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Also submitted electronically to <http://www.regulations.gov>.

Division of Dockets
Management (HFA-305),
Food and Drug Administration,
5630 Fishers Lane, Rm. 1061,
Rockville, MD 20852.

Subject: USP comments regarding the enhancement of the utility and usability of the Inactive Ingredient Database to help FDA identify and ultimately establish best practices and issue a technical guide or draft guidance. [Docket No. FDA-2015-N-2986]

Dear Sir/Madam:

The United States Pharmacopeial Convention (USP) is an independent, science-based, non-profit organization that throughout our nearly 200-year history has worked to help ensure patients receive high-quality, safe, and effective medicines. USP achieves this through our legally recognized role in setting public quality standards for drugs and their ingredients, including excipients. Furthermore, USP has a statutory role in the naming of drugs, including excipients, and utilizes scientific expert committees such as the Nomenclature, Safety, and Labeling Expert Committee for this purpose. The Food and Drug Administration (FDA) is actively involved in this Committee and the overall naming system.

USP is supportive of FDA's effort to enhance the utility and usability of the Inactive Ingredient Database (IID). The IID has the potential to help identify monographs that should be developed or updated by USP to help ensure the identity, strength, quality and purity of these ingredients. This in turn would improve the quality of the drugs in which these excipients are used and benefit public health.

USP appreciates the opportunity to provide comments to FDA on the enhancement of the IID and is submitting the following comments as set forth below.

1. How can we improve nomenclature in the IID (e.g., use of preferred ingredient names and synonyms in the database)?

USP Headquarters
12601 Twinbrook Parkway
Rockville, MD 20852-1790 USA
+1-301-881-0666

Europe/Middle East/Africa
Münchensteinerstrasse 41
CH-4052 Basel, Switzerland
+41 (0)61 316 30 10

USP-India Private Limited
IKP Knowledge Park
Turkapally Village, Genome Valley
Shameerpet, Ranga Reddy District
Hyderabad 500 076, A.P., India
+91-40-4448-8888

USP-China
Building 11
Lane 67 Libing Road
Zhangjiang Hi-Tech Park
201203, Shanghai, China
+86-21-51370600

USP-Brazil
Avenida Cecl, 1600-Tamboré
Barueri-SP
06460-120, Brazil
+55-11-3245-6400



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USP has a long-standing legal role in establishing the names of drugs, including excipients, under Section 502(e)(3) of the Federal Food, Drug and Cosmetic Act ("the Act"). Under this provision, the established name (nonproprietary name) of a drug or component is the official title used for the drug or component in an official compendium such as *USP* or *NF (USP-NF)*, unless FDA has designated another name via regulation. Thus, when a *USP-NF* standard exists, the excipient should appear in IID under the official title set forth in the *USP-NF*. If there is no *USP-NF* standard, the name appearing in *The USP Dictionary of USAN and International Drug Names* should be used. FDA can cross-reference additional information to the official title thus linking related information together. For example, FDA should consider always cross-referencing the UNII number¹ to the *USP-NF* official title. In addition, brand or proprietary names for excipients and their mixtures should be cross-referenced to the official title. This approach would avoid confusion, facilitate the search capability, and thereby enhance the utility and usability of the IID.

Currently, there are a number of inconsistencies in the IID that utilizing the official title as the primary reference could help resolve. The inconsistencies include but are not limited to the following: (I) the use of different names for the same excipient, or names that do not reflect the official title; (II) the rewording of the excipient name making it difficult to find when searching in the database; (III) the use of proprietary names instead of the nonproprietary name; and (IV) the use of different names with the same UNII number.

USP Headquarters

12601 Twinbrook Parkway
Rockville, MD 20852-1790 USA
+1-301-881-0666

Europe/Middle East/Africa

Münchensteinerstrasse 41
CH-4052 Basel, Switzerland
+41 (0)61 316 30 10

USP-India Private Limited

IKP Knowledge Park
Turkapally Village, Genome Valley
Shameerpet, Ranga Reddy District
Hyderabad 500 078, A.P., India
+91-40-4448-8888

USP-China

Building 11
Lane 67 Libing Road
Zhangjiang Hi-Tech Park
201203, Shanghai, China
+86-21-51370600

USP-Brazil

Avenida Ceci, 1600-Tamboré
Barueri-SP
06460-120, Brazil
+55-11-3245-6400

Examples of inconsistencies are:

- I. IID uses multiple names for excipients covered by a single *USP-NF* monograph and sharing a single official title:
 - a. IID has separate entries for each Hypromellose substitution type
 - *USP-NF* Monograph: Hypromellose (*USP-NF* includes a table that addresses the possible types of substitution (1828, 2208, 2906, 2910))
 - b. IID: Carrageenan Sodium, Calcium Carrageenan, Carrageenan Salt

¹ The UNII is a unique, unambiguous, non-semantic, alphanumeric identifier based on a substance's molecular structure and/or descriptive information.
<http://www.fda.gov/Drugs/InformationOnDrugs/ucm080123.htm#WhatUNII>



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- *USP-NF* Monograph: Carrageenan (monograph covers all salt forms)
 - c. IID: Croscarmellose
 - *USP-NF* Monograph: Croscarmellose Sodium
 - d. IID: Anhydrous Dextrose
 - *USP-NF* Monograph: Dextrose (monograph includes Anhydrous form)
 - e. IID: Saccharin Sodium Anhydrous
 - *USP-NF* Monograph: Saccharin Sodium (monograph includes both dihydrate and anhydrous forms)
 - f. IID: Octanoic Acid
 - *USP-NF* Monograph: Caprylic Acid
- II. IID database uses a slightly different phrasing of the official title and cannot recognize that this is the same substance covered by the monograph:
- a. IID: Calcium Phosphate, Dibasic, Anhydrous
 - *USP-NF* Monograph: Anhydrous Dibasic Calcium Phosphate
 - b. IID: Phospholipid, Egg
 - *USP-NF* Monograph: Egg Phospholipid
 - c. IID: Sodium Phosphate, Dibasic, Anhydrous
 - *USP-NF* Monograph: Dibasic Sodium Phosphate
 - d. IID: Methyl Pyrrolidone
 - *USP-NF* Monograph: Methylpyrrolidone
 - e. IID: Cellulose, Oxidized
 - *USP-NF* Monograph: Oxidized Cellulose
- III. IID uses the proprietary name rather than the official title:
- a. IID: Aquacoat ECD manufactured by FMC Biopolymer
 - *USP-NF* Monograph: Ethylcellulose Aqueous Dispersion
 - b. IID: Lubritab manufactured by JRS Pharma
 - *USP-NF* Monograph: Hydrogenated Vegetable Oil
 - c. IID: Melojel manufactured by National Starch & Chemical Company
 - *USP-NF* Monograph: Corn Starch
 - d. IID: Nipasept (Blend of Methylparaben, Ethylparaben, and Propylparaben)

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12601 Twinbrook Parkway
Rockville, MD 20852-1790 USA
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Europe/Middle East/Africa

Münchensteinerstrasse 41
CH-4052 Basel, Switzerland
+41 (0)61 316 30 10

USP-India Private Limited

IKP Knowledge Park
Turkapally Village, Genome Valley
Shameerpet, Ranga Reddy District
Hyderabad 500 078, A.P., India
+91-40-4448-8888

USP-China

Building 11
Lane 67 Libing Road
Zhangjiang Hi-Tech Park
201203, Shanghai, China
+86-21-51370600

USP-Brazil

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06460-120, Brazil
+55-11-3245-6400



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- *USP-NF* Monographs for each component, Methylparaben, Ethylparaben, and Propylparaben
 - e. IID: Phenonip (Blend of Phenoxyethanol, Methylparaben, Ethylparaben, Butylparaben and Propylparaben)
 - *USP-NF* Monographs for each component, Phenoxyethanol, Methylparaben, Ethylparaben, Butylparaben and Propylparaben
- IV. IID uses the same UNII number for two substances with different compendial names:
- a. UNII number (F76354LMGR) is assigned to two different names (Propylene Glycol Monopalmitostearate, and Propylene Glycol Monostearate).
 - b. A review of the official titles in *USP-NF* (for Propylene Glycol Monostearate) and the European Pharmacopeia (for Propylene Glycol Monopalmitostearate) indicate qualitatively different specifications for the ingredients. The compendia define three tests common to both monographs with differing acceptance criteria: 1) the content of monoesters, 2) the Saponification value and 3) the Free Propylene Glycol values.

3. How should we reflect updates to the current IID to ensure completeness and accuracy?

FDA should 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 will 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 require new or revised public quality standards in *USP-NF*.

4. Should we restructure the IID, and if so, how?

The FDA should improve the nomenclature system in the IID as described in our response to Question 1 above. The IID should utilize the search tool described in our response to Question 3 to enhance usability. Finally, FDA should provide a separate entry in the IID that

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USP—India Private Limited

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Turkapatty Village, Genome Valley
Shameerpet, Ranga Reddy District
Hyderabad 500 078, A.P., India
+91-40-4448-8888

USP—China

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201203, Shanghai, China
+86-21-51370600

USP—Brazil

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includes a listing of the excipient manufacturers much like the Orange Book for Active Ingredient (API) manufacturers. This could help drug manufacturers more easily qualify a suitable grade excipient. Additionally, FDA could create a separate list in the IID for "novel" excipients not yet used in humans and not yet used in approved US marketed drug products.

5. Are there additional suggestions or comments for IID improvement?

List only those excipients in IID that have a corresponding *USP-NF* monograph or encourage the excipient manufacturers to work with USP at the time of entry to develop a *USP-NF* monograph to support the use of quality excipients. FDA also should include excipients used in Over-The-Counter (OTC) products in the IID to support the use of quality grade excipients in OTCs.

Thank you for your consideration of these comments and your work to improve the quality and safety of excipients used in drug products. If I can be of further assistance, please feel free to contact me at (301) 230-6318 or jpv@usp.org.

Sincerely,

Jaap Venema, Ph.D.
Executive Vice President and Chief Science Officer

USP Headquarters
12601 Twinbrook Parkway
Rockville, MD 20852-1790 USA
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