



# Inactive Ingredient Database - FDA Update -

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# Disclaimer

*This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies.*

# Outline

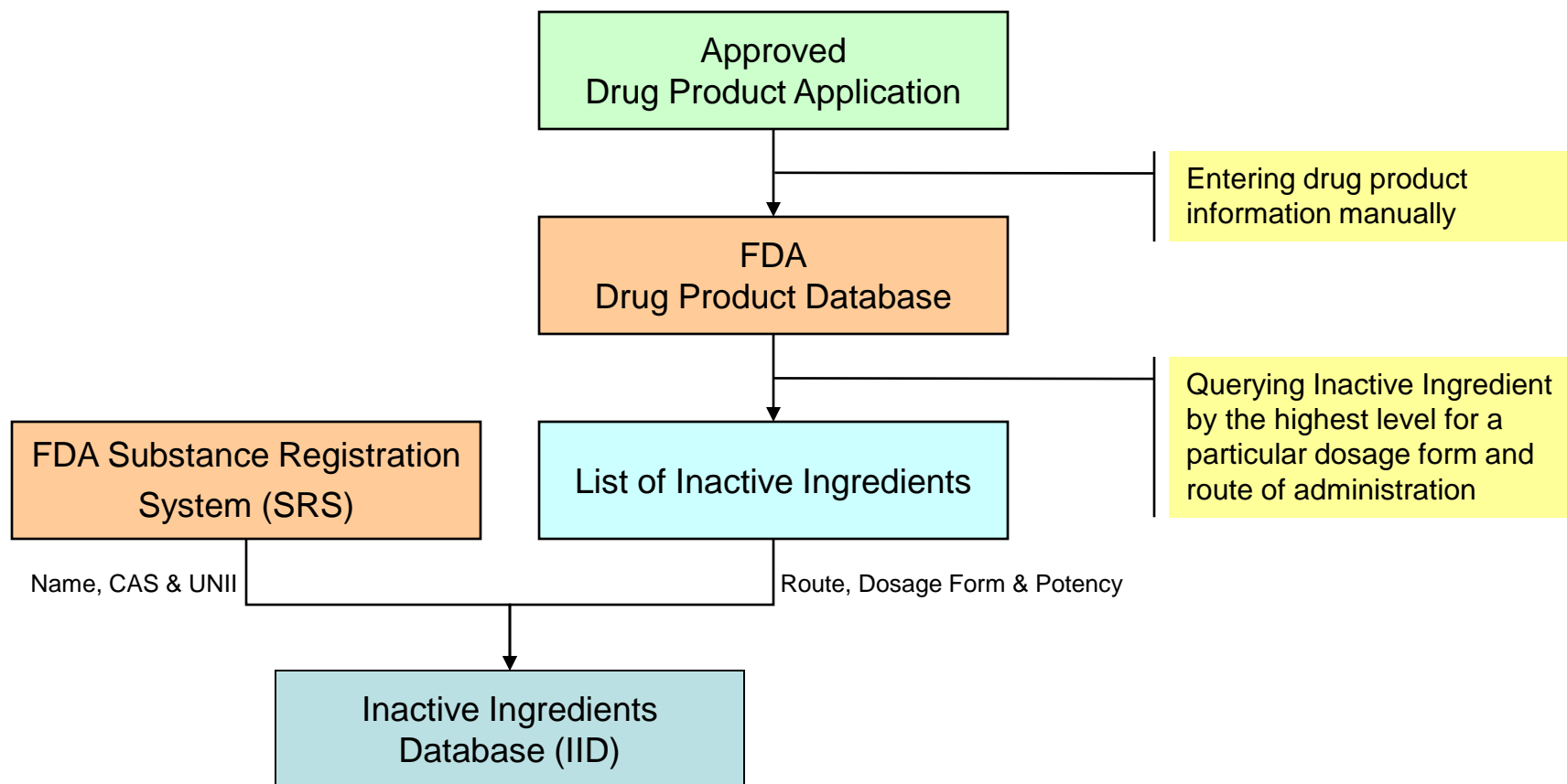
- Inactive Ingredient Database (IID)
- OGD IIG Working Group
- OGD prototype IID database
- Interactions with Stakeholders
- Identified issues and progress
- Summary / Resources

# Inactive Ingredient Database (IID)

The Inactive Ingredient Database (IID) contains inactive ingredients present in FDA-approved drug products currently marketed for human use.

- Only inactive ingredients in the final dosage forms of drug products are in this database.
- Once an inactive ingredient has appeared in an approved drug product for a particular route of administration and dosage form, it is not considered new and may require a less extensive review in a new drug product.

# Inactive Ingredient Database (IID)

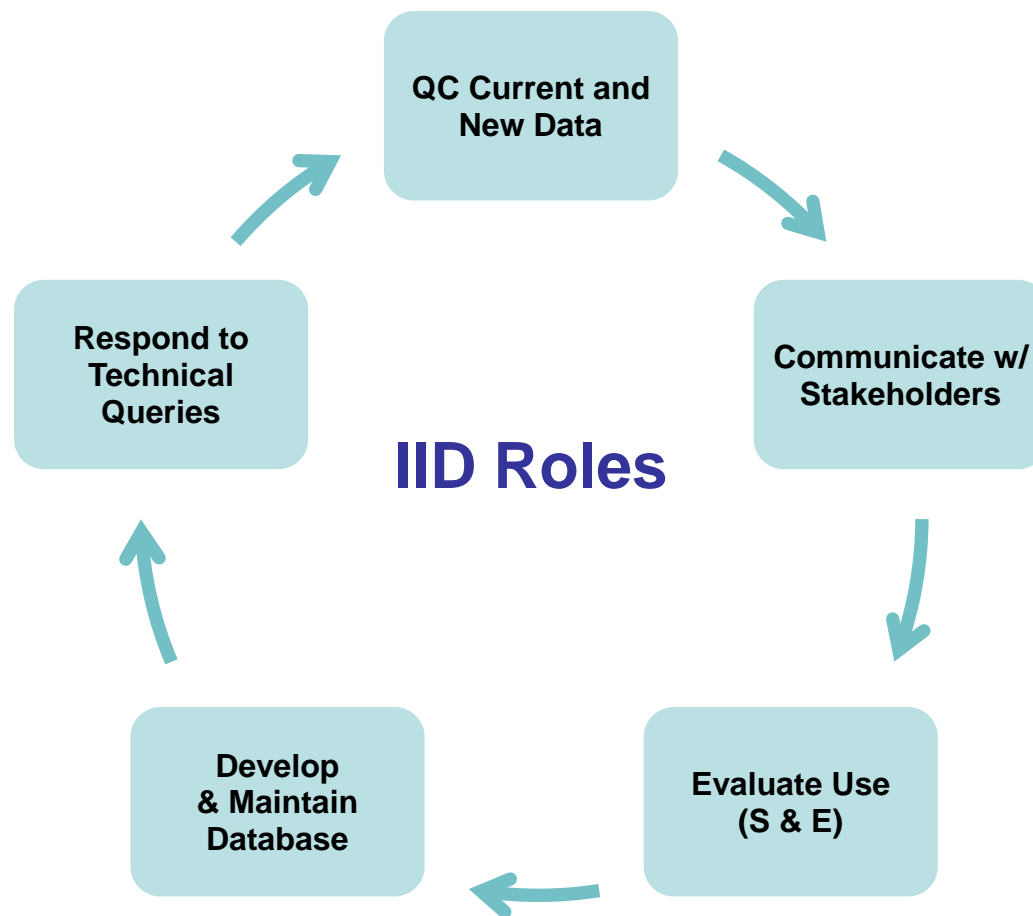


# OGD IID Working Group

- The working group established in September, 2011 with representatives from various disciplines within Office of Generic Drugs (OGD) including Chemistry, Bioequivalence, Clinical Review, the Regulatory Support Branch, the Immediate Office and Orange Book Staff.
- The goals of working group are:
  - Standardizing the ingredient names entry and ensuring the data point accuracy
  - Improving the database usability
  - Conducting surveys to collect needs from both FDA and industry users and looking for ways to improve the database to better meet those needs



# Inactive Ingredients Database WG



# Standardization of Ingredient Names

- Ingredient names are currently linked to the FDA Substance Registration System (SRS) database.
- Provision for including a listing for common, generic, compendia, cosmetic, brand and trade names, as well as any other synonyms, will be built into an improved database that is under development.



# Improve Usability of IID

- With growing demands from generic drug companies and new challenges in the pharmaceutical industry, OGD developed a prototype IID database to improve the usability of IID.
  - Includes Maximum Daily Intake (MDI) of excipients in addition to the potency per unit used in the current IID
  - Has more searchable functions and user-friendly interface

# Calculation of Maximum Daily Intake\*

- Maximum Daily Intake (MDI) for the inactive ingredient in IID is calculated based on Maximum Daily Dose (MDD), the highest recommended daily dose of the drug identified in the approved drug labeling.

$$MDI = \frac{MDD}{A} \times P$$

where,

A: Amount of drug per dosage unit (use the lowest strength to calculate)

P: Potency of the inactive ingredient per dosage unit

MDD: Maximum Daily Dose (MDD/A is maximum number of dosage units that could be consumed per day)

\* Copied from the Liang's AAPS 2012 poster titled "*FDA Inactive Ingredients Database (IID) and its Impact on Generic Drug Development, Filing and ANDA Review*".

# OGD Prototype IID Database

- OGD IID database with more searchable functions and user-friendly interface

**Inactive Ingredient Database (OGD only)**  
a database maintained by Jennifer Liang

hide search

Search for:

Inactive Ingredient

Route of Administration  ▼

Dosage Form  ▼

A/NDA

# OGD Prototype IID Database

- Capture the Maximum Daily Intake (MDI) of the inactive ingredient based on the maximum daily dose of the active ingredient

The screenshot displays the 'Inactive Ingredient Data (OGD only)' interface. It shows details for the inactive ingredient 'CELLULOSE' and its 'Maximum Daily Intake and Dose'. The 'Maximum Daily Intake' is 22.50, and the 'Maximum Daily Dose' is 50 (Total Amount). The route is BUCCAL/SUBLINGUAL and the dosage form is TABLET.

Inactive Ingredient	
ID Name:	CELLULOSE
ICHM:	0100685AA
INC:	SMO 23309H
IGI Number:	900406
Other Name:	POWDERED CELLULOSE
Reference Unit:	[REDACTED]
ANDI Code:	1

Maximum Daily Intake and Dose	
Maximum Daily Intake:	22.50
Route:	BUCCAL/SUBLINGUAL
Dosage Form:	TABLET
Maximum Daily Dose:	50 (Total Amount)
Dosage Unit:	[REDACTED]
Active Ingredient:	[REDACTED]
Consult:	[REDACTED]

NDA/ANDA Application	
Application Number:	[REDACTED]
Proprietary Name:	[REDACTED]
Route:	[REDACTED]
Dosage Form:	[REDACTED]
Active Ingredient:	[REDACTED]
Strength:	[REDACTED]
Applicant:	[REDACTED]
Approval Date:	[REDACTED]
Application Type:	[REDACTED]
Product Number:	[REDACTED]
Reference Unit/Code:	[REDACTED]

# Stakeholder Communication

- The first meeting with an IPEC WG held on December 9, 2011, and followed by seven more meetings up to the date.
- Some important action items:
  - IPEC will poll member companies and develop a list of priority excipients with identified issues based on recent IID list changes.
  - FDA and IPEC will consider development of a FAQ document to further assist potential sponsors.
  - FDA will post historical IID files by quarter for the past 3 years and proposed changes a quarter prior to them being made to allow public comment.
  - FDA will determine a mechanism to highlight changes that are made to subsequent postings of the IID.
  - FDA will explore adding synonyms and trade names to the IID to help companies map to the correct ingredient.
  - Additional meetings will be held, as needed, to continue the dialogue.

# List of Priority Ingredients

- IPEC has identified and provided summary spreadsheets for the following ingredients where safety data are available to justify the family of related products: Hypromellose, Polyethylene Oxide, Silicone, and Carbomers.
- OGD has completed most 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 review/use in the future.
- The final conclusions will likely be posted on the FDA website.

# IID FAQ Document

- A draft IID FAQ document has been developed.
  - The document includes proposed responses to common questions regarding the IID from stakeholders.
  - Currently pending internal review.
  - See OGD Website for more details.

# Updating the IID

- FDA has posted the past 4 years historical IID data files on its website:

<http://www.fda.gov/Drugs/InformationOnDrugs/ucm113978.htm>

- FDA is working on a method of posting some of IID revisions (*i.e.*, name of ingredient, *etc.*) on the external webpage, prior to become effective.
- FDA is evaluating a change log proposal to highlight periodic changes: e.g. new materials, revised routes of administration, increase or decrease of maximum potency, and changes in nomenclature (*i.e.*, SRS changes, *etc.*).



# Synonym and Trade Name

- Substance Registration System (<http://fdasis.nlm.nih.gov/>) can be used for exploring a list of other names:

The screenshot displays the Substance Registration System (SRS) interface. At the top, the FDA logo and the text "U.S. Food and Drug Administration Protecting and Promoting Your Health" are visible on the left, and the "United States National Library of Medicine National Institutes of Health" logo is on the right. The main heading is "Substance Registration System - Unique Ingredient Identifier (UNII)".

The search results section shows a search for "POLYETHYLENE GLYCOL" (circled in red). The search criteria are set to "By Name". The results show the "Preferred Substance Name" as "POLYETHYLENE GLYCOLS" and the "UNII" as "3WJQ0SDW1A". A link "[show more names]" is circled in red next to the preferred name.

A "Resources" section includes links to "ChemIDplus", "DrugPortal", and "NCI Thesaurus".

A "Synonyms" window is open, listing various names for the substance:

- MACROGOL
- MACROGOL [INN]
- MACROGOL [WHO-DD]
- MACROGOLS
- POLY(OXY-1,2-ETHANEDIYL, .ALPHA.-HYDRO.-OMEGA.-HYDROXY-
- POLYETHYLENE GLYCOL
- POLYETHYLENE GLYCOL [VANDF]
- POLYETHYLENE GLYCOLS [FCC]
- POLYETHYLENE OXIDE
- POLYETHYLENE OXIDES
- POLYOXYETHYLENE
- POLYOXYETHYLENE [VANDF]

At the bottom of the page, there is a footer with contact information and a copyright notice: "About, Contact Us, Copyright, Privacy, Accessibility U.S. National Library of Medicine, 8600 Rockville Pike, Bethesda, MD 20894 National Institutes of Health, Health & Human Services Freedom of Information Act Last updated: Apr 2013".

# RTR Draft Guidance

- Available 10/2013
- Filing Considerations for Inactive Ingredient information
  - *Inactive ingredients exceeding the inactive ingredient database (IID) limit*
    - *Pharm-tox studies*
    - *CDER approved drug – appropriate route*
    - *Control Correspondence*

# RTR Draft Guidance

- Excipient justifications for oral liquid drug products,
  - FDA recommends - justification not be based on a listed percentage in the IID.
  - Calculate the amount of inactive ingredient that is delivered per dose or per day (MDI) on dosing recommendations indicated in the RLD label
  - Justify the calculated amount based on an amount-per-unit IID listing that corresponds to a solid oral dosage form.
  
- Furthermore, inactive ingredients that are included in powders for oral suspension should be justified as described above, with calculations of amounts delivered per dose based on the dry powder composition (i.e., prior to reconstitution).

# Summary

- OGD formed a working group to deal with the IID related issues
- Developing a prototype IID database which is a model for future IID improvements
- Routine stakeholder communication is ongoing
- Some of issues related the current IID identified, have been addressed, other are in progress
- Under GDUFA, the IID revisions/tasks will likely fit into the efficiency enhancements / database commitments

# Some Useful Web Links

- FDA Inactive Ingredient Database (IID):

<http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm>

- OGD-IPEC meeting minutes and spreadsheets:

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

- IID specific questions can be submitted through controlled correspondence responses:

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm120610.htm>

# Acknowledgements:

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**Nilufer Tampal**

(Division of Bioequivalence I)

**Jeen Min**

(Orange Book)

**Robert L. Reinwald**

(Orange Book)

- **IPEC WG Members**



**THANK FOR YOUR  
ATTENTION!**

**QUESTIONS?**