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<tr>
<th>IPEC MEMBERS</th>
<th>MEMBER COMPANY</th>
<th>Title</th>
<th>e-Mail</th>
</tr>
</thead>
<tbody>
<tr>
<td>David Schoneker</td>
<td>Colorcon</td>
<td>Director, Global Reg. Affairs</td>
<td><a href="mailto:DSchoneker@colorcon.com">DSchoneker@colorcon.com</a></td>
</tr>
<tr>
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</tr>
<tr>
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</tr>
<tr>
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<td>Executive Director</td>
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</tr>
<tr>
<td>Jeff Pitt</td>
<td>Dow Chemical</td>
<td>Toxicologist</td>
<td><a href="mailto:jpitt@dow.com">jpitt@dow.com</a></td>
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<td>Dow Corning</td>
<td>Toxicologist</td>
<td><a href="mailto:Joe.tobin@dowcorning.com">Joe.tobin@dowcorning.com</a></td>
</tr>
<tr>
<td>Robert Vincent</td>
<td>Teva</td>
<td>Dir, RA Project Mgmt &amp; Review</td>
<td><a href="mailto:Robert.vincent@tevapharm.com">Robert.vincent@tevapharm.com</a></td>
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<tbody>
<tr>
<td>Lisa Tan</td>
<td>Associate Vice President Science and Regulatory Affairs</td>
<td><a href="mailto:ltan@gphaonline.org">ltan@gphaonline.org</a></td>
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<tr>
<td>Myra Weiner</td>
<td>TOXpertise LLC, Principal</td>
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</tr>
</tbody>
</table>
Meeting Summary

1. **Agenda Items for December 12 Meeting**
   Copy of presentation is attached

2. **Dave Schoneker and Meera Raghuram presented on evaluation of safety for an excipient family and acceptable levels in generic drugs using efficient scientifically-based mechanisms. Key elements of these slides include**
   - Introductions: FDA-IPEC Joint IID Team and Goals
   - Key issues from past discussions
   - Benefits for FDA and Industry
   - Appropriate Resource and Risk Management
   - Need for a Family Approach to Safety Evaluation of Related Excipient Grades and Similar Excipients
   - Spreadsheet Compilation and Model Excipient Safety Reviews
   - Implications to QbD from IID uncertainty
   - Implications to GDUFA Dates & Controlled Correspondence
   - Decisions and Clear Action Plan Needed

   - FDA guidance on Non-clinical Safety Evaluation of Excipients – Options and flexibility to allow for family approach

4. **Jeff Pitt presented on polymer chemistry and the science behind the family approach**
   - Polymer Chemistry – Typical safety evaluations performed by Industry
   - REACH and EPA definitions – Utilization of family approach
   - Examples of family models
   - Evaluation of polymers by other regulatory bodies (cosmetics, food, etc.)
   - Rationale for family approach
   - Jeff shared the “Standardized pharm tox template” previously developed and completed for Hydroxypropyl methylcellulose and provided to the OGD EWG
5. **Meera Raghuram presented on FDA Guidances - Conflicts and actions needed to resolve current issues**
   - FDA guidance & policies on Refuse to Receive (RTR) and ANDA Content
   - Related Routes of Administration – “New” Excipient Definition
   - Controlled Correspondence guidance & policies
   - Impact on Review Times and Patient Access
   - Next Steps

6. **Dave Schoneker concluded the presentation by stating the expectations of IPEC-Americas and GPhA and summarized the “Top Priorities and Current Focus Areas” that warranted FDAs immediate attention.**

7. **Q&A/Discussion**
   - **Robert Dorsman** – OGD Clinical reviewer shared his thoughts following the presentation:
     - Understands and agreed that there is a need to clean-up the nomenclature issues
     - Understands the need to minimize novel safety tox data requirements while maximize assurance of the safety of use of new/novel ingredients
     - Context of use….NDA looks at excipient in the “drug formulation” whereas in ANDAs they do not have the option to do so at time of filing because clinical studies are not required, OGD needs to ensure risk profile be spot on with the RLD.
     - Understand the need to clarify “novel” vs “new” excipients.

   - **Iain Margand** – OGD filing representative raised a question regarding using potentially “outdated data” to support a proposed level of an inactive ingredient often found in a DMF. The IPEC stated that new pharm/tox data is not being generated on already existing inactive ingredients and they see no need to update or reproduce the studies for inactive ingredients which are not listed in the IID (i.e., part of a family) but firms would like to utilize.

   - **Lisa Tan** – Representing GPhA, voiced concerns with FDA’s use of the IID in its current state to make regulatory decisions. Concerns with continued use included:
     - Limitations on drug manufacturers’ ability to utilize better inactive ingredients during drug product development
     - An incomplete IID impact manufacturers’ efforts to innovate by increasing the uncertainty associated with a particular ingredient level found in the database.

   Lisa noted that:
   - Industry wants to meet the quality expectations of the Agency and requested that FDA allow help to provide the tools necessary for industry to achieve quality standards FDA are expecting.
   - A possible alternative to the IID was proposed and Lisa stated she would follow up with key FDA stakeholders to explore all viable options.

   It was requested that members of the FDA further review the information provided in the slides, discuss the information internally, formulate additional questions, if required, and provide next steps. FDA was asked to have a decision on the Family approach by the next quarterly meeting.

8. **Adjournment and Date for Next Meeting**
   The next quarterly meeting will be held in late February.
Appendix 1
IPEC-OGD Meeting Discussion of Family Approach to Excipient Safety

IPEC-OGD Meeting Discussion of Family Approach to Excipient Safety Issues

December 12, 2014

Initial IPEC Discussions with FDA-OGD on IID Issues

December, 2011

December, 2014
2011 – Mutual Desired Outcome & Goals

- Acceptance of historical (pre-July 2011) maximum potency levels
  - Mechanism to supply "one-time" safety data/bridging studies for "families" of comparable materials
  - Interim transition process to support current ANDA filings
- Co-develop mechanism to apply "appropriate" nomenclature for all excipients (including mixtures)
- FDA/OGD utilization of DMF "safety info", for those excipients that have a DMF, during assessment for acceptance for filing
- FDA communication transparency with Industry to ensure accurate and complete data is captured in the IID for reference by the FDA and industry.
- Enhanced communication between the FDA and industry to ensure misleading and inaccurate data is identified and corrected.
- FDA to develop documented procedures on how to handle and correct discrepancies identified in the IID to ensure no delays are encountered during the filing review process.

IPEC-Americas Position on Family Approach

- IPEC-Americas position is
  - polymer excipients should be treated as a "family of substances" when considering toxicity
  - Spreadsheet concept
  - Individual UNII numbers would still be assigned
UNII Codes = Safety Assessment

Need to differentiate between Substance ID (particular material / substance) versus safety coverage (may have been designed to cover a family of materials).

- **SRS UNII code**
  - Identification of a specific substance which exists in a previously approved drug product
  - One-to-ONE

- **Safety assessment info and max use level**
  - All UNII codes for family of similar products
    - UNII #1
    - UNII #2
    - UNII #3
  - One-to-MANY

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IID Listings for Hypermellose

In the case of the new SRS nomenclature used to determine the acceptable level of hypermellose (e.g., 0.002 [MPA]), this would result in saying that levels over 0.002 mgkulose might require full safety data which doesn't make any sense!
Carbomer – Example of RTR Based on IID Information

- Different solvent grades have same UNII numbers (i.e. same chemical structure, similar viscosity)
- All listings have the same chemistry and toxicology
- Historical FDA approval of all 3 solvent grades in approved drug formulations

RTR issued since an equivalent ethyl acetate grade was not listed in the IID, even though other grades exist with more desirable solvents.

This IMPLIES that FDA prefers the benzene grade (since it is listed in the IID) even though other grades exist with more desirable solvents.

IID Team - Project status through 2014

<table>
<thead>
<tr>
<th>Project</th>
<th>Status (minutes posted at website below)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharm tox information to support prioritized families of excipients (hypromellose, polyethylene oxide, silicone, carbomers)</td>
<td>Data and references compiled and submitted since 2012, awaiting final review and posting</td>
</tr>
<tr>
<td>Interim process for providing family justification</td>
<td>Proposed and awaiting FDA internal agreement and support</td>
</tr>
<tr>
<td>NOTE: The ANDA RTR guidance needs updating to be consistent with the interim process</td>
<td></td>
</tr>
<tr>
<td>Pharm Tox table/template</td>
<td>Developed, awaiting final FDA approval and posting (Model product data submitted in 2012)</td>
</tr>
<tr>
<td>Phase I IID FAQ</td>
<td>Finalized in mid 2014, awaiting internal FDA vetting and posting</td>
</tr>
<tr>
<td>Phase II IID FAQ</td>
<td>Drafted but on hold until interim process for providing family justification is vetted within the FDA</td>
</tr>
</tbody>
</table>

http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm385388.htm
Use of Appropriate Risk Management Concepts

- **Focus should be on high risk issues**
  - ICH Q9 Risk Management Guidelines - focus should be on higher risk issues
  - FDA leadership (e.g., Hamburg, Woodcock) expressed their intent on focusing the Agency’s limited resources in higher risk areas

- **Reality for many common excipients (e.g., hypromelloses, polyethylene oxide, dimethicones, etc)**
  - Original safety data generated many years ago for “families” of products would require the same data to be submitted for each grade of material, multiple times to different reviewers.
  - Ingredients safely used often 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

**Is this the best utilization of FDA resources?**
**Is it value added and does it result in reduced risk??**

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**Susan Rosencrance, Ph.D.**

GPhA/FDA CMC Workshop
June 3-4, 2014

Chemistry-Related Controlled Correspondences

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**IID Confusion**

Calendar Year
NEED FOR FAMILY APPROACH

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.
- **Speeds FDA review** of NDA’s/ ANDA’s.
- **Minimizes errors and resources** to maintain IID
- **Supports** continued use of unique **UNII to identify individual polymers** by MW and degree of substitution.
Acceptance Needed Based on Safety Data Realities for Common Excipients

- **Acceptance of previous IID levels** based on safety data
- **Acceptance for use of "families of substances"** based on safety assessments which have resulted in group ADIs
- **A process for applying a maximum use level for "families" of similar excipients** based on similar "safety profiles",
- Need to maintain "proprietary" nature for certain excipient information, FDA OGD reviewer reference to safety information from excipient (Type IV or Type V) DMFs during ANDA assessment and review

SCIENCE BEHIND THE FAMILY DISCUSSION
FDA/CDER/CBER

Guidance for Industry - Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients

Robert E. Osterberg, RPh, PhD, Fellow-ATS
Osterberg Pharm-Tox Consulting LLC
Chevy Chase, MD 20815

The Guidance

• Why develop it?
• What was the intent?
  – pathway needed for qualification provide internal GUIDANCE for reviewers and external guidance for industry
  – never intended to be a binding regulation
  – allows for thinking and judgment on the part of the reviewer
The Guidance

- How developed?
- The guidance followed ICH M3 and other ICH Guidelines – Why?
  - to prevent duplication of animal testing
  - streamline the regulatory assessment process for NDAs
  - promote the economical use of animals and materials
  - without compromising safety

The Guidance

- The guidance discusses NEW excipients. These have been used in medicines before
- Additional safety data may be needed to comply with current standards OR the excipient needs a higher use (potency) level, duration or new route of exposure
- Novel excipients have never been used in drug products
The Guidance

- Exceptions to testing
  - Existing human data takes precedence over animal data but must be extensive
  - obtained from prior human use as direct food additives (applies only to oral use)
  - has been used for centuries in drugs
  - GRAS/JECFA substances – considerations for oral uses

Exceptions to testing?

- Excipients used in previously approved products
- those having GRAS status as a direct food additive
- similar route of administration
- similar level of exposure (potency), patient population, duration of exposure associated with prior use could qualify a new excipient
Exceptions to testing

- Polymers exceeding 1000 Daltons are not readily absorbed from the GI tract (CIR, EPA 49 CFR No. 226, Nov. 21, 1984) i.e., PEGs, Carbopol etc.

- Sect 3E: “... 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 other with regard to physical state, PK and levels of unreacted monomers and other impurities”

Exceptions to testing

- **Carcinogenicity** concern:
  - The Excipient guidance and ICH S1A state that:
    - If the excipient is not genotoxic, not from a family of carcinogens, has no structural alerts, no pharmacological activity, is not a reproductive toxicant, has a **very large** Margin of Safety, has no long-term tissue retention and shows no severe toxicities (preneoplastic lesions) in long term oral toxicity studies, carcinogenicity studies may be waived
Conclusions

- High molecular weight polymers are not absorbed (Oral - 1000 Daltons, Topical – 400) and would be nontoxic
- High MW PEGs are used as laxatives
- Prior human experience of a new excipient in food consumption (direct food additives) may have sufficient safety data to qualify a new excipient
- Prior NDA approval may qualify a new excipient
- Families of high MW polymer excipients have shown safety, i.e. PEGs, Carbomers
- The Guidance is just a guidance and NOT a regulation. It allows for judgment following thinking.

Excipients – A Family Affair

Polymers

Jeffrey Pitt
Senior Product Stewardship Manager
The Dow Chemical Company
jpitt@dow.com
How is Polymer Defined?

- **US FDA** (Callahan et al.,)
  - Structural repeating units, type, geometry, type of copolymer (block or random), ratio of monomers, modifications, molecular weight or properties related to molecular weight, biological source for many biopolymers
  
  http://www.fda.gov/aboutfda/centersoffices/officesofmedicalproductsandtobacco/cder/ucm380688.htm

CDER Regards Polymers as Individual Substances

- **Substance definition** (Callahan et al.,)
  - based on what something is, not on how it is made or used.
    - PEG vs. PEO
    - vitamin C from oranges vs. manufactured vitamin C
  - absolute properties separate from physical form, grade or purity
  - changes in molecular structure results in a new substance
    - hypromellose vs. cellulose
  - no ambiguity
    - PEG vs. PEG 3350
  - “Materials that are defined as the same substance are not necessarily bioequivalent or pharmaceutical equivalents.”
CDER Regards Polymers as Individual Substances

**HPMC Example**

<table>
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<tr>
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<th>UNIT</th>
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<tr>
<td>HYDROMELLOSE 210 [3 MPA.S]</td>
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<td>RYU13PM1Y82</td>
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EPA/ECHA: all HPMC (hypromellose) grades are the same.

**Typical Polymers**

- **PEG**
- **HPromellose**
- **Polyacrylamide**

**Key is ≥3 Repeating Monomer Units**

Di(2-ethylhexyl) phthalate *is not a polymer*.

Di(2-ethylhexyl) phthalate *is a polymer*.
Generally Polymers Are/Have

- High molecular weight
  - Carbohydrate: rye pentosans 225,000 to 700,000 Da
  - Hypromellose 4000 to 1,900,000 Da
  - PEO 200,000 – 8,000,000 Da
  - PEG 400 – 100,000 Da
- Not absorbed (exception water soluble fiber)
- Chemically inert
- Similar toxicity across MW
  - PEG 400 to PEO 8,000,000

Family Approach (Read-Across)

- What is a Family/Group (ECHA)
  - structurally similar with physicochemical, toxicological, ecotoxicological and/or environmental fate properties that are likely to be similar or to follow a regular pattern may be considered as a group of substances.
    - Common functional group (i.e. chemical similarity within the group) C14-16 (even numbered) and C16 (branched) saturated and unsaturated aliphatic hydrocarbons
    - Common precursors and/or likely common breakdown products via physical and/or biological processes which result in structurally-similar degrading chemicals
    - A constant pattern in the properties across the group (i.e. of physico-chemical and/or biological properties) CHELANTS - PDHA, NTA, EDTA, DTPA, sodium, zinc, iron, ammonium EDTA
Family Approach (Read-Across)

- **Read-Across (ECHA)**
  - technique for predicting endpoint information for one substance, by using data from the same endpoint from (an)other substance(s). The read-across approach must be considered on an endpoint-by-endpoint basis due to the different complexities (e.g. key parameters, biological targets) of each endpoint.

- **EPA**
  - Chemical Assessment Clustering Engine designed to help facilitate read across to fill data gaps for untested substances
  - HPV program: glycol ethers category; chelants

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Excipient Polymers

- **Model Excipient Polymers**
  - Meet EPA’s definition of Polymers of Low concern*
    - Includes functional groups carboxylic acids, aliphatic hydroxyl, unconjugated olefinic groups, etc (i.e. no reactive groups)
    - Stable non-reactive backbones of high molecular weight.
  - Polyethylene Oxide and Hypromellose (HPMC)
    - Peer reviewed in JECFA and/or CIR documents
    - HPMC – GRAS status for food additives
    - Pharmacokinetic and Oral Repeat Dose Studies in Animals and Humans

What Has Been Submitted to FDA & Other Agencies

- Hypromellose (HPMC)
  - GRAS: 20 g/day limit via food
  - JECFA: reviewed multiple cellulosics (HPMC, ethyl carboxymethyl, etc.); did not limit consumption via food, i.e., ADI “not specified” = does not represent a hazard to health.
  - CIR: toxicology data from 26 cellulosics show the family to be non-toxic.
  - Work with OGD Standardized tox templates have been provided for all 4 priority excipients

Conclusions

- The family approach and read across are appropriate for polymers
  - Non-toxic
  - Limited or no absorption (large inert molecules)
- Where dietary approvals exist, there is minimal concern for pharmaceutical use
  - HPMC GRAS ≤20 g/day indicate a lack of toxicity for entire family
  - JECFA ADI “not specified”
Impact of FDA/GDUFA Draft Guidances on the IID

Impact of FDA GDUFA Guidances and Goals on Industry related to Excipients

- Industry's non clarity and confusion pertaining to FDA's policy for inactive ingredients. The FDA's policy must be clarified and communicated, on a consistent bases, in guidance documents.
- Draft guidance's do not reflect historical practices for either the industry or FDAs review of inactive ingredient information.
- Failure to understand and clarify inactive ingredient issues prior to finalizing guidance documents will impact the overall goal and commitment of GDUFA - predictable and timely review of applications.
- The generics pharmaceutical industry is not able to submit "high quality applications" and reduce the number of review cycles without the Agency addressing the fundamental issues and concerns with inactive ingredients.
**ANANDA Submissions – Refuse-to-Receive Standards**

- Excipient level is considered justified if the proposed level is **at or below** the amount indicated in the IID.

- **Three options** provided for excipients exceeding IID levels:
  1. Submission of complete pharm/tox information. Agency is not prepared to offer its current thinking on this subject at this time. The Agency anticipates addressing this issue in a separate guidance.
  2. Cite a CDER-approved drug product with inactive ingredient at proposed levels.
  3. Request prior FDA evaluation through controlled correspondence prior to ANDA submission.

  **Note:** Pharm/tox data cannot be submitted with controlled correspondence.

- If FDA will refuse to receive an ANDA if the above criteria's are not followed.

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**ANANDA Submissions – Refuse-to-Receive Standards**

- **IPEC REQUESTS:** Amend the guidance to include the following information with regards to excipients:
  - Allow use of published studies in peer reviewed journals and other regulatory filings such as food additives, cosmetics etc.
  - Allow for exceptions where prior human exposures under conditions relevant to the proposed use would negate requirements for the full battery of toxicology studies.
  - Allow ANDA applicants to reference the excipient DMF for detailed study information, if available, rather than asking the sponsor to provide this information outside of the DMF system where confidentiality is no longer protected.
  - Allow for justification of the level of use of the excipient by citing the level listed in the IID for a related excipient within the same family.
Refuse-to-Receive Standards – NOTE 41

- Clarify the definition of the type of a novel excipient
- Articulate why an excipient with precedence in a related route of exposure and data supporting safe use will be considered a novel excipient and subject to an RTR
  - Requirement for submission as a 505(b)(2) application is not a viable approach

Controlled Correspondence Related to Generic Drug Development

- Topics not related directly to generic drug development will not be considered controlled correspondence
- Suggests that missing IID data would not be considered as controlled correspondence
  - Not given a number or tracking
  - Any correspondence related to missing or inaccurate information in the IID should come directly from ANDA sponsors (not suppliers who may have this knowledge)
- No clear pathway for industry to communicate data discrepancies in the IID
Expectations from Today’s Meeting

A committed timeline on when FDA will be able to respond to the information presented. FDA decision on the use of the family approach to justify inactive ingredient levels.

- Non-action by the FDA:
  - Impedes GDUFA goal metric for ANDA and Controlled Correspondence review
  - Creates redundant, non value added work for FDA
  - Impedes industry’s ability to comply with new FDA quality standards
  - Stifles innovation during the drug development phase
  - Denies timely patient access to high quality affordable generic alternatives

Summary - Top Priorities and Current Focus Areas

- Refining the excipient family approach to facilitate common pharm-tox evaluations
- Review of priority excipient families, including hypromellose, polyethylene oxides, silicone, and carbomers
- 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
We MUST Streamline this process and use good science to assess the REAL Risk!

Thank You!