22 June 2020

United States Pharmacopeia
12601 Twinbrook Parkway
Rockville, MD 20852

Pfizer Reference Number: 2020-0042R-002A
Subject: USP-NF General Notices and Requirements

Dear Dr. Simpson,

In response to proposed changes to the USP-NF General Notices and Requirements published in PF 46(3), Pfizer would like to submit the following comments for consideration by the USP:

- 5.60.40. Impurities that are Unusually Toxic and/or Mutagenic: ICH M7 (R1) allows for control strategies for Mutagenic impurities other than 'control and reporting' on the final specification. Control strategy option 4 in ICH M7 (R1) describes/discusses cases where some such impurities do not need to be listed on any specification (e.g. such impurities can be so reactive as to be readily purged). Therefore, no control of such an impurity is necessary (so no control and reporting). Accordingly, the following change is recommended to avoid confusion and to ensure alignment with ICH M7 (R1) is not misunderstood.

  "Reporting thresholds (disregard limits) are not intended to apply to unusually toxic impurities, including mutagenic impurities, which are to be ~~controlled and reported at levels appropriate~~ managed according to ICH M7 (R1) expectations to ensure safety of the product.

  Mutagenic impurities are to be identified and controlled by manufacturers as required by the applicable regulatory authority or as described in ICH M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk"

We appreciate the opportunity to participate in the compendial development process of the USP. Please feel free to contact me if you have any questions.

Sincerely,

July 31, 2020

Mr. Mario Sindaco
Executive Secretariat
The United States Pharmacopeial Convention, Inc.
12601 Twinbrook Parkway
Rockville, MD 20852

REF: 07-20-034-Z

Dear Mr. Sindaco:

This is regarding the proposed revisions to **General Notices 5.60.40. Impurities that are Unusually Toxic and/or Mutagenic** appeared as an In-Process Revision in Pharmacopeial Forum (PF), Vol. 46, No. 3. We have the following comments:
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General Comment: We agree that it would be beneficial to add a section in General Notices clarifying the use of the "Impurities" section in USP-NF monographs and alert users regarding the responsibility to assess compendial vs. non-compendial impurities. However, the current proposal includes terminology, concepts and approaches that are still under discussion. Therefore, we object to the proposal as currently written.

Specific Comments:

1. We note that USP added a statement that "Reporting thresholds (disregard limits) are not intended to apply to unusually toxic impurities, including mutagenic impurities, which are to be controlled and reported at levels appropriate to ensure safety of the product." This statement does not address all concerns FDA has on USP's practice for adding reporting thresholds (disregard limits) into monographs. FDA has fundamental concerns with USP's definition of "Reporting Threshold" and conflating it with "Disregard limit." Please refer to the FDA letter REF 07-20-021-N which provides detailed comments from the agency about the addition of reporting thresholds (disregard limits) in individual USP monographs. We recommend that USP carefully consider the recommendations from the agency and resolve the issues pertaining to reporting thresholds.

2. Regarding the statement that "Mutagenic impurities are to be identified and controlled by manufacturers as required by the applicable regulatory authority or as described in ICH M7 (R1) *Assessment of Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk*", we recommend further discussion with USP on addressing the acceptance criteria for potentially mutagenic impurities (PMIs) in USP monographs. We have noticed that some of the

limits for PMIs in USP monographs may have limits inconsistent with ICH M7 guidelines. The discrepancy creates conflicting situations as many manufacturers propose acceptance criteria for PMIs based on USP monographs with the understanding that the limits in USP monographs are acceptable for these PMIs. We recommend USP develop an enforceable General Chapter that can be referenced in monographs to address implementation of ICH M7 guidelines in USP standards. Since USP monographs supersede USP General Notices, this proposal does not address the issues involved with addressing PMIs in USP monographs.

We hope these comments will be helpful to USP. Please feel free to contact Dr. Jin Zhang on my staff at Jin.Zhang1@fda.hhs.gov if there are any questions. Please use the reference number provided above on any ensuing correspondence.

Sincerely yours,

Pallavi Nithyanandan, Ph.D.
Director
Compendial Operations and Standards Staff
Office of Policy for Pharmaceutical Quality
Center for Drug Evaluation & Research