VIA ELECTRONIC SUBMISSION

June 21, 2022

Food and Drug Administration
Division of Dockets Management
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2022-N-0236 for "Prioritizing the Addition of Maximum Daily Exposure Information and Removing Dosage Form Information from the Inactive Ingredient Database; Establishment of a Public Docket; Request for Comments"

Dear Sir/Madam,

The United States Pharmacopeia (USP)[1] appreciates the opportunity to comment on the Food and Drug Administration's (FDA or the Agency) Inactive Ingredient Database (IID), in particular, on maximum daily exposure (MDE) information.

USP supports FDA's recent enhancements to the IID. Users can now perform electronic queries to obtain accurate maximum daily intake (MDI) for oral drug products and MDE information for each route of administration, for which data are available. We appreciate that FDA added missing values in the IID and checked the IID for inaccuracies or naming inconsistencies for certain excipients.

The Federal Register Notice (FRN) indicates that FDA is exploring modifications of the IID's structure to eliminate dosage form information based on stakeholder feedback. USP is not in favor of removing dosage form information, including MDE and the Maximum Potency per Unit Dose (MPUD); from a formulation scientist's perspective, both quantities are useful for all routes of administration.

Used together, the MPUD and MDE can help drug manufacturers identify the excipients used in an FDA-approved drug product. This information is important for drug manufacturers because the amounts of the excipients are taken into consideration when developing drug products, and in particular, generic drug products. This information is also critical for an excipient's use from a safety and toxicological perspective, especially if used in drug product dosage forms that pose a higher risk to patients, such as injections and suspensions. Additionally, these values are important to help identify and control the level of excipient exposure which may be harmful to patients. The inclusion of certain excipients has recently been a concern in hand sanitizer products, due to benzene contamination that may have

[1] USP is an independent, scientific, nonprofit organization dedicated to improving public health for medicines, foods, and dietary supplements. USP public standards are developed through an open, transparent, expert-based process, offering the ability to confront public health emergencies, adapt to new industry practices, and support evolving science and technology.

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been related to excipients such as carbomers.[2] In addition, from a compendial perspective, the MPUD and MDE values are also important information for identifying the appropriate identity and purity tests and labeling requirements to be included in a compendial monograph.

Responses to Specific Questions in FRN

Questions 1 and 2
USP supports the prioritization of excipients currently listed in the IID without MDE information, and the prioritization of excipients based on the dosage forms of drug products in which they are used. These include excipients used in drug product dosage forms that are higher risk to patients, such as injections and suspensions. This inclusion of MDE information, based on the intended use of the drug products in which the excipients will be used, also helps USP in working with monograph sponsors to develop specifications, appropriate tests, and labeling for excipient monographs.

Question 4
USP has previously provided comments on the structure and format of the IID. These comments were part of USP's October 2015 response to Docket No. FDA–2015–N–2986, "Technical Document for Using the Inactive Ingredient Database; Establishment of a Public Docket,"[3] which requested feedback on IID enhancement. The relevant parts are captured below.

USP recommends that FDA employ a system for notifying users when changes are made to the IID. To enhance the functionality of IID, recent updates should be accessible by users through a search function tool designed to enable users to easily find updated information. With this tool, users would be able to determine whether a newly added excipient or a change to an existing excipient impacts dosage forms/routes of administration or dosage amounts. The current IID makes it difficult to identify newly added excipients and changes to existing excipients that may require new or revised public quality standards in the *United States Pharmacopeia-National Formulary* (*USP-NF*).

Finally, we recommend that FDA provide a separate entry in the IID that includes a listing of the excipient manufacturers much like the Orange Book for active pharmaceutical ingredient manufacturers. This could help drug manufacturers more easily qualify a suitable grade excipient.

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[2] FDA announcement, "alert[ing] drug manufacturers to the risk of benzene contamination in certain drugs," at https://www.fda.gov/drugs/pharmaceutical-quality-resources/fda-alerts-drug-manufacturers-risk-benzene-contamination-certain-drugs (June 9, 2022).

[3] USP Comments for Docket No. FDA–2015–N–2986, at, https://www.regulations.gov/comment/FDA-2015-N-2986-0017 (Oct. 2015). USP also submitted comments in response to Docket No. FDA–2019–D–2397, "Using the Inactive Ingredient Database; Draft Guidance for Industry; Availability Establishment of a Public Docket," at https://www.regulations.gov/comment/FDA-2019-D-2397-0005 (Sept. 2019).

Thank you again for the opportunity to comment. USP is committed to supporting the inclusion of important information in the IID, including MDE and MPUD. We would welcome the opportunity to work with FDA on soliciting stakeholder feedback, such as conducting a stakeholder survey on how best to prioritize excipients that are missing MDE information and determine the dosage forms of the drug products in which they are used. For more information, please contact Marissa Chaet Brykman, Esq., Director, U.S. Regulatory Policy, at marissa.brykman@usp.org; (301) 692-3660.

Sincerely yours,

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