Excipients in Pharmaceuticals

a Regulatory Perspective

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What are the connections?

- FD&C Act
- Guidance
- IID
- CGMP
- Innovation
- Regulations
- Policy
- Generic Drugs
- Atypical Actives
- Novel Excipients
1. Laws, regulations and guidance
2. Inactive Ingredient Database (IID)
3. GDUFA II enhancements
4. Novel Excipients
5. Atypical Actives
6. Final Thoughts
7. Contact Information
It’s the Law

Federal Food, Drug, and Cosmetic Act (FDCA)
Covers...
• Drugs
• Medical Devices
• Food
• Dietary Supplements
• Cosmetics
• Products that emit radiation
• Tobacco Products

www.fda.gov

Public Health Service Act (PHSA)
Covers...
• biologics
Excipients in Drugs; FDCA says...

FDCA §201(g)(a)(D)
The term “drug” means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C).

Excipients are drug components.
Excipients in Drugs; FDCA says...

FDCA § 505

- FDCA § 505(j)(2)(A) An abbreviated application for a new drug shall contain...(4) Subject to paragraph (5), the Secretary shall approve an application for a drug unless the Secretary finds—...

- (H) information submitted in the application or any other information available to the Secretary shows that (i) the inactive ingredients of the drug are unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or (ii) the composition of the drug is unsafe under such conditions because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included;

Excipients must be safe under conditions of use.
Regulations interpret the law

Drug Application Requirements: NDA and ANDA

§314.50 (d)(1)(ii)(a) ... specifications for each component

§314.94(a)(9)(ii) ... an applicant must identify and characterize the inactive ingredients in the proposed drug product and provide information demonstrating that such inactive ingredients do not affect the safety or efficacy of the proposed drug product.

Excipients must be identified, characterized, meet specifications and must not affect safety or efficacy.
Non-application OTC Drug Products
§330.1(e)
The product contains only suitable inactive ingredients which are safe in the amounts administered and do not interfere with the effectiveness of the preparation or with suitable tests or assays to determine if the product meets its professed standards of identity, strength, quality, and purity.

Excipient levels must be suitable and safe.
Guidances interpret policy on regulations

**Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients**

- It is important to perform risk-benefit assessments on proposed *new excipients* in drug products and to establish permissible and safe limits for these substances.
- ...*new excipients* means any inactive ingredients that are intentionally added ....and (2) are not fully qualified by existing safety data with respect to the currently proposed level of exposure, duration of exposure, or route of administration.


Guidances
interpret policy on regulations

ANDA Submissions –Refuse-to-Receive Standards Guidance for Industry

• FDA will RTR an ANDA if the submission proposes to use an inactive ingredient at a level that exceeds any of the inactive ingredient database (IID) listings without the justification...

• An inactive ingredient is considered justified, for receipt purposes, if the proposed level is at or below the amount indicated in the IID for the corresponding route of administration of the drug product.

Excipients in generic drugs should be based on a prior determination of safety in an FDA-approved product.

What is the IID?

- Searchable list
- Inactive ingredients in approved products
- Maximum levels
- Toolbox for development

https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm
Why was the IID created?

Evidence of Safe Use

• Once an ingredient is used in an approved drug product, it is **no longer considered new**
  – For a specific route of administration

• **Can be considered safe**
  – Used in a similar manner
  – For a similar type of product
  – Within listed potency (amount)
How do ingredients get into the IID?

- Higher level of existing ingredient
- New ingredient
- New route of administration/dosage form

IID algorithm:
- Selects each excipient
  - each route of administration
  - each dosage form
- Selects highest potency

New IID Entry Added to IID
IID Search

Inactive Ingredient Search for Approved Drug Products

Search the database

Search for Inactive Ingredient Name*:

Submit Clear

What’s new?
Future site of change control log

Our mailbox
Enter query

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

FDA/Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Policy for Pharmaceutical Quality
Mailbox for IID corrections IIDUpdate@fda.hhs.gov
Update Frequency: Quarterly
Data Through: June 4, 2017
Database Last Updated: July 5, 2017
### Search Results for: "BETADEX"

<table>
<thead>
<tr>
<th>Inactive Ingredient</th>
<th>Route</th>
<th>Dosage Form</th>
<th>CAS Number</th>
<th>UNII</th>
<th>Maximum Potency</th>
<th>Record Updated</th>
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</thead>
<tbody>
<tr>
<td>BETADEX</td>
<td>ORAL</td>
<td>TABLET</td>
<td>7585399</td>
<td>JV039JJZ3A</td>
<td>133.33MG</td>
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<td>ORAL</td>
<td>TABLET, FILM COATED</td>
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<td>JV039JJZ3A</td>
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<td>1196OHX6EK</td>
<td>15MG</td>
<td></td>
</tr>
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</table>

Showing 1 to 5 of 5 entries (filtered from 19 total entries)

Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

Language Assistance Available: Español | 繁體中文 | Tiếng Việt | 한국어 | Tagalog | Русский | العربية | Kreyol Ayisyen | Français | Polski | Português | Italiano | Deutsch | 日本語 |فارسی

Maximum potencies per unit dose in various dosage forms
IID Enhancements

FDCA Generic Drug User Fee Amendments
(GDUFA II) will impact the IID

GDUFA II requires that...

1. By October 1, 2020, FDA will complete enhancements to the Inactive Ingredient Database so users can perform electronic queries to obtain accurate Maximum Daily Intake and Maximum Daily Exposure information for each route of administration for which data is available.

2. FDA will update the Inactive Ingredient Database on an ongoing basis, and post quarterly notice of updates made. Such notices will include each change made and, for each change, the information replaced.

GDUFA II Commitment Letter 5/12/2016 FDA Website

GDUFA was reauthorized on August 18, 2017 (GDUFA II), with provisions that go into effect October 1, 2017 and remain in effect through September 30, 2022.
Novel Excipients
Novel Excipients

Potential to solve drug development problems

- Enhance solubility of poorly soluble active pharmaceutical ingredients (API)
- Create new drug delivery systems
- Facilitate new technologies
- Improve manufacturing processes

Analysis of the IID revealed few newly added excipients in the last 10 years.

Novel Excipients

- **novel excipients** may be used in new drugs
  - Novel excipients should be used during the IND phase
  - Clinical and **nonclinical studies** demonstrate suitability and safety of the excipient
  - Have discussions with FDA about formulation early in development

*Guidance for Industry, Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*
Atypical Active Pharmaceutical Ingredients
What are Atypical Actives? How are they regulated?

By definition, an Atypical Active is an “excipient, food additive or personal care ingredient” that is being used as an “active ingredient” in a formulation. ”
- IPEC Americas

Regulatory Framework for atypical APIs (FDA)

- FDCA §201(g)(a)(D) Defines components (ex. APIs) as drugs.
- FDCA § 510 Facilities manufacturing drugs are required to register as drug manufacturing establishments.
- FDCA §501(a)(2)(B) Requires drug manufacturing to conform with Current Good Manufacturing Practice (CGMP).
- API CGMP are not covered by 21 CFR Parts 210 and 211.
- FDA expects API manufacturers to follow ICH Q7 guidance to meet CGMP requirements.

D DiGiulio, A Mozzachio, FDA Regulatory Approaches on Atypical APIs, presentation at 8th PIC/S Expert Circle Meeting on API, Melbourne, Australia, April 5-7, 2017
Atypical Actives

**FDA expectations**

- Alternative approaches to Q7 may be acceptable if they satisfy §501(a)(2)(B).
- Applicants should identify the CGMP standard applied by the API manufacturer if Q7 is not used and provide a justification for deviating from Q7.
- Suppliers should be informed that their material is being used as an API.
- FDA recommends that drug product manufacturers’ pharmaceutical quality systems include processes for:
  - assessing suppliers ...to provide material using a **defined supply chain** (e.g., **audits**, materials evaluations, qualifications)
  - quality-related activities...**written agreement** between the contract giver and contract acceptor
  - monitoring and **review of the quality** of the material
  - **monitoring** incoming ingredients and materials to ensure they are from approved sources using the agreed supply chain.

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*Q7* Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients Guidance for Industry (2016)

Important Considerations

• Consider context of use
• Consider patient population
• Consider known adverse effects
• **Know the excipient**
  o Potential clinical effects
  o Residual solvents
  o Impurities
  o Interactions
IID mailbox

Users improving the IID

• Correcting errors in ingredient names
• Correcting potency errors
• Adding missing ingredients

• Understanding industry’s needs
• Crowdsourcing QC

You can help us make the system better!

IIDUpdate@fda.hhs.gov
Summary

- FDCA requires that excipients are safe under conditions of use.
- Regulations require that excipients must be identified, characterized, meet specifications and must not affect safety or efficacy.
- Novel excipients can enable innovation.
- Atypical actives should meet FDA’s expectations for CGMP.
- IID is a searchable list of excipients.
- IID provides evidence of previous safe use.
- IID staff may be contacted through the IID mailbox.
Contact Information

• Corrections and questions about the IID
  IIDUpdate@fda.hhs.gov

• Nomenclature corrections and questions about excipient names
  fda-srs@fda.hhs.gov

• Questions about excipients in development of generic products: Controlled Correspondence
  GenericDrugs@fda.hhs.gov

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Questions?