower detection levels outside of the typical monograph methods.

Thank you for the opportunity to comment on the proposed change for the policy. As always, it is a pleasure to participate in the standard setting process.

Regards,

GREG J MATHIEU
Associate Director, Compendia and Analytical Services
Corporate Compendia Liaison

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[redacted]

[redacted]

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Elena Gonikberg

[redacted]

Subject: Reporting Threshold in USP–NF Monographs: Proposed Policy Change for Public Comment [MARKETING]

Hello Dr. Gonikberg

My name is Lee Stockdale and I am contacting you on behalf of the Teva Florida site.

In response to the public comment for the reporting threshold in USP NF monographs we ask for clarification on the following.

1 We understand that the USP will remove the reporting threshold from all monographs, if the proposal goes thru. For many of the analysis we perform this will make integration very difficult, as some monographs analyze at a very low wavelength. (Clarithromycin UV@205 nm) The reporting thresholds really helps us on a day to day basis to integrate peaks of interest, not noise from the methods.

2 We also ask about the limit of quantitation studies we perform in the validation of analytical methods using <1225> and Verification <1226>
How will the removal of reporting thresholds impact these General Chapters Limit of Quantitation studies?
As an alternative, could the lack of reporting thresholds be stated in the monographs that have potential to produce potentially harmfull degradants?

3 The posting indicated that the FDA requested the reporting threshold to be removed from the drug product monographs.
The list of the impacted monographs included drug products and APIs.
Is the USP expanding the removal of reporting thresholds from drug products to include removal of reporting thresholds from APIs also?

We look forward to the public commentary and working with the USP to improve the standard.
Thanks
Lee

Elena Gonikberg

[redacted]

Subject: Comments on the Proposed policy change in the reporting threshold in USP monographs
Attachments: Comments on Proposed policy change in reporting threshold.docx

Dear Dr. Elena Gonikberg

Greetings!!

The communication is in reference to the proposed policy change in the reporting threshold in USP monographs posted as a general announcement dated 13-Aug-2019.

Based on the review of proposed changes in the policy, few comments are being shared in the attached word file for which clarification is needed from the USP.

Recommendation from our side on USP proposal is also mentioned along with the comments in the said file.

I shall appreciate to have your comments/clarification on the listed points.

Also, look forward for your kind consideration to our recommendation on the USP proposal.

Thanks for your time.

Best Regards

Amarpreet Kaur
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Analytical Research
Sun Pharmaceutical Industries Ltd.
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Please consider the environment before printing this email

The communication is in reference to the proposed policy change in the reporting threshold in USP monographs posted as a general announcement dated 13-Aug-2019.

Following are proposed in the policy for reporting threshold:

1. USP will delete the reporting threshold from section of acceptance criteria of monographs of drug substance and drug products

2. USP will continue to include sensitivity solution and signal to noise ratio requirement in the monographs for both drug substances and drug products.

The interpretation of these two changes is summarized as:

- As reporting threshold will no longer be applicable implies that all impurities which are quantifiable will be reported
- The Sensitivity Solution will continue to remain part of monographs

Clarification needed from USP on the following:

- Currently the concentration of Sensitivity solution is at reporting threshold level
- If reporting threshold is removed, will the sensitivity solution continue to remain at same concentration as in existing monographs
- Does this indicate that the purpose of the sensitivity solution will only be for system suitability assessment?
- As reporting threshold will be deleted from the monographs , the impurities which were being disregarded till now , with this revised policy all the impurities would be reported under Total impurities which will have impact on Total impurities. In view of this, will the limit for Total impurities be relaxed on implementation of this policy.

To elaborate we are citing some example from the current USP monographs.

Project	Monograph	Conc. of Sensitivity solution (% w.r.t. sample conc.)	Level of Reporting threshold	Remarks
Atomoxetine capsules	PF-44(1)	0.1	0.10%	• Requirement for reporting threshold would be deleted. • Will the conc. of sensitivity solution be 0.1 % • Or conc. of sensitivity solution be revised.
Rabeprazole Sodium	PF-45(3)	0.05	0.05%	• Requirement for reporting threshold would be deleted. • Will the conc. of sensitivity solution be 0.05 %. • Or conc. of sensitivity solution be revised.

Our Recommendation on USP Proposal:

- Impurities observed at level below the concentration of sensitivity solution should not be reported

Additionally, USP should evaluate the impact of this policy on USP general chapter <476>, where it is mentioned as “Unless otherwise indicated, total degradation products in the drug product monographs are the sum of all specified and unspecified degradation products **above the reporting threshold**”.

Mark G. Schweitzer, PhD
Global Head AS&T and
Scientific Initiatives
Novartis Technical Operations
Quality

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NOVARTIS

To Elena Gonikberg, Ph.D.
Principal Scientific Liaison
United States Pharmacopoeia
12601 Twinbrook Parkway
Rockville, MD 20852-1790

Copy To

November 11, 2019

Concerning **Reporting Threshold in USP-NF Monographs: Proposed Policy Change**

Dear Dr. Gonikberg,

Proposed Novartis Response:
In response to proposed USP policy change: Reporting threshold in USP-NF monographs published 13 Aug 2019, Novartis would like to provide the following comments.

- Novartis supports the removal of the reporting thresholds for the reasons summarized in the published policy change. However, with the implementation of risk assessments, e.g. route of synthesis assessments and potential cross-contamination assessments, the understanding of potential toxic impurities is greatly enhanced. Driving routine analytical limits lower than currently described in ICH Q2 is not warranted. We are concerned that if the intent is to introduce requirements to significantly lower the identification and qualififcation thresholds, the broad availability of medications to patients is at risk.
- The recommendation to include a sensitivity solution in the organic impurities method(s) is also a positive step to ensure that the methods included in the specific monographs are suitable for their intended purpose and provides a positive confirmation of the level at which the organic impurities need to be quantified. However, we encourage USP to establish the reporting limit as not less than the limit of quantitation of the relevant analytical procedure.
- We would also recommend that the concept of the sensitivity solution be maintained for targeted analyses, such as those for quantitation of potential genotoxic impurities to ensure that the test procedure included in the monograph is fit for purpose. In this way, the sensitivity solution would have broader applicability than just to determine which impurities should be included in the calculation of the total organic impurities.
- Simple inclusion of S/N ratios in our opinion requires additional description related to the specific definition intended by their use. For example, the S/N ratio defined in the monograph should be associated with the Limit of Quantitation (LOQ) of the analytical

NOVARTIS

procedure. The globally acceptable definition of the LOQ is peak responses S/N $\geq$ 10. Attempts to define sensitivity solutions lower than this level in our opinion would imply reliability of data below the LOQ which is not the case. The policy change should in our opinion clearly state that measurements below the LOQ are unreliable due to the high inherent variability of the analysis at levels below the LOQ. .

- Finally, while not explicitly stated in the notice of policy change, Novartis assumes that the limits for specified impurities and degradation products would be aligned with the approved specification limits for comparable API and drug products (aligned with FDA approved limits).

If you have questions or require clarification of any of the comments provided, please contact me directly. Thank you in advance for your consideration.

With best regards,

Schweitzer Mark

Digitally signed by Schweitzer Mark
DN: dc=com, dc=novartis, ou=people, ou=TO, serialNumber=1814900, cn=Schweitzer Mark
Date: 2019.11.11 16:47:46 -06'00'

Mark G. Schweitzer, Ph.D.
Global Head AS&T and Scientific Initiatives
Novartis Technical Operations Quality

kinapse

a SYNEOS HEALTH company

November 13, 2019

Elena Gonikberg, Ph.D.,
Principal Scientific Liaison
United States Pharmacopeia

Subject: Reporting Thresholds in USP-NF Drug Product Monographs: Proposed Policy Change for Public Comment, Posting Date 13-Aug-2019.

Dear Ms. Gonikberg,

Kinapse, a Syneos Health™ company, is pleased to submit comments on the proposed United States Pharmacopeia's (USP) policy changes related to reporting thresholds in USP-NF Monographs of Drug Substances (DS) and Drug Products (DP). Kinapse is a global technology-enabled service provider, offering expert advisory, capability building and operational solutions to life sciences organizations across the R&D and Commercialization life cycle. As a regulatory consultancy, we have significant expertise in strategy, authoring and submission of CMC dossiers including critical aspects of analytical method development for drug substance and drug products.

Kinapse welcomes the USP commitment to ongoing modernization, in which the USP is updating organic impurities testing for articles subject to USP–NF standards and USP policy change pertaining to reporting thresholds in USP-NF Monographs.

In relation to the proposed policy changes for reporting thresholds, Kinapse has a number of suggestions/recommendations for consideration:

- *Monographs could reference USP <476> and USP <1086> chapters in their organic impurities section*- As per the current USP approach, USP-NF monograph impurities tests with specifications for total impurities or total degradation products in many cases include a reporting threshold consistent with the ICH guidelines. The new USP <476> chapter (which is still in draft stage) on control of organic impurities in drug substances and drug products uses current scientific and regulatory best practices for controlling organic impurities. The USP <476> and USP <1086> chapters directly align with ICH guidelines including ICH M7 (genotoxic impurities). During the development of impurity control strategies, ICH guidelines will be followed and sound scientific principles applied. Therefore, we understand that the USP approach is aligned with ICH hence it is acceptable to remove reporting thresholds from the USP-NF Monographs.

- Please include disregard limit along with reporting threshold in the text of the proposed policy change for better clarity because reporting threshold is presented as disregard limit in USP-NF Monographs e.g. 'reporting threshold (i.e. disregard limit)'.
- As per the text included in the proposed USP policy change, the US FDA is concerned that the inclusion of reporting thresholds could result in very toxic impurities not being identified or reported. We propose that the USP expert committee include examples of toxic impurities not being identified or reported along with name of the drug substance/drug product in the proposed USP policy change statement. This would help applicants to be more conscious in identifying and reporting toxic impurities in the registration applications. This is consistent with ICH M7 and related guidance.

Given the points outlined above, Kinapse requests USP expert committee to consider these suggestions on policy changes related to reporting threshold in USP-NF Monographs. If you have any questions regarding Kinapse's comments or would like further information, please contact deepti.jagga@kinapse.com.

Sincerely,

Deepti Jagga
Senior Manager, Regulatory Affairs Operational Services
Kinapse, a Syneos Health™ company

SANOFI

Proposed Policy Change: Reporting Threshold in USP/NF Monographs

Pharmacopoeia: ***USP*** ***Reference***

General comment(s) if any

Paragraph / line N°	Comment / Rationale	Proposed change / suggested text
As part of our commitment to ongoing monograph modernization, USP is updating organic impurities testing for articles subject to *USP–NF* standards. Our approach applies the ICH Q3A/B-based limits for identification and reporting of organic impurities and degradation products in drug substances and drug products. Currently, USP drug substance and drug product monographs' impurities tests with specifications for total impurities or total degradation products will in many cases include a reporting threshold consistent with the ICH guidelines. In addition to setting criteria for a peak to be included in the total impurities, the reporting threshold also aligns with the approach to	The concerns raised by FDA are fully understood and the risk that very toxic impurities are not identified and reported is seen. However, the proposed deletion of the reporting thresholds in compendial monographs is not seen as an efficient measure to solve this issue for the following reasons: 1) The methods in question were developed to test on related substances originating from the synthesis or degradation of the drug substances during synthesis, storage and use in the drug product. The specificity and sensitivity of the methods were optimized with regard to	**The policy change should not be implemented.**

Paragraph / line N°	Comment / Rationale	Proposed change / suggested text
verify the system sensitivity. Monographs with recently modernized or new impurity procedures are expected to contain a sensitivity solution at a concentration corresponding to the reporting threshold, and a signal-to-noise requirement as a part of system suitability requirements. This approach is used for both drug substance and drug product monographs. Beginning in 2016, the U.S. Food and Drug Administration (FDA) provided comments requesting that reporting thresholds not be included in drug product monographs. Since compendial monographs are not intended to identify every impurity and degradation product, the FDA is concerned that the inclusion of reporting thresholds could result in very toxic impurities not being identified or reported. The FDA commented that reporting thresholds for drug products vary based on product-specific factors and should be addressed as an application assessment issue. FDA uses ICH reporting thresholds as guidelines and deviates from them as needed based on application specific considerations. FDA has recently notified USP that the same public health and safety concerns regarding the inclusion of reporting thresholds would also be applicable to drug substance monographs. Since a drug substance may be used in different products with different maximum daily doses, ICH Q3A limits (including reporting threshold) will vary due to product specific factors and should also be addressed as an application assessment issue. To address the FDA's recommendation, USP is proposing the following policy change pertaining to inclusion of reporting thresholds in drug substance and drug product monographs which is presented here for a 90-day public comment period. 1. For the impacted monograph proposals, the Expert Committees will have an option of deleting the proposed reporting threshold at the ballot, without republishing the	the detection and quantification of these related compounds in ranges down to about 0.01 % of the main compound. If UV is used as the most common detection mode the detection wavelengths were in most cases selected to detect compounds showing absorbance of comparable intensity than that of the main compound or of known related compounds. The intended use of these methods is not to detect trace amounts, which would be necessary to determine and limit very toxic impurities. 2) The deletion of the reporting thresholds will lead as consequence to the reporting of all minor peaks as related compounds and a slight increase of the sum of impurities, when the chromatograms are evaluated. As there will be no limitation of these minor impurities and no requirement to evaluate the nature of these impurities it is not seen how the proposed change can help to detect very toxic impurities and to draw the attention on them. 3) The reporting thresholds based on the ICH Q3A and Q3B were fixed after many years of discussion and are the worldwide accepted standard. The issue of usage of drug substances with different maximum daily doses is already included in ICH Q3A by consideration of these doses. The proposed policy change will thwart this standard. 4) The limitation of very toxic substances is fully taken into account by ICH (e.g. ICH M7 on mutagenic impurities) and it is obvious that the general limits of ICH Q3A and Q3B cannot be applied to very toxic impurities. These limits are foreseen to be used for related substances where no significant issues concerning toxicity are expected. 5) For testing on very toxic substances a specific knowledge of the synthetic pathways and manufacturing processes and the chemical properties of the products is needed and specific methods have to be developed	

Paragraph / line N°	Comment / Rationale	Proposed change / suggested text
proposal in *Pharmacopeial Forum* (*PF*). 2. If this policy is finalized, USP will no longer include reporting threshold in *PF* proposals for drug substance and drug product monographs. 3. USP will continue including a sensitivity solution and signal-to-noise requirement in monographs, to ensure that the sensitivity of the equipment is sufficient to reliably integrate any impurities that are included for calculating the total impurities result. 4. For monographs that are already official, USP will not solely revise these monographs to remove the reporting threshold as a result of this policy change. However, as these monographs are identified for revision as part of the ongoing revision process, USP will remove the reporting threshold at that time. After the 90-day public comments period, USP will review the comments and post an updated Compendial Notice. Until the policy is finalized, USP will continue including reporting thresholds in the drug substance and drug product monograph proposals being submitted for publication in *PF*. Stakeholders are encouraged to contact USP and provide their comments and recommendations. The lists of drug product and drug substance monograph proposals impacted by FDA comments is included at the end of this Notice. Should you have any questions or comments, please contact Elena Gonikberg, Ph.D., Principal Scientific Liaison, at EG@usp.org.	and applied to determine these impurities. Thus, if there is any hint that a compendial article may contain very toxic impurities additional methods with specific limits covering this issue should be added to the monograph. 6) Each analytical method has its limitation and it should be avoided to evaluate signals where it is not clear if the signal can be assigned to an analyte or to the noise of the method. A deletion of the reporting threshold will lead to the evaluation of all peaks the chromatograms obtained and thus, also to the evaluation of peaks which are not related to an analyte.	

December 10, 2019

Perrigo (Consumer Self Care Division, Allegan, MI) respectfully submits the following comments regarding the General Announcement, *Reporting Threshold in USP-NF Monographs: Proposed Policy Change for Public Comment*, posted August 13, 2019.

As a leading global supplier of over-the-counter (OTC) medications, Perrigo manufactures drug products marketed through both ANDA/NDA and non-registration pathways. Because of the breadth and depth of our complex portfolio, harmonization of analytical procedures and monograph content is vitally important to us. We are fully supportive of harmonization efforts which work toward clear and unambiguously written guidance and instructions which can be consistently implemented across a broad range of products.

Globally deliberated and accepted, ICH Q3A and Q3B Guidelines establish default reporting thresholds for drug substances and drug products based on dosage. In addition, they describe the appropriate use of reporting thresholds, and stipulate the use of lower reporting thresholds when necessary for impurities that have known toxicity. Further, FDA guidance documents are aligned with ICH in the use of reporting thresholds and other compendia provide reporting thresholds (e.g., disregard limits in EP and BP) in individual monographs. The current policy of inclusion of reporting thresholds in USP monographs is consistent with existing guidance.

Perrigo understands and appreciates FDA's concern for very toxic impurities that may not be identified or reported during routine chromatographic analysis. However, simple removal of reporting thresholds from all USP monographs without additional guidance will not alleviate this concern. We are supportive of the application of a "sensitivity solution at a concentration corresponding to the reporting threshold", as it assures adequate detector signal at the time of method use, but such a solution does not serve to improve low level peak characterization, nor does it replace a clear and unambiguously stated reporting threshold. Since ICH guidance will still contain reporting thresholds, laboratory scientists will continue to look to ICH for practical guidance on reporting impurities. In fact, if FDA strongly holds that the currently harmonized practices are inadequate, it seems that a more effective and comprehensive way to address the issue is by publishing additional guidance and/or by working to change the ICH guidelines.

Reporting thresholds are critical information for analytical chemists during method development and validation to ensure method capability for low level impurity quantitation. Reporting thresholds are also critical to quality control chemists during routine method execution to confirm instrument sensitivity and to guide peak integration and proper processing parameters. Additionally, reporting thresholds provide the basis for rounding reported results; per ICH Q3B, "Below 1.0%, the results should be reported to the number of decimal places...in the applicable reporting threshold...".

Removal of existing reporting thresholds carries the risk of introducing unwarranted compliance issues, as products may meet all requirements related to specified impurities, but not meet an established total impurity limit when using a lower reporting threshold than what was used during method validation for

a specific formulation. Since chromatographic activity depends on formulation, low level peaks arising from placebo components, for instance, may cause false failures of total impurity requirements if a different reporting threshold were used for product surveillance. A surveillance lab would also have no way to distinguish a placebo peak from impurity peaks. Ultimately, it is the manufacturer's responsibility to understand the chromatographic profile for a product and to adjust reporting thresholds if needed to quantitate peaks known to represent a safety concern.

Reporting thresholds currently included in many monographs reflect the method approved by FDA. The notable exception to approved methods occurs in the case of products marketed under the FDA OTC Monograph Review, for which pre-market review and approval processes do not exist. The implications of removal of reporting thresholds for this large class of products may not yet be well understood, especially in light of the ongoing collaborative work of USP, FDA, and CHPA to generate more flexible approaches to monograph development for this class of products. Often containing multiple active ingredients, flavors, and dyes, these products can require multiple analytical wavelengths or even multiple chromatographic methods for full organic impurities analysis. Clarity in reporting threshold is especially important when tracking peaks across multiple wavelengths and methods.

Finally, a policy change of removing reporting thresholds from USP monographs creates multiple other issues which must be addressed:

1) General Chapter <476> or General Notices would require additional language to emphasize the need for manufacturers to determine and implement reporting thresholds, including practical guidance on how to set an appropriate reporting threshold in the region between the true method limit of quantitation (10 x signal to noise) and the current ICH reporting threshold default values. The absence of specific instructions would create the risk that some companies may set reporting thresholds higher than the current ICH guidance. This could increase potential for unreported impurities at higher levels, and ultimately, loss of the current level of public health protection.
2) Specifically for OTC monograph products (and because of the lack of a review mechanism), ICH default limits would need to be recognized in General Chapter <476> or General Notices as a starting point to be adopted in the absence of further information indicating the presence of low level peaks with known or suspected toxicity.
3) General Chapter <476> or General Notices would need additional language to strengthen the requirement for inclusion of sensitivity solutions in the monograph to establish that the method provides adequate signal for low-level quantitation of relevant impurities at time of use.
4) Any existing proposal or official monograph without instructions for a sensitivity solution would need the addition of a sensitivity solution prior to or at the time of reporting threshold removal. Addition of sensitivity solutions would require supporting method validation data. Examples of monographs lacking sensitivity solutions include Cetirizine Hydrochloride (official) and Selegiline Hydrochloride Capsules (PF 45(2) proposal).
5) Rounding instructions in *General Notices 7.20. Rounding Rules* would need to be revised. The current USP rounding instructions are well suited for potency determination and other test contained in monographs, but do not appropriately address rounding for impurities.

6) To promote consistency, revisions to individual monographs would need to occur within a specified period of time. While this minor revision may not warrant immediate revision of all monographs that contain reporting thresholds, allowing the existence of reporting thresholds to remain in some monographs for a potentially long period of time will contribute to confusion and misalignment. A designated revision window (e.g., one, two, or three years) should be established and USP should ensure that all monographs align with the new policy within the designated time frame.

Because the use of reporting thresholds is well established in ICH guidelines and FDA guidance, reporting thresholds are critical information at all stages of the lifecycle of analytical methods, and significant changes to multiple sections of USP text would be needed to accommodate this policy change, Perrigo recommends that the compendium retain the use of reporting thresholds within individual drug substance and drug product monographs. We question how removal of guidance information leads to improved public health. To the contrary, without clear and visible instructions, the door would be opened for industry to push the limits of reporting of impurities. Retaining reporting thresholds maintains alignment with ICH and other compendia and avoids introducing unwarranted de-harmonization, compliance issues related to total impurities, and challenges to the current level of public safety.

Perrigo appreciates the opportunity to provide comments on this proposed policy change.

Respectfully,

medichem

UNITED STATES PHARMACOPEIA

Attn. Dr Elena Gonikberg

Celra, December 16, 2019

Ref. Proposal for removal of "Reporting Threshold" requirements in monographs

Dear Sirs,

MEDICHEM is a supplier of Drug Substances and Drug Products approved for the US and other markets (EU, Japan, Australia...) and regularly co-operates with the USP in the effort to set adequate standards to ensure the safety and efficacy of Drugs.

We strongly believe that **"Reporting Threshold" must be regularly included in the Chromatographic tests of the USP monographs.**

First and most important, the reporting threshold concept has been set by the ICH tripartite scheme and agreed by the Regulatory Authorities of the three involved regions (i.e. USA, EU and Japan), so it is currently an internationally agreed requirement that must be observed. The ICH effort has enhanced and harmonized the requirements for quality standards.

The "Reporting Threshold" is applied together with the "Identification Threshold" and the "Qualification Threshold" which are the concepts used to establish the limits for the impurities according to ICH. These three thresholds must be taken together to define a suitable safe standard. If one is not to be included in USP monographs but based on particular product applications, what about the other two which are also dependent on daily dose. We strongly believe that, in general, all the thresholds have to be taken into account in the USP monographs using the maximum daily dose as prescribed in the ICH.

Some argue that not reporting impurities below the "Reporting Threshold" will lead to overlook very toxic impurities, but very toxic impurities are not necessarily detected by the general chromatographic method or even if detected not properly identified, limited or assessed at the needed level. Toxic impurities must be limited by methods suitable to detect them at appropriate level, most probably through a specific analytical method.

Reporting threshold also is used to assess adequate sensitivity of the analytical method and equipment. For example, by setting a signal to noise ratio 10:1 for the reporting threshold concentration.

USP represents a standard used in many countries, so if the "Reporting Threshold" is based on particular applications, the USP will lose the "universal standards" character that now represents.

Truly yours,

Josep M. de Ciurana

Senior Advisor

MEDICHEM,S.A.

jmciurana@medichem.es

Reporting Threshold in USP-NF Monographs: Proposed Policy Change for Public Comment

Type of Posting: General Announcement
Posting Date: 13–Aug–2019
Comment Deadline: 12–Nov–2019

As part of our commitment to ongoing monograph modernization, USP is updating organic impurities testing for articles subject to *USP–NF* standards. Our approach applies the ICH Q3A/B-based limits for identification and reporting of organic impurities and degradation products in drug substances and drug products. Currently, USP drug substance and drug product monographs' impurities tests with specifications for total impurities or total degradation products will in many cases include a reporting threshold consistent with the ICH guidelines.

In addition to setting criteria for a peak to be included in the total impurities, the reporting threshold also aligns with the approach to verify the system sensitivity. Monographs with recently modernized or new impurity procedures are expected to contain a sensitivity solution at a concentration corresponding to the reporting threshold, and a signal-to-noise requirement as a part of system suitability requirements. This approach is used for both drug substance and drug product monographs.

Beginning in 2016, the U.S. Food and Drug Administration (FDA) provided comments requesting that reporting thresholds not be included in drug product monographs. Since compendial monographs are not intended to identify every impurity and degradation product, the FDA is concerned that the inclusion of reporting thresholds could result in very toxic impurities not being identified or reported. The FDA commented that reporting thresholds for drug products vary based on product-specific factors and should be addressed as an application assessment issue. FDA uses ICH reporting thresholds as guidelines and deviates from them as needed based on application specific considerations.

FDA has recently notified USP that the same public health and safety concerns regarding the inclusion of reporting thresholds would also be applicable to drug substance monographs. Since a drug substance may be used in different products with different maximum daily doses, ICH Q3A limits (including reporting threshold) will vary due to product specific factors and should also be addressed as an application assessment issue.

To address the FDA's recommendation, USP is proposing the following policy change pertaining to inclusion of reporting thresholds in drug substance and drug product monographs which is presented here for a 90-day public comment period.

1. For the impacted monograph proposals, the Expert Committees will have an option of deleting the proposed reporting threshold at the ballot, without republishing the proposal in *Pharmacopeial Forum* (*PF*).
2. If this policy is finalized, USP will no longer include reporting threshold in *PF* proposals for drug substance and drug product monographs.
3. USP will continue including a sensitivity solution and signal-to-noise requirement in monographs, to ensure that the sensitivity of the equipment is sufficient to reliably integrate any impurities that are included for calculating the total impurities result.
4. For monographs that are already official, USP will not solely revise these monographs to remove the reporting threshold as a result of this policy change. However, as these monographs are identified for revision as part of the ongoing revision process, USP will remove the reporting threshold at that time.

Comments from Bachem AG, Switzerland:

The company Bachem AG, a manufacturer of drug substances, in particular synthetic peptides, would like to comment on USP's proposed policy change to no longer include reporting thresholds in monographs of drug substances and drug products.

While it may seem reasonable to delete reporting thresholds from USP monographs, we do regard some consequences of this policy change indeed as critical and would thus like to address them. Bachem's comments and questions are presented in the following.

- In the proposed policy change, it is stated: 'Since compendial monographs are not intended to identify every impurity and degradation product, the FDA is concerned that the inclusion of reporting thresholds could result in very toxic impurities not being identified or reported'.
  We do not regard the FDA's concern as justified for the following reason:
  Removing the reporting threshold from a monograph does not automatically improve the identification and determination of very toxic impurities. The approach to control such impurities is based on considerations of the risks associated with the manufacturing process rather than a simple application of an established purity method outlined in a compendial monograph which may even have been developed for a different manufacturing process. The absence of potential impurities of toxicological concern must be shown with methods specific for these compounds, and very often this cannot be achieved by using already established methods, even those of a compendial monograph. A hazard assessment as outlined in ICH guideline M7 'Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk', which has also been implemented by the FDA, is a key element; it is the responsibility of the FDA to judge the defined risks and the measures to minimize them during the approval process.
  Simply deleting reporting thresholds from monographs would thus not contribute to an improvement of the toxicological safety of a product.

- In addition, deleting thresholds from USP monographs would mean that the establishment of a reporting limit for a USP method would now be an individual decision of the applicant based on the quality of the product and its future application. We acknowledge that this is obviously the intention of the FDA, namely the individual definition, justification, and approval of reporting limits based on the product characteristics so that all relevant impurities, including potentially toxic ones, are suitably covered.
  However, as it can be expected that different products referring to the same USP monograph are approved, different reporting thresholds will then exist for different products although the purity method may be the same. Specific impurities of these products may even require their own reporting thresholds.
  Question: For future monographs (new or updates), how will USP handle the different reporting thresholds in combination with the different impurity profiles that may exist for the same method?

  In the US, the FDA would still have the oversight of the approvals granted and the conditions for these approvals. However, if an applicant took the USP monograph as a standard for applying with 'USP quality' in a country outside the US, it would be the responsibility of this

country's authority to grant approval. This would mean that additional reporting thresholds could be implemented for the USP method, but of foreign approvals neither the FDA nor the USP would have any knowledge or oversight.
This could lead to a situation with products of considerably different quality on the market (in the US and elsewhere) but nevertheless referring to the same USP monograph method. The chosen reporting limit would thus be the responsible factor for a difference in quality, which would mean that certain products may appear of better quality (higher purity) only because of a higher reporting limit, i.e. because lesser impurities are reported. We are of the opinion that this would be a rather undesired effect which should be avoided as it could negatively affect the reputation of USP's monographs and methods.

- The quality and suitability of a compendial chromatographic method is not only, but also defined by the reporting threshold. Here, at least a minimum requirement should be provided as a guidance for users of the monograph and in order to transport USP's expectations on adequate reporting.

- However, in USP's general chapters on method validation and verification, nothing specific is stated about the reporting of impurities.
  Question: Where are USP's general requirements defined? What are USP's expectations for the reporting of impurities of all product classes for which the ICH guidelines Q3A/B are not applicable?

- It is presently also not clear if eliminating the reporting threshold means that no disregard limit is provided; however, the disregard limit is needed for any calculation of the purity and the related impurities.
  Question: How will USP resolve this issue? Will disregard limits still be provided even if reporting thresholds are no longer given?

- If it should nevertheless be decided to eliminate reporting thresholds from USP monographs, we would strongly suggest that the USP prepare a new general chapter (in analogy to general chapter <1503>) describing USP's expectations for limiting impurities in non-peptidic drug substance and drug product monographs.

Bubendorf, 20 December 2019

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December 24, 2019

Comment to "Reporting Threshold in USP-NF Monographs: Proposed Policy Change for Public Comment"

Type of Posting: General Announcement

Posting Date: 13–Aug–2019

Comment Deadline: 31–Dec–2019

< Comment 1>

In Methionine and Glycine USP monographs, it is explained as "Disregard any impurities less than 0.05%" and "Disregard any impurity peak less than 0.05%," respectively. Since "disregard limits" is as same as "reporting threshold," is it possible to use only "disregard limits" or "reporting threshold" to avoid any confusion?

<Comment 2>

Monographs with recently modernized or new impurity procedures are expected to contain a sensitivity solution at a concentration corresponding to the reporting threshold, and a signal-to-noise requirement as a part of system suitability requirements.

If the concentration of sensitivity solution is 0.05% and Signal-to-noise ratio is set as "NLT 10 determined from the substance peak, *Sensitivity solution,*" reporting threshold and Quantitation limit is 0.05%. Is this understanding correct? If yes, we think there may be no difference removing reporting threshold from the monographs because concentration of the sensitivity solution is as same as the reporting threshold.
In this case, indicate the reporting threshold clearly in the monograph is helpful for us to understand the specification correctly.

<Comment 3>

Since compendial monographs are not intended to identify every impurity and degradation product, the FDA is concerned that the inclusion of reporting thresholds could result in very toxic impurities not being identified or reported. The FDA commented that reporting thresholds for drug products vary based on product-specific factors and should be addressed as an application assessment issue. FDA uses ICH reporting thresholds as guidelines and deviates from them as needed based on application specific considerations.

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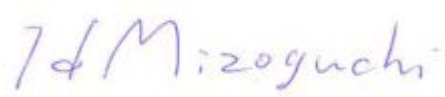
If there are very toxic impurity, specific analysis method should be set to control this impurity. Different impurities may be included when the API manufactured by different manufacturing process and about the potential impurities and their control should be reviewed by FDA when each DMF is newly submitted. If acceptance criteria of unspecified impurities set very strict in order to control very toxic impurities not being identified or reported, there may be a case that already approved API could not conform to the specification and have to get out the market.

Therefore we think just setting the acceptance criteria of unspecified impurities strict to control very toxic impurities not being identified or reported in new API manufactured by different process must be a wrong approach to set a new test method in current monograph.

Sincerely yours;



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Date 2019.12.27

Subject: Comments Regarding the Proposed Policy Change for Reporting Threshold in USP-NF Monographs

Dear Elena,

Xellia Pharmaceuticals ApS is a manufacturer of several fermentation based antibiotic drug substances and drug products that are covered by USP monographs. We are therefore concerned about the proposed policy change to remove reporting thresholds from all monographs, especially as our fermentation products have often very complex impurity profiles and for these product the reporting thresholds are particularly important.

We believe that the reporting threshold is an integral part of the test method description and have a significant impact on the reported result. In *table 1* an example is presented with comparison of results for colistin sulfate Ph. Eur. HPLC method obtained with and without report threshold in the calculation. The colistin sulfate Ph. Eur. method is selected as example as the Ph. Eur. monograph was recently updated with HPLC method with improved separation and the reporting threshold was set to 0.35%. The threshold was set based on the limit of quantitation of 0.33% obtained in the validation of the method. For fermentation products it is sometimes the case that the reporting threshold cannot be set in accordance with the ICH Q3A and Q3B guidelines, and have to be set higher due to limited method capability or other considerations due to the complex impurity profile. These guidelines are also not valid for fermentation products.

Table 1. Impurity results for Colistin Sulfate Ph. Eur. method with and without the reporting threshold 0.35%.

	Specification	Batch A1620395		Batch A1620396	
		With reporting threshold	No reporting threshold	With reporting threshold	No reporting threshold
Impurity A	NMT 2.5%	1.36	1.31	1.34	1.28
Impurity B	NMT 4.0%	1.27	1.23	1.20	1.15
Sum of Impurities	NMT 11.0%	8.8	**11.2**	8.3	**12.2**

As can be seen there is not a big impact on the results for individual impurities but for the sum of impurities the difference is significant and without reporting threshold the tested batches becomes out of specification. Without the reporting threshold more impurities are integrated and the sum of impurities result becomes higher and the total purity result lower. The presented case illustrates that the ability to meet set specification limits are dependent on the reporting threshold and that reporting thresholds are very important part of a pharmacopeia standard in order to obtain similar results between labs and users.

The use of sensitivity solution and signal-to-noise requirement are valuable part of the monograph method to ensure that the analytical system employed works properly and that sufficient sensitivity is obtained. This does not however replace the role of the reporting threshold, as the sensitivity can vary greatly between different analytical systems the obtained results can be very different if the peak area from the sensitivity solution is used as disregard limit.

Another aspect of removing the reporting threshold is that users of the USP monographs would be discouraged to use new and more sensitive analytical equipment. If an old detector is used which barely obtain a signal-to-noice ratio of 10 for the sensitivity solution fewer peaks would be included in the calculation and a high product purity is obtained. The user with a new detector which obtain a signal-to-noice ratio far above 10 would include more impurities in the calculation and obtain a lower purity for their product. With a reporting threshold that is the same for everybody there are no negative consequence for the user with a very sensitive state of the art analytical equipment.

The consideration that the use of reporting thresholds in monograph methods would result in very toxic impurities not being identified or reported does not hold water as unspecified peaks are in any case not identified and reported in routine analysis, if they are below the limit for “any unspecified impurity” in the approved specification. In the case of new applications or variations the impurity profile should be evaluated down to the identification threshold according to the ICH Q3A and Q3B guidelines if the capability of the analytical method allows. If assessed that there is potential for the presence of very toxic impurities other thresholds apply and specific analytical methods with higher sensitivity are anyway usually needed.

We hope that the proposed policy change regarding reporting threshold can be withdrawn and not implemented for USP monographs. If it is pursued that this policy change is needed, we hope that products with complex impurity profiles, such as antibiotics produced by fermentation can be excluded and that reporting thresholds can be maintained for such products or other special cases.

Yours truly
Xellia Pharmaceuticals ApS

Robert Klasson
Specialist, Global Regulatory Affairs

December 30, 2019

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RE: Reporting Threshold in USP-NF Monographs: Proposed Policy Change for Public Comment

Dear Elena,

This letter is in response to the Compendial Notice posted August and extended November 2019: *Reporting Threshold in USP-NF Monographs: Proposed Policy Change for Public Comment*. This Compendial Notice proposes to remove reporting thresholds from drug substance and drug product monographs per requests made by the FDA.

Lilly scientists have reviewed the proposal with interest, and we advocate for aligning with the FDA requests. The proposal to gradually phase out reporting thresholds from monographs is acceptable to us. Such thresholds are agreed upon during the registration of the drug substance and/or drug product. We request that updates be made to the General Notices section 5.60, consistent with this policy.

Additionally, we concur that sensitivity solutions and quantitation limits should continue to be built into the system suitability requirements of applicable monographs and chapters as described within Chapter <1225>, Validation of Compendial Procedures.

Detailed responses are included in the following attachment. Thank you for your attention in reviewing our requests. If you have questions or other concerns, please contact me.

ELI LILLY AND COMPANY

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Attachment – Detailed Comments applicable to the Proposed USP Policy Change on Reporting Thresholds

Attachment
Lilly's Response to Proposed USP Policy Change on Reporting Thresholds

	Location	Comments	Suggested revisions
1.	General Notices (GN), 5.60, Impurities and Foreign Substances	General Notices form the background upon which all monographs are built. Wording in the GN should be consistent with the plan to remove reporting thresholds from drug substance and drug product monographs in lieu of reporting thresholds agreed upon during the registration of the drug substance and/or drug product.	Recommend that a statement be added within 5.60, such as: "*Where an acceptance criterion for total impurities is included in a monograph, use the reporting thresholds agreed upon during the registration of the drug substance and/or drug product*." Additionally, we recommend that the GN reference (new) chapter <476> along with <1086>. See Detailed Comment #2 for additional recommendations for <476>.
2.	Chapter <476>, Control of Organic Impurities in Drug Substances and Drug Products [last draft provided Jan 2019 in PF 45(1)], Identification of Impurities	The PF 45(1) draft, section on Reporting Impurities, states: "*Impurities present above the reporting threshold shall be reported according to the relevant analytical procedure*." And "*All impurities at a level greater than (>) the reporting threshold shall be summed and reported as a value for total impurities*." However, it is not clearly stated that adopted reporting thresholds are based upon the regulatory application assessment process.	Recommend that Chapter <476> continue to include ICH recommended thresholds (e.g., Table 1, Table 2), and state that "*thresholds agreed upon during the registration process takes precedence over such guidelines*."
3.	Chapter <476> (PF 45(1)], (under Table 2, ICH Recommended Thresholds for Degradation Products in Drug Products)	Guidance already takes patient safety and impurity toxicity into account: "The acceptance criteria shall be based on applicable guidances or other acceptable scientific means, with safety as the primary consideration and not solely based on process capability" And "Manufacturers should provide rationale and supporting data to justify the acceptance criteria for impurities associated with each drug substance."	These points address the safety concerns raised by the FDA and we recommend these be retained in <476>. Additionally, we recommend the expert committee for <476> consider including the decision process that is represented by the Decision Tree for Identification and Qualification of a Degradation Product that is in the ICH Q3B (R2), Attachment 3.

	Location	Comments	Suggested revisions
4.	Chromatography <621>, System Suitability	Though this chapter addresses the calculation of the signal-to-noise (S/N) ratio, it does not address the use of sensitivity solutions and Quantitation Limits. We recommend that Chapter <621> be updated to align with the use of sensitivity solutions and Quantitation Limits.	Add description and examples showing the value of a sensitivity /system suitability solution, for example: "*Sensitivity solutions (also called system suitability solutions) are dilute solutions prepared from a standard or other solutions as specified in the individual monograph. These solutions are used to perform various system suitability tests, such as S/N, precision, and limit of quantitation*." Additionally, a description of Quantitation Limits could be added into Chapter <621>, similar to the definition in <1225>: *"It* (Quantitation Limit) *is the lowest amount of analyte in a sample that can be determined with acceptable Precision and Accuracy under the stated experimental conditions. The quantitation limit is expressed as the concentration of analyte (e.g., percentage or parts per billion) in the sample.*"
5.	Chromatography <621>, Calibration Procedure	This section addresses threshold setting, which is not currently aligned with the new direction per the Notice: "*In such tests the limit at or below which a peak is disregarded is generally 0.05%."*	Recommend that the specified disregard value be removed, for example: "In such tests the limit at or below which a peak is disregarded is based upon *reporting thresholds adopted during the drug's regulatory application process. Such threshold setting of the data collection system should* correspond to at least half of this limit.
6.	Chapter <1086>, Impurities in Drug Substances and Drug Products [last draft provided Jan 2019 in PF 45(1)]	The PF 45(1) draft explains the use of the reporting threshold: "*Total impurities in the drug substance monographs are the sum of all specified and unspecified impurities above the reporting threshold*."	We recommend adding a comment similar to Comment #2 for <476>. This could be a reworded statement (2 paragraphs before Appendices): "Typically, the disregard limit for substances covered by a monograph is set in accordance with the *thresholds agreed upon during the drug registration process* and in accordance with ⟨476⟩."