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June 21, 2022

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2022-N-0236 - 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

The Consumer Healthcare Products Association (CHPA)[1] appreciates the opportunity to provide feedback on the notice requesting comments on the Food and Drug Administration (FDA) Inactive Ingredient Database (IID). Responses to each of the questions listed by FDA in the March 22, 2022 notice are provided below.

1. **Should FDA focus on adding MDE information for certain excipients? If so, which excipients should be prioritized for inclusion of MDE information and why?**

CHPA agrees that FDA should focus on adding Maximum Daily Exposure (MDE) to the IID and is aligned with the list of priority excipients identified in the June 9, 2022, letter from the International Pharmaceutical Excipients Council of the Americas (IPEC; letter attached to these comments). In addition, CHPA suggests that FDA prioritize inclusion of MDE information for the following inactive ingredients:

- Potassium sorbate
- Titanium dioxide
- Starch

2. **Should FDA focus on prioritizing excipients used in certain categories of drug products (*e.g.*, oral or topical products)? If so, which categories and which specific excipients used in those categories should be prioritized and why?**

CHPA asks that FDA prioritize the following dosage forms for addition of MDE information on inactives.

i. topical (e.g., lotions, creams, ointments, patches, etc.)

[1] The Consumer Healthcare Products Association (CHPA), founded in 1881, is the national trade association representing the leading manufacturers and marketers of consumer healthcare products, including over-the-counter (OTC) medicines, dietary supplements, and consumer medical devices. CHPA is committed to empowering self-care by ensuring that Americans have access to products they can count on to be reliable, affordable, and convenient, while also delivering new and better ways to get and stay healthy. Visit chpa.org

ii. oral (e.g., solutions, suspensions, tablets, capsules, gums, lozenges, etc.)
iii. nasal (e.g., solutions, sprays, etc.)
iv. ophthalmic (e.g., emulsions, solutions/drops, etc.)

3. Is dosage form information in the IID helpful to your drug development program?

Inclusion of dosage form information is helpful to CHPA member companies, and we ask that FDA retain dosage form information in the IID. This information helps companies align with development progress and provides a baseline for over-the-counter (OTC) monograph product development. However, CHPA recommends that FDA adopt a tiered approach to collapsing information for oral dosage forms given the large number of dosage forms associated with this route of administration and the lack of a demonstrated effect on safety between the various oral routes of administration. This should be performed only after all current IID records for the oral route of administration are populated with a MDE value.

Collapsing of other dosage forms for additional routes of administration (e.g., topical) should be implemented in a phased approach based on industry input. This should be considered once all MDEs have been populated for a particular route of administration.

4. Is the current structure or format of the IID difficult to navigate? If so, how can it be improved?

CHPA suggests the following edits/additions to the IID to improve accessibility and searchability:

- Allow all fields to be searchable (e.g., by CAS number, UNII #, Dosage form)
- Allow searches which include multiple fields; examples include
  - **inactive ingredient** (starch), **route** (oral), **dosage form** (tablet)
  - **route** (topical), **Maximum Daily Exposure (MDE)**
- Allow searches based on commonly used ingredients[2]
- Allow (or provide) generation of a list of all available dosage forms in the IID – link to the FDA dosage forms document

[2] Example formulations Remington – The Science and Practice of Pharmacy. 23rd edition, October 2020

Other comments to FDA concerning the IID

CHPA asks that FDA enhance the information available on the FAQ page[3] related to the following items:

- Provide an explanation for cases where different MDE values are listed for dosage forms administered via the same route (e.g., two different MDEs for tablet and capsule oral dosage forms)
- Provide an explanation of the process from excipient review (including color additives and flavors) under an application to inclusion in the IID (including lag time)
- Provide an explanation of the impact of FDA MAPP 5021.2[4] on ingredient listing in the IID
- Provide examples of how to search on the IID landing page

CHPA also asks that FDA allow stakeholders to sign up to receive regular updates of the IID.

CHPA and our member companies appreciate the opportunity to comment on this process. Should you have any questions, please do not hesitate to contact me.

Regards,

Jay Sirois, Ph.D.
Vice President, Regulatory & Scientific Affairs
Consumer Healthcare Products Association

[3] Inactive Ingredients in Approved Drug Products Search: Frequently Asked Questions; accessed June 13, 2022
[4] FDA Manual of Policies and Procedures, Office of Pharmaceutical Quality - Evaluating Color Additives and Flavors Intended for Oral Drug Products Submitted or Referenced in INDs and NDAs. Effective June 18, 2021

International Pharmaceutical Excipients Council
Of The Americas

Nigel L. Langley, Ph.D.
Chair

June 9, 2022

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

cc: Lauren K. Roth, FDA, Susan Zuk

RE: Docket No. FDA-2022-N-0236: 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 or Madam,

Members of the International Pharmaceutical Excipients Council of the Americas (IPEC-Americas) have reviewed the docket titled, *"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."* Since June 2021, IPEC-Americas has been working with our members and the Association for Accessible Medicines (AAM) to provide FDA with priority lists of excipients to convert "maximum potency" to "MDE." IPEC-Americas supports streamlining the IID and recommends collapsing dosage forms in a systematic tiered approach, as described in our docket comments. We believe the proposed enhancements will aid the industry's ability to use the information in the IID to make better informed decisions related to the selection and level of use (quantity) of inactive ingredients in generic drug formulations and appreciate the opportunity to provide comments to questions posed in this Docket.

IPEC-Americas Background

IPEC-Americas represents more than 50 excipient manufacturers, distributors and pharmaceutical/biopharma companies to support the safe production and use of excipients. This letter represents the IPEC-Americas membership. A complete list of IPEC-Americas member companies can be found at: https://ipecamericas.org/what-ipec-americas/member-companies. IPEC-Americas is dedicated to working closely with regulatory authorities, industry organizations and scientific bodies (globally) to advance public health on matters relating to the quality, safety, manufacture, distribution, use and functionality of excipients. IPEC is the sole association representing excipients.

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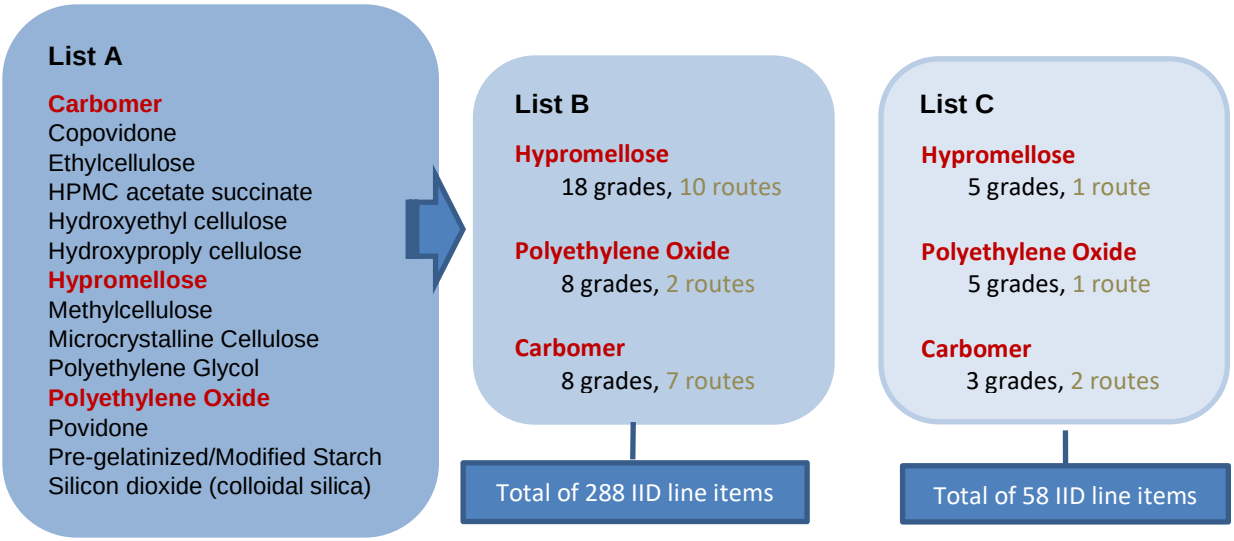
Below are comments from IPEC-Americas to specific questions asked in the Docket:

1. **Should FDA focus on adding MDE information for certain excipients? If so, which excipients should be prioritized for inclusion of MDE information and why?**

   IPEC-Americas strongly supports FDA continuing to add MDE information for certain excipients.

   By invitation from the Association for Accessible Medicines (AAM), on April 1 and June 29, 2021 members of IPEC-Americas participated in FDA-industry meetings to discuss IID issues/concerns related to GDUFA II commitments. As follow-up to the meetings, FDA was provided with multiple priority lists of excipients/excipient grades for updating maximum potency to MDE, including those highlighted below in Figure 1. Based on recommendations from FDA, List A was further refined to specify grades and routes, as illustrated below in Lists B and C (refer to tables in Exhibit 1[1] for more details).

   Figure 1: List of priority excipients from IPEC-Americas*



   * Presented by IPEC-Americas at a GDUFA II – IID Commitments meeting held June 29, 2021.

   IPEC-Americas recognizes and applauds FDA for having already populated MDE for many of the excipient grades/routes listed in Priority List 1-3, Exhibit 1. In addition, we have included our 4th priority list of excipient grades/routes in Priority List, Exhibit 1.

   In terms of general priorities for adding MDEs IPEC-Americas recommends the following order:

   - Common excipients that have different grades as shown above.
   - Common excipients with multiple listings in the IID for oral route of administration
   - Common excipients with multiple listings in the IID for topical route of administration

[1] Industry Proposed Priority List of Products for MDE Calculation

- Colorants and dyes with multiple listings in the IID

Upon selection of a specific excipient grade/route of administration, further recommendations from IPEC-Americas include:

- Populate all the lines for the excipient grade/route of administration.
- Determine the "actual" highest MDE for a given excipient grade/route of administration.
- Collapse line-items for similar excipient grades, when scientifically justified. IPECs recommendations on collapsing dosage forms is discussed in #3 below.

2. Should FDA focus on prioritizing excipients used in certain categories of drug products (e.g., oral or topical products)? If so, which categories and which specific excipients used in those categories should be prioritized and why?

Assuming FDA will prioritize the excipients described above, preferred routes of delivery would include oral, topical and parenteral.

3. Is dosage form information in the IID helpful to your drug development program? If so, please explain how dosage form information in the IID is used in your drug development program.

In determining the requirement for retaining dosage form information, it is important to consider the utility of the IID and information it contains that drives excipient decision making for both NDA and ANDA applications. As explained by FDA in many different documents and presentations, the function of the IID is to list the maximum daily exposure (intake) of an excipient that has precedence of use in an approved drug. The route of exposure and the MDE are important considerations for industry formulators when deciding whether to include an excipient in a formulation, based on precedence of use. It is understood that during review of an excipient for a drug application, the FDA may take additional safety factors into consideration, including exposed population and other drug product attributes.

Although dosage form may not be a key factor or determinant of safety for all routes of administration, in some instances, it may be an important factor to consider. For example, formulation characteristics and the amount of excipient used may be impacted by some dosage forms for topical and parenteral routes of administration. In order to systematically address this issue, as further discussed below, IPEC-Americas recommends that FDA take a tiered approach to dosage form collapsing.

Priority 1: As found in the IID searchable database, there are 57 different dosage forms associated with the oral route of administration. IPEC-Americas believes that there is no safety driven advantage in having all these dosage forms included for oral administration since the excipient safety, based on the highest MDE listed, would apply to all orally administered dosage forms. IPEC-Americas therefore strongly recommends that dosage forms for the oral route of administration be collapsed. It is unclear why some few dosage forms for example, aerosol, metered; inhalant etc., are associated with the oral route of administration, and IPEC-Americas

recommend that these dosage form records be investigated and possibly realigned with other routes of administration.

Any collapsing of dosage forms should be undertaken only after all the current IID records for the oral route are populated with MDE. This is critical to ensure that the highest MDE is captured in the IID.

Priority 2: There may be valid reasons to keep some granularity in dosage forms for other routes of administration. Upon completion of dosage form collapsing for the oral route of administration, streamlining/collapsing dosage forms for other routes of administration should be determined and implemented in a phased approach based on further input from industry. However, priority for collapsing any dosage forms should only be considered once all MDEs have been populated for that route of administration.

4. Is the current structure or format of the IID difficult to navigate? If so, how can it be improved?

The IID is difficult to navigate because it is incomplete and contains some misleading and/or inaccurate information. The challenge in determining which IID record is most appropriate to reference is complicated by two main factors:

1) incomplete or inaccurate records (e.g., silicon is listed as the inactive ingredient for oral drops, powder and suspension as well as for topical cream and TDDS; however, silicon is a metal and it is highly unlikely that it is present in any drug product formulation) and

2) lack of guidance for how an applicant might bridge to IID records when referencing the IID in an NDA or ANDA.

If all records were complete and accurate in the current format (i.e., listed route, dosage form, CAS, UNII, maximum potency, and MDE) a user could make a straightforward selection of the most appropriate entry for their product. However, as described above in Question 3, the database could be simplified by taking a phased approach to streamlining/collapsing dosage forms.

As shown in Table 1 below, the IID currently has missing values and multiple entries for the same route of administration and dosage forms.

Table 1: For specific grade & route of admin, MDEs missing for multiple IID listings*

Ingredient Name	Route	Dosage Form	UNII	Potency Amount	MDE
HYPROMELLOSE 2208 (15000 MPA.S)	ORAL	CAPSULE	Z78RG6M2N2	80.25 mg	
HYPROMELLOSE 2208 (15000 MPA.S)	ORAL	CAPSULE, DELAYED RELEASE	Z78RG6M2N2		75 mg
HYPROMELLOSE 2208 (15000 MPA.S)	ORAL	CAPSULE, EXTENDED RELEASE	Z78RG6M2N2	336 mg	
HYPROMELLOSE 2208 (15000 MPA.S)	ORAL	TABLET	Z78RG6M2N2	323.28 mg	
HYPROMELLOSE 2208 (15000 MPA.S)	ORAL	TABLET, COATED	Z78RG6M2N2	33 mg	

HYPROMELLOSE 2208 (15000 MPA.S)	ORAL	TABLET, EXTENDED RELEASE	Z78RG6M2N2		**4050 mg**
HYPROMELLOSE 2208 (15000 MPA.S)	ORAL	TABLET, FILM COATED, EXTENDED RELEASE	Z78RG6M2N2	300 mg	400 mg

* Previously presented by IPEC-Americas at a GDUFA II – IID Commitments meeting held June 29, 2021

Furthermore, MDEs listed should be higher than maximum potency listings for a specific grade of material/route of administration, but in several cases the current MDEs posted are lower than the max. potency, as shown below in Table 2.

Table 2: For specific grade & route of admin, MDEs are lower than max potency values

Ingredient Name	Route	Dosage Form	UNII	Potency Amount	MDE
HYPROMELLOSE 2910 (15000 MPA.S)	ORAL	TABLET, FILM COATED	288VBX44JC	60 mg	
HYPROMELLOSE 2910 (15000 MPA.S)	ORAL	TABLET, EXTENDED RELEASE	288VBX44JC	250 mg	
HYPROMELLOSE 2910 (15000 MPA.S)	ORAL	TABLET, COATED PARTICLES	288VBX44JC	445 mg	
HYPROMELLOSE 2910 (15000 MPA.S)	ORAL	FILM, SOLUBLE	288VBX44JC		18 mg
HYPROMELLOSE 2910 (15000 MPA.S)	ORAL	TABLET, ORALLY DISINTEGRATING	288VBX44JC		25 mg
HYPROMELLOSE 2910 (15000 MPA.S)	ORAL	CAPSULE	288VBX44JC		45 mg
HYPROMELLOSE 2910 (15000 MPA.S)	ORAL	TABLET, FILM COATED, EXTENDED RELEASE	288VBX44JC		80 mg
HYPROMELLOSE 2910 (15000 MPA.S)	ORAL	TABLET, MULTILAYER, EXTENDED RELEASE	288VBX44JC		84 mg

* NOTE: values in this table were from April 2021 because all listings for Hypromellose 2910 (15000 MPA.S) oral route of administration have been missing from the IID since June 2021)

While industry appreciates the work already completed by FDA, these gaps have created confusion resulting in an increased need to submit Controlled Correspondence and could also lead to an increase in Refuse to Receive situations. Further, this can adversely impact drug development and commercialization timelines. Therefore, IPEC-Americas recommends:

- Collapse IID dosage form listings for a given excipient grade/route of administration in a tiered approach (refer to IPEC-Americas comments for Question 3, above).
- Maintain both Maximum Amount Per Unit Dose (MAPUD) and MDE since they can both be relevant in formulation design and development. MDE exposure in a single dose could theoretically have a higher Cmax (acute) exposure or lower Area Under Curve (AUC) than spreading the MDE across multiple doses per day (e.g., 6-8 tablets). In other instances, the MDE amount given in one dose may not be tolerated well by the patient, whereas the same total amount spread over several doses throughout the day would be. This could apply to oral, topical, intra venous, and possibly other routes of administration. Thus, both MAPUD and MDE are important and could be used by industry to avoid the need for repeated human tolerability trials by using information that is already available.

- Provide a detailed explanation as to what and why a change was made in the change log when Max Potency or MDE levels are reduced or records eliminated.
- Change the term “maximum potency, per unit dose” to “maximum amount, per unit dose” or something similar in order to minimize/eliminate confusion.
- Improved linkage/reference for IID inactive ingredient nomenclature to synonym listings found in the Substance Registration System (SRS).

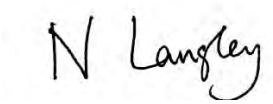
5. Other

Additional considerations should be to update the Draft Guidance for Industry on Using the Inactive Ingredient Database[2]. Although the current draft Guidance provides a good description of the IID (how it is structured and how nomenclature, maximum potency levels, and units of measure are presented), it does NOT cover how the database should be used. As described in IPEC-Americas comments to docket FDA-2019-D-2397-0010,[3] suggestions include:

- More clearly define purpose and utility of IID (how industry and reviewers look at the IID).
- Provide clear definition of routes of administration and dosage forms remaining in the IID. This will be helpful to both industry and FDA to improve consistency in future listing.
- Include information on how best build bridging justifications. Clarity around how to reference an IID listing that differs somewhat from the excipient targeted for use (e.g., different grade) would address some current issues.

Thank you for your consideration in reviewing our comments. IPEC-Americas would welcome further discussion on this topic with the FDA. Should you require further clarification to our comments, please let us know.

Respectfully yours,



Nigel L. Langley, Ph.D.
Chair, IPEC-Americas

[2] Using the Inactive Ingredient Database Guidance for Industry, Draft Guidance, U.S. Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (CDER), Pharmaceutical Quality/CMC, July 2019.

[3] https://www.regulations.gov/comment/FDA-2019-D-2397-0010

Exhibit 1

Industry Proposed Priority List of Products for MDE Calculation

Industry Priority List #1 – Shared with FDA June 28, 2021

Ingredient Name	Route of Administration
Hypromellose 2208 (100000 MPA.S)	Oral
Hypromellose 2208 (4000 MPA.S)	Oral
Hypromellose 2208 (100 MPA.S)	Oral
Hypromellose 2910 (5 MPA.S)	Oral
Hypromellose 2906 (4 MPA.S)	Oral
Polyethylene Oxide 200000	Oral
Polyethylene Oxide 5000000	Oral
Polyethylene Oxide 7000000	Oral
Polyethylene Oxide 2000000	Oral
Polyethylene Oxide 4000000	Oral
Carbomer Homopolymer Type B (allyl pentaerythritol crosslinked)	Oral
Carbomer Homopolymer Type B (allyl sucrose crosslinked)	Oral
Carbomer Homopolymer Type C (allyl pentaerythritol crosslinked)	Topical

Industry Priority List #2 – Shared with FDA Sept 7, 2021

Ingredient Name	Route of Administration
Hypromellose 2906 (4000 MPA.S)	Oral
Hypromellose 2910 (15 MPA.S)	Oral
Hypromellose 2910 (3 MPA.S)	Oral
Hypromellose 2910 (4000 MPA.S)	Oral
Polyethylene Oxide 100000	Oral
Polyethylene Oxide 1000000	Oral
Polyethylene Oxide 600000	Oral
Carbomer Copolymer Type B (allyl pentaerythritol crosslinked)	Topical
Carbomer Homopolymer Type B (allyl pentaerythritol crosslinked)	Topical
Carbomer Homopolymer Type B (allyl sucrose crosslinked)	Topical
Carbomer Homopolymer Type B (allyl sucrose crosslinked)	Topical
Carbomer Homopolymer Type B (allyl pentaerythritol crosslinked)	Transdermal
Carbomer Homopolymer Type C (allyl pentaerythritol crosslinked)	Transdermal

Industry Priority List #3 – Shared with FDA Nov 5, 2021

Ingredient Name	Route of Administration
Hypromellose 2208 (15000 MPA.S)	Oral
Hypromellose 2208 (3 MPA.S)	Oral
Hypromellose 2910 (4000 MPA.S)	Ophthalmic
Hypromellose	Oral
Polycarbophil	Buccal
Polycarbophil	Ophthalmic
Povidone K30	Oral
Povidone	Oral
Povidone K90	Oral
Polyethylene Glycol 400	Oral
Polyethylene Glycol 3350	Oral
Polyethylene Glycol 8000	Oral
Polyethylene Glycol 400	Topical
Starch, Modified	Oral

Industry Priority List #4 – Shared with FDA May 2022

Ingredient Name	Route of Administration
Carbomer Homopolymer	Topical
Carbomer Homopolymer Type A (allyl pentaerythritol crosslinked)	Oral
Carbomer Homopolymer Type B (allyl pentaerythritol crosslinked)	Ophthalmic
Copovidone K25-31	Oral
Crospovidone	Oral
Povidone K25	Oral
Povidone K12	Intravenous
Polyethylene Glycol 4000	Oral
Polyethylene Glycol 6000	Oral
Polyethylene Glycol 1450	Oral
Polyethylene Glycol 600	Oral