Glycine, Status Update

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This Notice provides background information regarding the postponement and deferral of the proposed Interim Revision Announcement (IRA), published in *PF* 45(1), to the USP Glycine monograph.

As part of USP's efforts to modernize *USP-NF* monographs, an HPLC Related Compounds procedure was added to the USP Glycine monograph to detect and quantitate specified and unspecified impurities, which was published for public comments as an In Process Revision (IPR) to *USP* 38–*NF* 33 *1S* in *Pharmacopeial Forum* (*PF*) 40(3). It was later republished in *PF* 43(2) with an improved procedure. The procedure included limits for monochloroacetic acid (MCA) at NMT 0.05% and other specified and unspecified impurities at NMT 0.1%. Several comments were received from the U.S. Food and Drug Administration (FDA) and the industry, which prompted the postponement of the limits for MCA and unspecified impurities via a Revision Bulletin (RB) posted on July 27, 2018.

Based on further comments from FDA, it was decided to propose reinstating the limit for MCA, and a dual limit for unspecified impurities linked to a labeling requirement for maximum daily consumption of glycine, with a note indicating that FDA could implement a different limit depending on glycine's unique and specific uses. FDA also requested deleting the note about disregard limits (i.e. reporting thresholds) to allow reporting of lower levels of MCA and unspecified impurities, which is the subject of a Compendial Notice recently posted on USP website for public comments (https://www.uspnf.com/notices/reporting-threshold-proposed-change-for-comment).

USP published these proposals as IRA in *PF* 45(1). The following comments were received from FDA and the industry:

- FDA acknowledged USP's acceptance of their previous comments and stated that, although MCA possesses a structural alert for genotoxicity, the main concern associated with MCA is unusually potent general toxicity and recommended modifying the footnote to state: "Monochloroacetic acid (MCA) is an impurity associated with unusually potent toxicity, for which the primary concern is its general toxicity. MCA warrants lower limits than other non-genotoxic, non-carcinogenic impurities, and these limits will depend on the context of use of the proposed drug product (e.g., route of administration, duration of exposure, patient population, and dose)."
- A comment from industry objected to labeling the ingredients based on the maximum daily consumption of drug products or dietary supplements
- Several comments from industry objected the removal of disregard limits proposed in IRA because it presents technical challenges. Instead, the commenters proposed establishing a lower disregard limit, e.g. 0.02% or 0.03%
- Another commenter stated that glycine is also used as an excipient, and ICH Q3A "Impurities in New Drug Substances" expectations should not be applied to excipients. The commenter indicated that requirement for such impurity levels in glycine may cause drug shortages.

The postponements published in the 2018 RB are still current and the proposal published in *PF* 45(1) IRA is deferred.

Stakeholders are encouraged to contact USP and provide their comments and recommendations for possible solutions to address these issues.

Should you have any comments or questions, please contact Fatkhulla Tadjimukhamedov, Ph.D., Scientific Liaison to the Non-Botanical Dietary Supplements (301–230–3216 or fkt@usp.org).

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