



IPEC Americas –GPhA-FDA-OPQ Face-to-Face Meeting, Inactive Ingredient Database (IID)

July 30, 2015

Attendees

FDA STAFF	ORGANIZATION: DHHS/FDA/	JOB POSITION	e-Mail
Susan Zuk	CDER/OPQ/OPPQ	Lead Chemist	Susan.Zuk@fda.hhs.gov
Rogelio Ruvalcaba, MS, RD	CDER/OPQ/OPPQ	Project Manager	rogelio.ruvalcaba@fda.hhs.gov
Karen Davis Bruno	CDER/OND/IO	OND Associate Director for Pharm/Tox	Karen.davisbruno@fda.hhs.gov
Robert Dorsam	CDER/OGD/DCR	Pharmacology/Toxicology Team Leader	robert.dorsam@fda.hhs.gov
Mohamed Ghorab	CDER/OPQ/OPPQ/DRGS/PD	Lead Chemist	Mohamed.Ghorab@fda.hhs.gov
Tim Jetton	CDER/OGD/ORO/DFR	Senior Regulatory Supervisor	Timothy.Jetton@fda.hhs.gov
John Leighton	CDER/OND/OHOP/DHOT	Supervisory Pharmacologist	leightonj@cderr.fda.gov
Abigail Jacobs	CDER/OND/IO	Pharmacologist, ODE Associate Director for Pharm/Tox	abigail.jacobs@fda.hhs.gov
Timothy McGovern	CDER/OND/IO	Toxicologist, ODE Associate Director for Pharm/Tox	Timothy.Mcgovern@fda.hhs.gov
Shahnaz Read	CDER/OPQ/OPPQ/DIPAP/P	Chemist	reads@cderr.fda.gov
Jason Woo	CDER/OGD/IO	Senior Medical Officer	Jason.Woo@fda.hhs.gov

IPEC MEMBERS	MEMBER COMPANY	Title	e-Mail
Katherine Ulman	Dow Corning Healthcare	Global Reg. Compliance Manager	Katherine.I.ulman@dowcorning.com
David Schoneker	Colorcon	Director, Global Reg. Affairs	DSchoneker@colorcon.com
Priscilla Zawislak	Ashland Inc.	Global Regulatory Affairs Manager	pszawislak@ashland.com
Meera Raghuram	The Lubrizol Corporation	Manager, Global Reg. Affairs & Strategies	Meera.Raghuram@lubrizol.com
Raphael Nudelman	Teva Pharmaceutical Industries Ltd.	Associate Director, Head of Chemical & Computational Toxicology	Raphael.Nudelman@teva.co.il
Kim Beals	IPEC-Americas Staff	Executive Director	Kim.beals@ipecamericas.org
Jeff Pitt	Dow Chemical	Toxicologist	jpitt@dow.com
GPhA		Title	e-Mail
Lisa Tan, R.Ph.	Generic Pharmaceutical Association	Associate Vice President, Sciences and Regulatory Affairs	ltan@gphaonline.org
Pharma	Consultant	Title	e-Mail
Bob Osterberg	Osterberg Pharm-Tox Consulting, independent consultant		pharmdrugs@cox.net

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Meeting Summary

1. Meeting purpose

Lisa Tan, GPhA (former FDA lead contact for the Office of Generic Drugs Inactive Ingredient Database Excipient Working Group - OGD IID EWG) provided a brief overview as outlined below:

Early in 2011, OGD started to receive concerns from industry about data integrity issues related to the IID, including missing and inaccurate data. In response, OGD formed the OGD IID Working Group in the fall of that year. The OGD IID Working Group, composed of representatives of review disciplines from across OGD, was charged with investigating concerns from industry as they related to inactive ingredients and the IID. The group looked at data discrepancies and various issues and concerns related to completeness, accuracy, and misleading data in the IID.

OGD, IPEC-Americas and GPhA have had numerous discussions focused on potential improvements and enhancements needed to be made to the IID to ensure that the IID can adequately support industry and Agency efforts to address growing concerns of safety, innovation and timely access to quality generic drug products. For the purpose of today's discussion, we will focus on just one of the enhancements, the Family Approach.

Susan Zuk spoke on behalf of FDA and stated that the FDA attendees were there to listen and discuss and that they would not be able to make any decision, pro or con on the discussion topic.

2. Meeting Agenda

a. Introductions

Susan Zuk called the meeting to order. Introductions were provided from the FDA and from the industry.

Susan indicated that the next IID update would occur within the next couple of weeks.

b. Overview presentation

To bring the new FDA attendees up to speed, a short presentation was provided by IPEC-Americas to provide the scope and perspective of the ongoing discussion and collaborative work with the FDA (see Appendix A).

The key topics included:

- Facilitating the Review of Excipients in ANDA Submissions
- IPEC-Americas Position on Family Approach
- Family Approach for Excipient Safety Assessment

- Using Appropriate Risk Management Concepts
- Exceptions to Testing
- Benefits of the Family Approach
- Risk Based Considerations

The presentation highlighted the pharm/tox studies completed for “families” of excipients were defined and designed across the entire family, and not just for individual members of a family. In addition, IPEC-Americas reiterated that many of the studies were generated years ago and the SAME safety data had been submitted to the Agency for review and re-review every time an excipient within the same family was used in a proposed drug product formulation. As a result, it is IPEC-Americas and GPhA’s belief that the maximum potency IID listings for a family of ingredients should reflect the highest level of use, for a specific route of delivery, by a given family member. Further, it is IPEC-Americas and GPhA’s belief that the adoption of such a process would dramatically reduce the current redundancy in the review of excipients and facilitate future IID review for maximum potency, especially at the time of filing for Abbreviated New Drug Application (ANDA).

A recent example was shared with the Agency which illustrated the need for a family approach. The example was of a Refuse-to-Receive (RTR) issued for an ANDA formulation which used an ethyl acetate version of a carbomer that exceeded the listed IID level. As a result, an alternative for the drug manufacturer would have been to reformulate using the benzene version (since it was listed at a higher acceptable concentration) vs the ethyl acetate version (toxicologically preferred solvent per ICH Q3C recommendations). *It is to be noted that these two excipients share the same UNII number.*

IPEC-Americas expressed numerous benefits of the family approach, including (but not limited to): transparency, minimize review time/resources, reduce errors and support use of UNI codes.

c. Example of DRAFT Pharm/Tox Templates

IPEC-Americas provide a backdrop to the development of the draft Pharm/Tox Template:

- July 17, 2013 IPEC-Americas/OGD IID EWG - J. Osterhout (FDA/OGD) developed a Pharm/Tox Template for IPEC-Americas IID members to review and provide feedback of safety information to the Agency.
- September 27, 2013 - a sub-team consisting of IPEC-Americas IID sub-team members and their company toxicologists revised the initial template to be more applicable for excipients vs drug product. Examples of the revised template were then populated with information for oral and topical delivery using hypromellose, polyethylene oxide, silicones and carbomers. Completed templates were forwarded to the Agency for review and comment; however, due to other priorities at the Agency (GDUFA commitment time-lines, moving campuses and Agency reorganization) final review/agreement on the content/organization of the templates was never officially confirmed.
- Due to the participant changes made from the FDA, three examples of the templates that were forwarded to the Agency’s for review from September 27, 2013 were shared again.
 - Hypromellose (oral route of delivery)
 - Carbomer (topical route of delivery)
 - Dimethiconol/trimethylsiloxysilicate crosspolymer (transdermal route of delivery)

Key points from the review included:

- For many family of excipients, members of the family are not only “chemically” equivalent but also have the same impurity profiles and utilized the exact same tox studies.
- Many of these excipient families are high molecular weight polymeric materials that are not absorbed (orally or topically) and have been shown to be non-toxic.

- For hypromellose there are more than 30 sub-members (identified by different UNII codes) ranging in viscosity from 3 MPa.s to 1,200,000 MPa.s.
- For hypromellose there is a wealth of historical, published pharm/tox studies/data to support their safe use in oral applications. In addition, they are currently approved at much higher concentrations (20 g/day by FDA and 30 g/day by JECFA) as food additives.
- There are over 200 “oral” IID listings for hypromellose which suggests that the exact same “safety” information for hypromellose may have been reviewed >200 times
- Although Type V DMFs including bridging documents have sometimes been prepared to support the family approach review, the Agency does not currently have access to these files during an ANDA filing review.
- Minor changes in substitution or end-capping often would NOT impact the pharm/tox safety study results (e.g. substitution of a methyl group for an “OH” on the ends of a polymer that has a degree of polymerization > 500).

d. Expected Outcome

- Formalized acceptance for use of the family approach.
- Posting of maximum levels of reviewed excipient family IID listings in spreadsheets on FDA websites (hypromellose, polyethylene oxide, carbomers and dimethicone).
- Process for submitting Pharm/Tox Templates for other “priority” excipient families.
- Revision of Refuse-to-Receive and Controlled Correspondence Guidance documents.

e. Open discussion and feedback from FDA on Pharm/Tox template structure and content

After reviewing the three examples of the populated Pharm/Tox Templates for oral, topical and transdermal delivery, the industry team posed the bulleted questions to the FDA attendees:

- What are the Agency’s safety concerns?
- What is needed at the time of filing vs. during the review for a family?
- What can industry do to provide the Agency the information they need to make a scientific safety assessment?

FDA’s response:

- During an ANDA application review, if an excipient is “not” listed or not listed at the desired “concentration” in the IID, the submitter needs to provide solid justification why that excipient should be considered acceptable (e.g. a bridging justification)
- As part of the justification or bridging argument for a family of ingredients, the author should not only include “what is the same”, but also “what are the differences” between each member of the family.

Follow up comments from industry:

- Although prior to the Refuse-to-Receive (RTR) and Controlled Correspondence (CC) Guidances excipient suppliers were able to contact FDA and indicate where ingredients had been previously used in approved drug products, even though the ingredient and/or higher levels of the ingredient were not listed on the IID, with the issuance of the RTR and CC Guidances, this pathway is no longer available to excipient suppliers.
- In most cases, where pharmaceutical ingredients have been shown to be safe for decades and where they may be used in high volumes for personal care products, the industry is not justified to perform additional animal studies because of European regulations banning animal testing for cosmetic ingredients.

3. Next Steps

- Jeff Pitt was tasked to prepare and submit Pharm/Tox Template for polyethylene oxide.
- FDA agreed to have further internal discussions on how they might use information from the meeting to develop a pathway for providing acceptable justification for families of excipients.
- In addition to the family approach, there are other significant issues related to the IID and inactive ingredients that need to be discussed. Kathy to work with Susan to schedule the next IPEC Americas –GPhA-FDA-OGD face-to-face meeting (to discuss non-family related topics/issues) for September 18th.

In closing, the industry team summarized that the difficulty is twofold, (1) getting past the OGD “gate keepers,” making reference to the ANDA Filing Reviewer and the current filing review process and (2) having the science speak to the justification of safety assessment of excipients. As the Agency moves towards risk based review and risk based assessment, it is imperative that the science and safety assessment be reviewed and a safety determination be made by subject matter experts during the technical review process and not during the filing review for a completeness assessment.

IPEC Americas - GPhA

IPEC-Americas and GPhA Proposals for Inactive Ingredient Reviews and the IID

Multiple
stakeholders;
one objective.



▶ International Pharmaceutical Excipients Council ◀
Collaborative solutions for excipient industry stakeholders

Today's Agenda

- ▶ Introductions
- ▶ Overview presentation
- ▶ Example of DRAFT Pharm/Tox Templates
- ▶ Open discussion and feedback from FDA on Pharm/Tox template structure and content
- ▶ Next steps
- ▶ Wrap-up

Facilitating the Review of Excipients in ANDA Submissions

We recognize and applaud the FDA for their recent work at updating and improving information listed in the inactive ingredients database (IID); however,

The ANDA process should be more efficient to help the Agency and industry meet GDUFA goals and reduce redundant reviews

- ▶ Use the excipient family approach to facilitate common pharm-tox evaluations for related excipients, especially at the time of filing
- ▶ Prioritize the one time review of excipient families, including hypromellose, polyethylene oxides, silicone, and carbomers
- ▶ Implement a standardized approach for supplying inactive ingredients information to streamline the submission and review processes
- ▶ Revise FDA guidance documents by correcting contradictory and inconsistent information

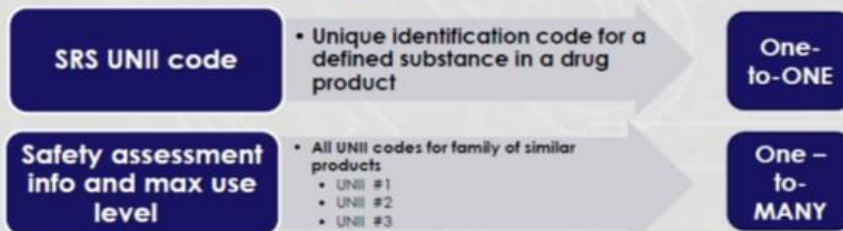
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IPEC-Americas Position on Family Approach

- Polymer excipients should be treated as a "family of substances" when considering safety/toxicity
- Update and streamline the IID, short-term-use spreadsheet approach
- Individual UNII numbers identify different grades within a family



UNII Codes ~~≠~~ Safety Assessment



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Family Approach for Excipient Safety Assessment

- ▶ **The current IID is insufficient to support efficient drug development and approval**
- ▶ Requiring toxicology data for **every grade** of an excipient is **not substantiated by scientific rationale and is not aligned with a risk-based approach.**

Synonyms	Solvent	UNII	Preferred Substance Name
Carbopol® 71G NF polymer	ethyl acetate	F68VH75CJC	Carbomer homopolymer Type A (allyl pentaerythritol crosslinked)
Carbopol® 971P NF polymer	ethyl acetate	F68VH75CJC	Carbomer homopolymer Type A (allyl pentaerythritol crosslinked)
Carbopol® 981 NF polymer	cosolvent	F68VH75CJC	Carbomer homopolymer Type A (allyl pentaerythritol crosslinked)
Carbopol® 941 NF polymer	benzene	F68VH75CJC	Carbomer homopolymer Type A (allyl pentaerythritol crosslinked)
Carbopol® 980 NF polymer	cosolvent	4Q93RCW2E	Carbomer homopolymer Type C (allyl pentaerythritol crosslinked)
Carbopol® 940 NF polymer	benzene	4Q93RCW2E	Carbomer homopolymer Type C (allyl pentaerythritol crosslinked)

- ▶ Different solvent grades have same UNII code
- ▶ All listings have the same chemistry and toxicology
- ▶ FDA has approved drugs with all 3 solvent grades

- ▶ **Utilizing a family approach during a safety review of related grades of excipients** used in a generic drug could lead to a **more efficient review and reduction of need for FDA resources** without compromising patient safety.

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Family Approach for Excipient Safety Assessment

- ▶ IPEC-Americas has been meeting with FDA's IID Expert Working Group since 2011 **and has supplied significant information to FDA to justify the use of a Family approach** to excipient safety assessment for related excipient grades
- ▶ Currently, FDA reviewers are "*re-reviewing*" the **same excipient toxicology data over and over for each grade of excipient in a family** – since new data does not exist for each grade - *redundant work!*
- ▶ Applying the family approach **will reduce the amount of redundant, non-value-added resources** needed to evaluate excipients under GDUFA

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Using Appropriate Risk Management Concepts

- ▶ Focus should be on high risk "safety" issues
 - ▶ Many common excipients are NOT high risk (e.g. hypromelloses, polyethylene oxide, dimethicones and carbomers)
 - Data has been available for years for families of these products. Submitting the same data for each grade material, multiple times to different reviewers is not value-added
 - These excipients have been used for **DECADES** without adverse "safety" events
 - Risk of adverse event due to "safety" issues/concerns are relatively low
 - FDA CURRENTLY uses this approach for food additives and cosmetic ingredient and in the past has used it for pharmaceutical excipients
 - Recent article¹ authored by FDA discusses a risk based approach for evaluating excipients in generic drugs
- ¹Toxicological Sciences, 146(1), 2015, 2-10.

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Exceptions to Testing

- ▶ High molecular weight polymers are **not readily absorbed** (oral >1,000 Daltons, topical >400 Daltons) and are **nontoxic**, (EPA 49 CFR No. 226, Nov, 21, 1984) i.e., PEGs, carbomers, hypromellose.
- ▶ High MW PEGs are used as laxatives.
- ▶ CDER, Excipients Guidance, Sect. 3 E:

*"excipients that are **large polymers** that differ from previously characterized excipients only in molecular weight (chain length) can be **adequately characterized** in an abbreviated manner **using less safety data**, provided that the new excipient is **sufficiently similar** to the others with regard to **physical state, PK, levels of unreacted monomers and other impurities**"*

- ▶ ICH Principles:
 - Reduce animal testing (duplication)
 - Streamline regulatory assessment (save time)
 - Maximize resources
 - All without compromising safety

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Benefits of the Family Approach

- ▶ **Transparency** to drug formulators on maximum excipient use levels by route as supported by toxicity data.
- ▶ **Minimizes** need for **multiple FDA reviews** of the same excipient toxicology data once a maximum use level has been accepted.
- ▶ **Expedites FDA review** of NDA's/ ANDA's.
- ▶ **Minimizes errors and resources** to maintain IID
- ▶ **Reduces the complexity** of the IID
- ▶ **Supports** continued use of unique **UNIs to identify individual polymers** by MW and degree of substitution.

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Risk Based Considerations

- ▶ High molecular weight polymers are not absorbed and would be nontoxic
- ▶ Prior human use of an excipient in food (direct food additives) and cosmetics should have sufficient safety data to qualify a new excipient for oral or topical applications
 - HPMC uses in food products: beverages, pie fillings, ice cream, bread, pasta, breaded coatings, breakfast cereals, tortillas, cakes, cookies, biscuits, granola bars, fruit juices, fish sticks, meat substitutes, peanut butter, sugar substitutes, candy bars, fruit roll-up type snacks, etc..
 - Most of these food substances are among the top 25 sources of calories among American children ages 2 years and older according to the NHANES 2005-2006 survey
- ▶ High MW polymer families have a demonstrated history of safety, e.g. hypromelloses, PEGs, dimethicones and carbomers.

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Example of DRAFT Pharm/Tox Templates

- ▶ Hypromellose (oral route of delivery)
- ▶ Carbomer (topical route of delivery)
- ▶ Dimethiconol/trimethylsiloxysilicate crosspolymer (transdermal route of delivery)

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Open discussion and feedback from FDA on Pharm/Tox template structure and content

- ▶ What are the Agency's safety concerns?
- ▶ What is needed at the time of filing vs. during the review for a family?
- ▶ What can industry do to provide the Agency the information they need to make a scientific safety assessment?

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IPEC-Americas/GPhA Expectations

- ▶ Formalized acceptance for use of the Family Approach by **Fall of 2015**
 - Use of the Family Approach for
 - Hypromellose
 - Polyethylene oxide
 - Carbomers
 - Dimethicone
 - Post "reviewed" Family Approach spreadsheets on FDA website
 - Process for submitting pharm/tox templates for other "priority" excipient families
 - Initiate revision of Refuse-to-Receive and Controlled Correspondence Guidances

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Questions?

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