Keynote Speaker

FDASIA- One Year Later: The Current Status and Impact on Excipients

Bretta Lichtenhan

IPEC Americas (EMD Millipore)
FDASIA: FDA Safety and Innovation Act - Over one Year Later: The Current State and the Impact of Recently Published Guidelines on Excipients

Bretta Lichtenhan
Regulatory Affairs Manager - Advocacy and Surveillance
EMD Millipore Corp.
Chair - Excipient Qualification Committee, IPEC-Americas
Bretta.lichtenhan@emdmillipore.com
Outline

FDASIA
- Overview

GDUFA – Title III
- Overview, draft guidances, implications for atypical actives and excipients
- IPEC-Americas view points

Drug Supply Chain – Title VII
- Overview, draft guidances, implications for excipients
- IPEC-Americas view points
**Food and Drug Administration Safety and Innovation Act (FDASIA)**

- Signed into law on July 9th, 2012 by US president Barack Obama
- Effective October 1st, 2012
- Amendment of the Federal Food, Drug, and Cosmetic Act
- Result of nearly 2 years negotiations involving:
  - FDA, Regulated industry (trade associations), Stakeholders
- Largest change for drug and medical device regulations in many years

*Public Law 112–144*
112th Congress

An Act

To amend the Federal Food, Drug, and Cosmetic Act to revise and extend the user-fee programs for prescription drugs and medical devices, to establish user-fee programs for generic drugs and biosimilars, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

**SECTION 1. SHORT TITLE.**

This Act may be cited as the “Food and Drug Administration Safety and Innovation Act”.
Food and Drug Administration Safety and Innovation Act (FDASIA)

- **TITLE I—FEES RELATING TO DRUGS**
- **TITLE II—FEES RELATING TO DEVICES**
- **TITLE III—FEES RELATING TO GENERIC DRUGS**
  - Also known as: *Generic Drug User Fee Amendments* of 2012 (GDUFA)
  - Largely affects APIs, FDFs (Finished dosage forms)
  - Atypical Actives (*excipients*)
- **TITLE IV—FEES RELATING TO BIOSIMILAR BIOLOGICAL PRODUCTS**
- **TITLE V—PEDIATRIC DRUGS AND DEVICES**
- **TITLE VI—MEDICAL DEVICE REGULATORY IMPROVEMENTS**
- **TITLE VII—DRUG SUPPLY CHAIN**
  - Affects APIs, *Excipients*, Generic drugs
- **TITLE VIII—GENERATING ANTIBIOTIC INCENTIVES NOW**
- **TITLE IX—DRUG APPROVAL AND PATIENT ACCESS**
- **TITLE X—DRUG SHORTAGES**
- **TITLE XI—OTHER PROVISIONS**
Food and Drug Administration Safety and Innovation Act (FDASIA)

TITLE III—FEES RELATING TO GENERIC DRUGS

SEC. 301. SHORT TITLE.

(a) SHORT TITLE.—This title may be cited as the “Generic Drug User Fee Amendments of 2012”.

(b) FINDING.—The Congress finds that the fees authorized by the amendments made in this title will be dedicated to human generic drug activities, as set forth in the goals identified for purposes of part 7 of subchapter C of chapter VII of the Federal Food, Drug, and Cosmetic Act, in the letters from the Secretary of Health and Human Services to the Chairman of the Committee on Health, Education, Labor, and Pensions of the Senate and the Chairman of the Committee on Energy and Commerce of the House of Representatives, as set forth in the Congressional Record.

SEC. 302. AUTHORITY TO ASSESS AND USE HUMAN GENERIC DRUG FEES.

Subchapter C of chapter VII (21 U.S.C. 379f et seq.) is amended by adding at the end the following:
Food and Drug Administration Safety and Innovation Act (FDASIA)

- TITLE I—FEES RELATING TO DRUGS
- TITLE II—FEES RELATING TO DEVICES
- TITLE III—FEES RELATING TO GENERIC DRUGS
  - Also known as: **Generic Drug User Fee Amendments** of 2012 (GDUFA)
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- TITLE V—PEDIATRIC DRUGS AND DEVICES
- TITLE VI—MEDICAL DEVICE REGULATORY IMPROVEMENTS
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  - Affects APIs, **Excipients**, Generic drugs
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- TITLE IX—DRUG APPROVAL AND PATIENT ACCESS
- TITLE X—DRUG SHORTAGES
- TITLE XI—OTHER PROVISIONS
SECTION 701. REGISTRATION OF DOMESTIC DRUG ESTABLISHMENTS.

Section 510 (21 U.S.C. 360) is amended—
(1) in subsection (b)—

(A) in paragraph (1), by striking “On or before” and all that follows through the period at the end and inserting the following: “During the period beginning on October 1 and ending on December 31 of each year, every person who owns or operates any establishment in any State engaged in the manufacture, preparation, propagation, compounding, or processing of a drug or drugs shall register with the Secretary the name of such person, places of business of such person, all such establishments, the unique facility identifier of each such establishment, and a point of contact e-mail address.; and

(B) by adding at the end the following:

“(3) The Secretary shall specify the unique facility identifier system that shall be used by registrants under paragraph (1).
IPEC-Americas FDASIA Task Force

- **Project charter** supports FDASIA programs/projects/initiatives potentially impacting the manufacture, supply and/or use of pharmaceutical excipients.

- **Objectives:**
  - **Study** the US FDASIA legislation.
  - **Develop and document** IPEC-Americas’ comments and position on the portion of the legislation applicable to excipient manufacture or use in order to reflect the view of our membership.
  - **Coordinate** future opportunities for interactions with FDA to ensure we deliver clear, consistent industry viewpoints while maintaining a constructive and cooperative approach.
<table>
<thead>
<tr>
<th>Title</th>
<th>Authorization to FDA</th>
<th>Impact for Excipient and/or API Suppliers</th>
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<tbody>
<tr>
<td>Title III</td>
<td>Permission to charge fees for generic drug applications, inspection of API mfg sites and supporting ANDA documentation (DMF)</td>
<td>• Register and pay annual fee for “facility” (manufacturing site used in manufacture of API referenced in ANDA)&lt;br&gt;• One-time fee for “completeness assessment” of Type II API DMF referenced in an ANDA&lt;br&gt;• Requires separate DMF for each API and each mfg site (~$21K 2013)</td>
</tr>
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# FDASIA Overview - Impact on Excipients

<table>
<thead>
<tr>
<th>Title</th>
<th>Authorization to FDA</th>
<th>Impact for raw material and/or API Suppliers</th>
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</table>
| **Title VII** Drug supply chain | • Registration and risk based inspection of domestic/foreign establishments and handlers of drug products/components.  
• Includes supply chain security initiatives such as: importing drug product/components, sharing information with foreign reg. authorities, penalties for counterfeiting/adulteration | • As with title 3, this was originally interpreted as eventual requirements for registration of excipient manufacturing sites... which would be subject to FDA risk based inspections  
• **FDA has recently clarified that there is no intention of required registration of excipient manufacturing sites** |

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**DEFINING QUALITY**
FDASIA Draft Guidances

1. **Specification of the Unique Facility Identifier (UFI) System for Drug Establishment Registration** (Sept. 2013)
   - Addresses provisions in sections 701 and 702
     - Directs the Secretary to specify the UFI system for registration of domestic and foreign drug establishments
     - At this time FDA’s preferred UFI for a drug establishment is the Data Universal Numbering System D-U-N-S (DUNS) number, assigned and managed by Dun and Bradstreet

2. **Delaying, Denying, Limiting or Refusing a Drug Inspection** (July. 2013)

3. **ANDA Submissions - Refuse-to-Receive Standards** (Oct. 2013)
   - IPEC-Americas has many comments based on inconsistencies in the IID (inactive ingredient database)
   - Asking for updates that include the discussions that are ongoing with the OGD working group
Title III - G DUFA
GDUFA Draft Guidances

- 4 Specific GDUFA Guidances published through May 2014
  1. ANDA Submissions - Refuse-to-Receive Standards (Oct. 2013)
  3. Initial Completeness Assessments for Type II API DMFs Under GDUFA (Oct. 2012)
GDUFA – One-Time Fees

- GDUFA fees began on October 1st 2012

<table>
<thead>
<tr>
<th>Type of Fee (in USD)</th>
<th>FY 2014 Cost</th>
<th>FY 2013 Cost</th>
<th>Applies to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>API DMF fee (one time)</td>
<td>$31,460</td>
<td>$21,340</td>
<td>API Manufacturers</td>
</tr>
<tr>
<td>Abbreviated New Drug Application (ANDA) Backlog fee (one time)</td>
<td>Not applicable</td>
<td>$17,434</td>
<td>Drug Makers</td>
</tr>
<tr>
<td>Abbreviated New Drug Application (ANDA) PAS fee</td>
<td>$31,930</td>
<td>~$21,000</td>
<td>Drug Makers</td>
</tr>
<tr>
<td>Abbreviated New Drug Application (ANDA) Application fee</td>
<td>$63,860</td>
<td>$51,520</td>
<td>Drug Makers</td>
</tr>
</tbody>
</table>
Facilities must pay annual fee and submit or reconfirm data on an annual basis.

For fiscal year 2015 self-identification reporting period will begin on May 1, 2014, and will close June 1, 2014.

<table>
<thead>
<tr>
<th>Annual Facility Fees</th>
<th>FY 2014 Cost</th>
<th>FY 2013 Cost</th>
<th>Applies to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Domestic Finished Dosage Form (FDF) facility:</td>
<td>$220,152</td>
<td>$175,389</td>
<td>Drug Makers</td>
</tr>
<tr>
<td>Foreign Finished Dosage Form (FDF) facility:</td>
<td>$235,152</td>
<td>$190,389</td>
<td>Drug Makers</td>
</tr>
<tr>
<td>Domestic API facility:</td>
<td>$34,515</td>
<td>$26,458</td>
<td>API Manufacturers</td>
</tr>
<tr>
<td>Foreign API facility:</td>
<td>$49,515</td>
<td>$41,458</td>
<td>API Manufacturers</td>
</tr>
</tbody>
</table>
Title III - GDUFA
What is an “Atypical Active”? 

- A material that is being used as an “active ingredient” in a formulation
- Atypical actives:
  - Commonly seen in Generic and OTC products
  - Over 100 known currently in use in thousands of products
  - Many produced using IPEC-PQG Excipient GMP Guidelines not ICH Q7 GMP
  - Usage volume may be small and inconsequential to the overall production of the product
  - In some cases is the only ingredient

Because long history of safe use
Excipient manufacturers may not be aware of how material is being used
Use as an “active” may not be communicated by customer

* Study by AESGP, European self-medications group
Drug Master File Requirements

• Many DMFs for “atypical actives” include:
  – Multiple grades / products
  – Multiple manufacturing sites

• GDUFA requires a separate DMF for each API and manufacturing facility
  – Require splitting existing Type II DMFs into multiples?
  – Each with initial fee and internal maintenance costs that differ little from the current DMF

• Suppliers historically may have inadvertently submitted a Type II DMF (API)
  – Clarification needed from FDA as to whether these can be reclassified

Added regulatory expenses may result in companies no longer supporting atypical actives for sale as APIs
Excipients used as atypical actives often already in Type IV Excipient DMFs or available in compendial monographs

- Some cases – regulators audited materials for API compliance in certain drug applications

For materials not produced and marketed for use as APIs, we believe they should be:

- Excluded from manufacturing requirements to ICH Q7 GMP
- Exempt from the fee/listing requirements for manufacturing site as producing an API
- Exempt from the DMF compliance assessment of the DMF fee
If a drug product manufacturer chooses use of excipient in an atypical active capacity
- Believe it is inappropriate to publicly list the manufacturer of the atypical active as being in arrears for not listing their site

Believe a one-time completeness assessment fee should cover all additional changes and updates to a Type II DMF

Where Type II DMFs do not exist:
- Agency should only charge a single fee for the completeness assessment of the same atypical active/manufacturing site combination
  - When referenced in multiple ANDAs by the same ANDA holder
In February the FDA released the **FY2013 Report to the President and Congress**

**October 1st 2012 - September 30th 2013**

Discusses accomplishments for first year as well as expectations for the future

**Some Highlights***:

- Number of **improvements** to enhance the efficiency of the review process and improve the quality of generic drug submissions
- FDA has **increased its capacity** to conduct foreign drug inspections
- More than 3,500 unique manufacturing and testing facilities submitted **self-identification information** to the FDA during the FY 2013
- FDA engaged in industry **outreach and education** efforts to industry participants

*some highlights taken directly from report*
Title VII - The Drug Supply Chain
Sec. 702. Registration of foreign establishments

- Sec. 701 and 702 direct the Secretary to specify the **Unique Facility Identifier (UFI)** system for registration of domestic and foreign drug establishments
  - Location, Point of contact, Email address, and Unique facility identifier
- At this time, FDA’s preferred UFI for a drug establishment is the **Data Universal Numbering System D-U-N-S** (DUNS) number
  - Assigned and managed by Dun and Bradstreet
  - Per recent guideline
Sec. 703:

Identification of Drug Excipient Information with Product Listing

- Unique identifier designated to assign, monitor, and track inspections of regulated firms
- Includes all establishments in production of such materials
  - Location
  - Point of contact
  - Email address
  - Unique facility identifier (aka Facility Establishment Identifier (FEI))

- Lobbying efforts of IPEC enabled *excipient* language in final law

"...in the case of a drug contained in the applicable list, the name and place of business of each manufacturer of an *excipient* of the listed drug with which the person listing the drug conducts business, including all establishments used in the production of such *excipient*, the unique facility identifier of each such establishment, and a point of contact e-mail address for each such *excipient* manufacturer."
Sec. 703:

Identification of Drug Excipient Information with Product Listing

- IPEC-Americas would support unique facility identifiers for excipients using the DUN #s
- However, FDA comments at recent meeting indicated that 703 is not meant as a requirement for excipient sites to have registration
  - Implementation of FDASIA 703 may someday compel transparency among members of the excipient supply chain
  - “Traceability promotes quality assurance”
Sec. 705: Risk-based inspection frequency

- Risk ranking of excipient facilities needs clarification
- Will excipient facility inspections increase due to:
  - For cause?
  - Criticality of the excipient?
- Will the Agency recognize the EU FMD Draft:
  - “Guidelines on the Formalized Risk Assessment for Ascertaining the Appropriate Good Manufacturing Practices for Excipients of Medicinal Products for Human Use”?
- IPEC-Americas would support defining and refining risk-ranking criteria
  - Discuss impact of accredited excipient GMP certification on the risk-based inspection schedule
Title VII - Drug Supply Chain

Sec. 706

**Sec. 706: Records for inspection**

- Requires annual report of inspections
- Number of domestic and foreign facilities registered & inspected
- Number of API & **Excipient** facilities inspected
- IPEC would support identification of certain records that the Agency would be likely to request
  - As related to excipient establishments
Sec. 707: Prohibition against delaying, denying, limiting or refusing inspection

- Clarification needed in the case of manufacturers who do not intend for their product’s use in pharmaceutical applications

- IPEC-Americas supports inspection based on the manufacturer’s intent to sell
Title VII - Drug Supply Chain
Sec. 710

Sec. 710: Exchange of Information

- IPEC suggests that there should be strong mechanism in place for the Agency to handle confidential information.
- Does “sponsor” giving written permission for disclosure of information implicate the company submitting a drug application or the owner of the information?
- Clarify the criteria the Agency will use to assess the ability of the foreign government to protect trade secret and confidential information:
  - Use same high standard already used by the Agency.
  - Propose that Agency considers provisions to notify the owner of the confidential information prior to sharing such information with the foreign government.
Sec. 711: Enhancing the safety and quality of the drug supply

- Redefines meaning of cGMP:
  "Includes the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing role of and establishing the safety of raw materials, materials used in the manufacture of drugs and finished products"

- Requirement for manufacturers to implement quality oversight over their suppliers
  - IPEC-Americas strongly supports and believes additional guidance is needed to better define the minimum requirements for raw material/excipient GMPs
  - IPEC-Americas endorses:
    - EXCiPACT's Standard for Excipient GMP/GDP (published 2012)
    - ANSI - NSF/IPEC 363: Good Manufacturing Practices (GMP) for Pharmaceutical Excipients (expected publication 2014)
Sec. 712: Recognition of Foreign Government Inspections

- Sec. 612 allows for recognition of 3rd party inspections of medical device manufacturers and guidance documents published by CDRH
  - Regarding Accreditation and Reaccreditation Process for Firms under the Third Party Review Program*
- What is the feasibility of extending a similar allowance for the recognition of 3rd party inspections of excipient manufacturers
  - Can increased oversight be facilitated for the drug supply chain to safeguard the security of finished drug products and ingredients?
Sec. 713: Standards for Admission of Imported Drugs

- Requires indication of:
  - Compliance with cGMPs
  - Test results
  - Certification related to satisfactory inspections
  - Compliance with export country requirements

- Clarification needed:
  - Will provisions apply only to the import of finished dosage forms or to drug components including excipients?
  - Will drug components be identified at the time of import?
    - Shipping documents would not necessarily identify the substance for use in drug formulations
Sec. 714: Regulation for Commercial Importers

- Required to register and have unique identifier
  - Assumed that excipient distributors will not be included in the listing requirement
  - Per thoughts on Sec. 703
- FDA to promulgate regulations “Good Importer Practices” (within 36 months)
- IPEC-Americas could assist with the development commercial importer registration program, if applicable to importers of excipients
FDASIA Resources

FDASIA

http://www.fda.gov/ForIndustry/UserFees/default.htm

- **GDUFA (Generic Drug User Fee Act/Amendment)**
  - Website: https://www.fda.gov/gdufa
  - Email: AskGDUFA@fda.hhs.gov
  - Call: (866) 405-5367

- **PDUFA (Prescription Drug User Fee Act/Amendment)**
  - [http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm](http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm)

- **MDUFA (Medical Device User Fee and Modernization Act/Amendment)**
  - [http://www.fda.gov/ForIndustry/UserFees/MedicalDeviceUserFeeandModernizationAct/default.htm](http://www.fda.gov/ForIndustry/UserFees/MedicalDeviceUserFeeandModernizationAct/default.htm)

- **BsUFA (Biosimilar User Fee Act/Amendment)**
  - [http://www.fda.gov/ForIndustry/UserFees/BiosimilarUserFeeActBsUFA/default.htm](http://www.fda.gov/ForIndustry/UserFees/BiosimilarUserFeeActBsUFA/default.htm)
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  – **Megan Bevill**, CP Kelco/Huber Engineered Materials
Questions?

It's QUESTION TIME!!