



IPEC Americas-OGD Meeting, Inactive Ingredient Database (IID) – March 1, 2013

IPEC Americas –FDA-OGD Meeting, Inactive Ingredient Database (IID)

March 1, 2013

FDA Center in Rockville

Meeting Attendees

FDA STAFF	ORGANIZATION: DHHS/FDA/	JOB POSITION	e-Mail
Robert Iser	CDER/OPS/OGD/DCIV	Director, Div. of Chemistry IV	robert.iser@fda.hhs.gov
Lisa Tan	CDER/OPS/IO	Project Management/Special Project	felecia.tan@fda.hhs.gov
Jennifer Liang	CDER/OPS/OGD/DCIV	Chemist, Div. of Chemistry IV	jennifer.liang@fda.hhs.gov
Naiqi Ya	CDER/OPS/OGD/DCIV	Deputy Director, Div. of Chemistry IV	naiqi.ya@fda.hhs.gov
Huong Huynh	DHHS/FDA/CDER/OMPT/CDER/OPS/OGD/DBII	Pharmacologist, Division of Bioequivalence II	huong.huynh@fda.hhs.gov
Robert Reinwald	CDER/OPS/OGD/DLPS	Regulatory Support	robert.reinwald@fda.hhs.gov
James Osterhout	DHHS/FDA/CDER/OMPT/CDER/OPS/OGD/DCR	Senior Regulatory R	james.osterhout@fda.hhs.gov
Iain Margand	DHHS/FDA/CDER/OMPT/CDER/OPS/OGD/DLPS/RB	Senior Regulatory M	iain.margand@fda.hhs.gov
Johnny Young	CDER/OPS/OGD/DLPS/RSS	Reg. Health Proj. Manager	johnny.young@fda.hhs.gov
Nilufer Tampal	DHHS/FDA/CDER/OMPT/CDER/OPS/OGD/DBI	Lead Pharmacologist	nilufer.tampal@fda.hhs.gov
Jeen Min	CDER/OPS/OGD/DLPS	Orange Book staff	jeen.min@fda.hhs.gov

IPEC MEMBERS	MEMBER COMPANY	Title	e-Mail
David Schoneker	Colorcon	Director, Global Regulatory Affairs	DSchoneker@colorcon.com
Katherine Ulman	Dow Corning Healthcare	Global Regulatory Compliance Mngr	Katherine.l.ulman@dowcorning.com
Priscilla Zawislak	Ashland Inc.	Global Regulatory Affairs Manager	pszawislak@ashland.com
Ann Van Meter	Dow Wolff Cellulosics	Senior Quality Systems Specialist	vanmetma@dow.com
Meera Raghuram	The Lubrizol Corporation	Manager, Global Regulatory Affairs & Strategies	Meera.Raghuram@lubrizol.com



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Meeting Purpose

This meeting was the fifth meeting between IPEC Americas and the FDA OGD team identified to help resolve current issues with the FDA IID which have ultimately impacted abbreviated new drug applications (ANDAs). This team was created based on IID concerns identified at a joint meeting between IPEC Americas members and FDA OGD personnel back on December 9th, 2011. Minutes from previous meetings can be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm142112.htm>

Meeting Agenda and Actions

1. Introductions

Brief introductions and review of meeting agenda.

2. Review of Minutes from December 7, 2012 meeting

A review of the six action items from the December 7, 2012 showed that they were aligned with current agenda items and would therefore be discussed during the normal course of the meeting. No additional comments or changes were recommended.

3. Follow-up on status of the Family Spreadsheet for Hypromellose

a. Will approval occur by the end of Q1 2013?

Members of the FDA-OGD Excipient Working Group are currently working on

- activities to meet current GDUFA goals,
- hiring additional staff to help with IID update / backlog work and
- FDA reorganization activities.



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Historically the FDA-OGD Excipient Working Group (EWG) has been operating with limited resources dedicated to /aligned with the IID update project. In addition, as a result of work on GDUFA goals/objectives, activities associated with interviewing and hiring new employees (full time equivalents, FTEs) and reorganization of FDA personnel/departments, progress in the development and implementation of IID actions has been reprioritized. However, to ensure continued support for these activities, members of the EWG are currently working within their organization (OGD and OPS) to try and get additional resources approved to continue work with the IPEC-Americas IID committee and the identified committee activities. FDA personnel stressed several times that they believe it is very important for all team members to continue working on IID activities. Therefore, they are currently actively working to align the recommended IID refinements with GDUFA objectives to ensure development of a new/improved IID database equipped with appropriate change controls, update mechanisms, etc.

b. When will updated IID spreadsheet(s) be posted on the FDA website and where will they be located?

James (Jim) Osterhout commented that limited progress has been made towards being able to post the populated spreadsheets on the FDA website. Progress has been slowed by the need to focus on the design and development of GDUFA related activities, including identifying and hiring of FTEs. Team members noted that review, vetting and posting of these spreadsheets continue to be a high priority for the team and they will continue to seek Agency support to move forward with this.

IPEC-Americas members requested that FDA consider initially focusing and expediting their review, approval and posting of the hypromellose spreadsheet so that this could be referenced as an industry model for other excipient products. Additionally, since the hypromellose nomenclature issues caused much confusion regarding an appropriate Maximum Potency (per unit) limit to be used for various grades of hypromellose, there could be some major benefits for both FDA and industry if this one was completed and posted soon.

Jim noted that he has completed most of the work on the hypromellose review and is working to develop a table/template similar to the Agency's current pharm-tox table that could be used to expedite things in the future. Once complete, he would vet the "template" with the Agency and then provide IPEC with a copy to facilitate review. It is expected that this template could then be used by industry to provide a summary of relevant information (including bridging arguments, resource references and summaries for similar materials) to FDA ANDA reviewers in order to assist them in their review process.

ACTION 1: IPEC-Americas IID team to review the December 2011 IID minutes for the agreed upon interim process for including bridging family "safety" information at the time of filing an ANDA and create a summary process document including any additional refinements for industry to use. Document to be reviewed and discussed at next FDA-OGD EWG/IPEC-Americas working group meeting.

Once the summary document is developed and agreed upon, FDA personnel will review internally and propose a timeline for posting on the web site.

c. What type of training will OGD be providing to reviewers and industry to allow for an understanding of how to use the spreadsheet system in place of the IID for listed excipients?

Any new training pertaining to the use of the spreadsheets currently being developed will be aligned with new hire training, when possible. The current intent is to use the OGD webpage to communicate the process/information to industry. Where appropriate, an attempt will be made to



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hyperlink relevant items in the database to new/relevant information for ingredients currently being reviewed.

IPEC-Americas members offered to help communicate the process / templates / strategy to industry.

Information on the availability and use of the new spreadsheet would need to be sufficiently communicated both internally (to current FDA reviewers) as well as externally (to industry).

Once the database is available, it was suggested that FDA-OGD personnel and IPEC-Americas members conduct a joint webinar to help industry and reviewers understand the new concepts and how to use the new information /databases.

4. Follow-up on status of the Family Spreadsheets for Polyethylene Oxide, Silicones and Carbomers

Review timeline for these excipients have been delayed due to competing GDUFA priorities. It is anticipated that information on these excipients will be reviewed during 2013 and more definitive timelines will be discussed at the next meeting in May 2013.

5. Status of publication of a Change Log which could show what changed at each quarterly IID update on the website to allow for easier understanding of what changed since the last version of the IID

During the initial (December 7, 2011) working meeting with the FDA, it was agreed that FDA would try to create a “change log” that would provide industry with an overview of what changes had been made to the IID since the last IID update (quarterly).

FDA personnel noted that they are currently brainstorming what to include in the change log so that it would be useful to industry, while also maintaining the confidentiality of relevant products to which the changes might be in reference.

IPEC-Americas members noted that industry would like to know when:

- new materials are added
- routes of delivery or maximum potency concentrations increase or decrease
- as appropriate, explanation for why a maximum potency would need to be decreased.
- changes in nomenclature occur, including both prior and updated nomenclature (ie; SRS changes, etc.) .

Although FDA personnel noted that they are still actively working on developing and implementing a change log, they still need to finalize their design, develop procedures and acquire approval. In the interim, they are actively working to reduce the backlog of ingredient listings currently missing from the database. For specific questions related to information contained (or not contained) in the current IID, the FDA continues to recommend industry use the “controlled correspondence” mailbox to solicit clarification and support from the FDA.

Although not directly linked to GDUFA objectives at this time, the plan is to include response times to “controlled correspondence” as part of the new GDUFA measures. Based on current GDUFA goals, the target response time are as follows:

- FY 2015: FDA will respond to 70% in 4 months
- FY 2016: FDA will respond to 70% in 2 months
- FY 2017: FDA will responde to 90% in 2 months.

**If the control correspondence requires input from the clinical division, one additional month will be added to the goals outline. In cases in which issues or questions are subject of one or more pending



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citizen petitions, or petitions for stay or reconsideration, the above goals will apply from the date FDA issues the response to the pending petition(s).

IPEC-Americas members mentioned that industry would also still like to have advance notice of changes, if possible.

6. Review of Proposed Frequently Asked Questions and IPEC generated tentative answers

a. Status of FDA review

FDA-OGD EWG had reviewed the DRAFT FAQ responses proposed by IPEC-Americas members at the previous meeting (December 7, 2012) and had documented additional comments/responses to about half of the questions. Copies of their comments were provided to the IPEC-Americas team members. Due to limited time for discussion at the March 1 meeting, review of the Q&A and additional FDA comments were postponed until the next meeting (mid-May, 2013).

ACTION 2: FDA-OGD EWG and IPEC-Americas IID team to spend time reviewing FAQ questions and responses at our next working meeting in May 2013.

b. Additional questions submitted March 1, 2013

IPEC-Americas provided an additional set of questions and proposed answers to the FDA-OGD EWG for consideration:

1. What type of supporting information should be provided to OGD in an ANDA for Proprietary Flavors which are not specifically listed in the IID? Since these are usually complex mixtures and designed primarily for food applications, the composition will typically not be available to the ANDA sponsor except potentially in a Type IV DMF reference. Can food references be used to support the safety of these flavors in an oral dosage form when a flavor has not been previously used in pharmaceuticals?
2. For Proprietary formulated excipient systems like flavors, fragrances and coating mixtures, is it possible to ONLY provide a DMF reference with the specific page number(s) where the quantitative composition is listed since these confidential formulations cannot always be shared with sponsors? FDA could then determine if IID listings and levels are exceeded during the application review instead of at the time of filing? If this cannot be done, it defeats the entire purpose for a Type IV DMF.
3. What should ANDA sponsors do when FDA lowers a maximum potency level of an excipient in an IID quarterly update due to some type of mix-up in what was actually used in a previously used drug (ie; Titanium Dioxide was lowered twice recently)? What should be done if ANDA drugs which are under review may have been formulated with a level of this excipient that was lower than what was previously in the IID but is now above the new level that was changed in the quarterly update? Will the ANDA sponsor have to submit additional safety data to support this use even though they followed FDA's own guidance in the IID during product development?
4. What Maximum Potency levels should be used when doing an IID assessment for materials which may be very similar to other materials within a family of products or may be a subset of a broader family but the maximum potency levels may be quite different for excipients listed under related names? Examples which need clarification would be items such as Corn Syrup and High Fructose Corn Syrup or Glyceryl Mono-oleate and Monoglycerides?

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5. Can the IID listing for a complex material such as Ethylcellulose Dispersion Type B NF (listed currently as Surelease E-7-19010 - made with animal derived oleic acid) be used for a version of the same exact product which simply uses vegetable derived oleic acid in place of the animal derived oleic acid but has a different formulation number (Surelease E-7-19040)? Both grades meet the same NF monograph.

7. *Miscellaneous discussion topics*

a. **Discussion of IPEC Americas Excipient QbD Training Initiatives and possible opportunities to collaborate with OGD**

IPEC-Americas members offered to support additional QbD training for reviewers (OGD and OND). Part of the discussion pertained to potential team member support in developing guidelines for excipient QbD sampling. This was further discussed with specific future plans after the meeting.

b. **Discussion of IPEC Americas FDASIA/GDUFA related activities**

The IPEC-Americas team members informed the FDA-OGD EWG members that IPEC-Americas is currently preparing letters to the FDA pertaining to 3 areas of FDASIA: 1) Title 3 pertaining to site registration and DMF completeness assessment fees for APIs, specifically as related to atypical APIs, 2) Title 7 pertaining to supply chain requirements, including but not limited to excipient site registration and listing requirements and 3) Title 11, subsection on nanomaterials. Plans are to copy Bob Iser on these letters, specifically for OGD awareness and future reference.

IPEC-Americas also noted that they would be updating the IPEC-Americas Master File Guide in 2013; therefore, they would be interested in meeting with personnel at the FDA to ensure IPEC understands what information (and in what format) the FDA is most interested in including for excipient DMF submissions. IPEC-Americas members also thought they could help communicate the need, desire and relevant information/instructions for electronic DMFs, given additional guidance from the FDA.

ACTION 3: Jeen Min agreed to help define a small FDA team for the IPEC-Americas regulatory members to work with pertaining to information (and format) for industry to include in excipient DMFs.

Subsequent to the meeting Lisa Tan also communicated that she had contacted the FDA DMF Team leader pertaining to some of our questions/concerns about excipient DMFs, especially where excipients might be used as atypical APIs. The DMF Team leader recommended inquiries be sent to DMFOGD@fda.hhs.gov, an email account that is monitored by the FDA DMF team.

c. **Missing information from current IID list**

IPEC-Americas again asked for the best mechanism for getting something added to the IID that industry knows is used in an approved NDA or ANDA. FDA response was to continue to use the “controlled correspondence” mailbox to provide information about name and use of the missing ingredients (or higher max potency levels), including filing references (NDA / ANDA number) and to specifically request for the FDA to review and, as appropriate, add the ingredient to the IID if its use in a CDER-approved drug product can be confirmed.



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8. *Select Next Meeting Dates for the rest of 2013*

The next meeting date was proposed for May 17, 2013. Since the meeting, Lisa Tan has communicated back to the team to confirm that May 17th from 9:30-11 should work for the FDA-OGD EWG. Final data/time/agenda to be confirmed in early May.

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