AAM Fall Tech Conference 2017

November 6-8, 2017

Rockville, MD

Excipients Breakout Session

Highlights of FDA-USP workshop on "*Critical Importance of Excipients in Drug Development* – Why Excipients are Important Now and In the Future" The Need to update USP Excipient Standards

Catherine Sheehan, Sr. Director, Science – Excipients
United States Pharmacopeia

Presentation outline

- The FDA/USP Workshop: February 27-28, 2017
- Goals and objectives
- Key Highlights of the Workshop
- Summary/Conclusions

FDA/USP Workshop – Agenda Highlights

- 27 presentations over two days with speakers from:
  - USP Staff
  - USP Expert Committees
  - FDA
  - Industry & Academia:
    - BASF
    - UCSF
    - G&W Laboratories
    - U of Michigan
    - Neo-Advent Technologies LLC
    - Lonza
    - Genentech
    - Boehringer Ingelheim

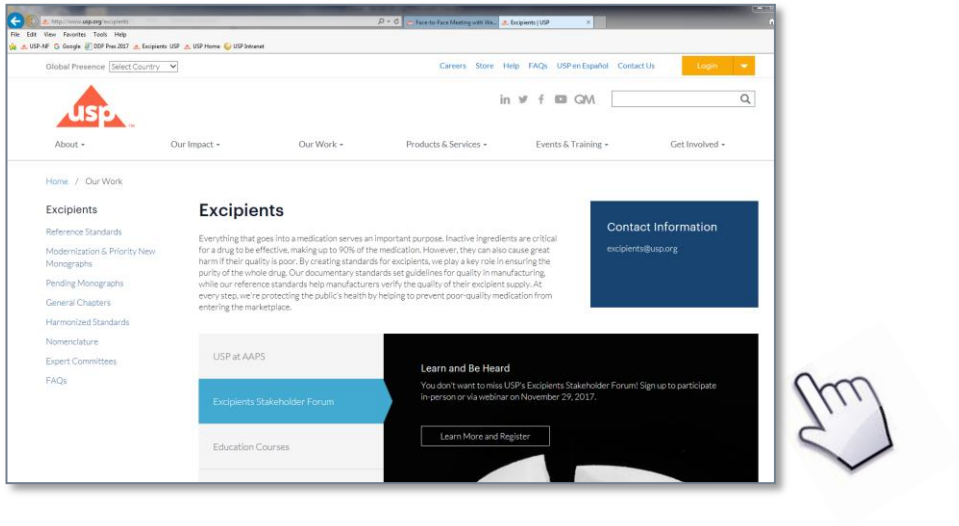
- Presentation topics included:
  - Introduction to Pharmaceutical Excipients
  - Impact of Excipients on Drug Product Quality, Bioequivalence of Generic Drugs and Complex Drug Products
  - Excipient Quality and Continuous Manufacturing
  - Risk-based Evaluation of Drug Product Quality: Impact of Excipients
  - Bridging studies supporting the Safety Assessments for Excipients in Generic Drugs
  - impact of excipients on parenteral drug products such as liposome, microsphere, emulsion, implant.
  - Impact of Excipients on Absorption of Oral Dosage Forms
  - Emerging topics on excipients - novel excipients

FDA/USP Workshop, Feb 27-28, 2017 – Highlights

- Great interest in Excipients!
  - The largest public forum ever held at USP's HQ in Rockville, MD
    - 300+ registered attendees (from outside USP)
    - The overflow room was overflowing
    - 100+ attendees from FDA
    - Attendees from Asia, South America and Europe as well as the US

FDA/USP Workshop, Feb 27-28, 2017 – Videos

- Videos from most of the sessions are available on the USP Excipients website:



Reason for workshop – FDA sharing research

- Oftentimes, stakeholders focus only on the compatibility of the excipient with the API
  - leads to product failure/recalls during commercialization.
- The impact of excipients on drug release and absorption is often overlooked
  - especially for drug products with a waiver of *in vivo* study option.
- The impact of excipients on those special drug delivery systems were evaluated for both
  - *in vitro* properties (e.g., stability, dissolution, physicochemical properties),
  - *in vivo* performance such as drug absorption

The benefits of this workshop are engaged stakeholder sponsorship and collaboration

- Discuss the challenges experienced due to excipient compatibility with the API, with the manufacturing process, and with the intended use/dosage form.
- Seek constructive input from a wide range of stakeholders including industry (generics, biopharmaceuticals as well as users, makers and suppliers of pharmaceutical excipients) and regulatory agencies
- Share ideas on excipient compatibility, composition, absorption and toxicity.
- Seek input in establishing a quality NF specification through up-to-date and harmonization initiatives.

FDA-USP Excipient Workshop
Goals and Anticipated Outcomes

Critical Importance of Excipients in Product Development
Why Excipients are Important Now and In the Future

- Advance the science of excipient selection and regulatory evaluation:
  - Regulatory science – a 'decision science'.
  - Enable better and faster regulatory decisions about excipients.
- Encourage innovation in product development
  - Value of excipient function to drug product performance and equivalence.
  - Expand access to complex generics.

(Robert Lionberger, US FDA)

Key areas of interest identified

- **Session I**: General Introduction to Excipients
- **Session II**: Toxicity and Pharmacology
- **Session III**: Considerations for Complex Drug Products
- **Session IV**: Emerging Topics with respect to Excipients

Session I

General Introduction to Excipients

Presentation Summaries

- **Impact of Excipient Grade (Q1/Q2) on Bioequivalence of Generic Drug Products**

  Stephanie Choi, Ph.D., U.S. FDA

  - To investigate changes in excipient grade and their impact on bioequivalence and bioavailability, FDA has an ongoing research program for generic drugs for various product categories to guide development of guidances and recommendations to industry on excipient selection for generic products.

- **Impact of Excipient Quality Attributes on Bioequivalence of Complex Drug Products: Pharmaceutical Industry Perspectives**

  Tony Wei-Qin Tong, Ph.D., G&W Laboratories

  - Excipients can significantly impact the bioequivalence of complex drug products. Applying Quality by Design (QbD) in product development to fully understand these impacts and putting in place proper controls are essential to ensure drug product quality.

Presentation Summaries

- **Understanding the Impact of Material Attributes on Product Quality for Continuous Manufacturing**

  Thomas O'Connor, Ph.D., U.S. FDA

  - For continuous manufacturing processes, the impact of variation in material attributes on material feeding and process dynamics should be characterized and appropriate controls implemented if needed.

- **Improved Excipient Characterization Beyond USP Monographs**

  Eric Munson, Ph.D., Chair, USP Excipient Monographs 1 EC

  - This presentation focused on understanding USP–NF excipient monographs and the structural/functional properties of excipients, including the role of each in developing drug products.

Session II

Toxicity and Pharmacology

Presentation Summaries

- **Safety Assessments for Excipients in Generic Drugs: A Regulatory Perspective**

  Sruthi King, Ph.D., U.S. FDA

  - Excipients in generic drug products are evaluated from clinical and nonclinical perspectives to ensure that they do not alter the safety profile of the formulation, as compared to the Reference Listed Drug.
  - FDA Pharmacology/Toxicology Review of the proposed level of an excipient includes an evaluation of toxicology data to support the dose, route of administration, duration of exposure, and patient population.

Presentation Summaries

Bridging Justifications: Supporting the Safety of Excipients in Generic Drug Products*

Robert Dorsam, Ph.D., U.S. FDA

- A bridging justification is an approach for safety assessments where toxicology data for one or more compounds is applied to a different compound.
- Important elements of a bridging justification include the similarity and difference between excipients, existing nonclinical and clinical data, data gaps, and the proposed context of use.
- OGD Pharm/Tox reviews bridging justifications within ANDAs to ensure excipient safety in generic drugs. Each case is unique but similar principles apply.

*Presented again at the USP workshop held at the April 2017 ExcipientFest, Rhode Island

Session III

Considerations for Complex Drug Products

Presentation Summaries

Impact of Excipients on Topical Drug Formulation Microstructure and Performance

Norman Richardson, M.S., BASF

- Selection of excipients (Q1) and quantity of each excipient (Q2) determines the nature of the heterogeneous, multiphasic microstructure (Q3) of the topical semi-solid composition. Q3 plays a critical role in driving performance.

Presentation Summaries

Impact of Excipients on Inhalation Drug Products

Kimberly Witzmann, M.D., U.S. FDA

- Differing levels of excipients within inhalation products may have a significant impact on product performance, and from a scientific and regulatory perspective, will need to be evaluated on a case-by-case basis.

The Role and Influence of Excipients in Orally Inhaled Drug Products

Anthony Hickey, Ph.D., Member, USP General Chapters – Dosage Forms EC

- Orally inhaled products contain formulation excipients, the effects of which on quality, performance, safety, and efficacy must be considered.
- Only a few excipients are employed in orally inhaled drug products, but their properties are critical to the quality and performance of these dosage forms.

Presentation Summaries

Excipients in Parenteral Drugs

Wenlei Jiang, Ph.D., U.S. FDA

- More research and clarification on regulatory requirements of complex parenteral excipients are needed for developing complex parenteral drug products.

Excipients in Complex Drug Products

- Excipients can impact the bioequivalence of complex drug products.
- We can implement and apply QbD in product development to better understand these impacts:
  - Identify critical material attributes for the excipients.
    - Use of risk assessments, etc.
    - Communication with between supplier and user.
- We can use this enhanced understanding to:
  - Develop robust formulations and processes which can accommodate typical excipient variability without impacting drug product performance.
  - Implement proper controls, including excipient specifications, to ensure drug product quality.

Excipient characterization

- What are we looking for:
  - Better and faster chemical characterization
    - Better understanding of excipient composition.
  - Better and faster physical characterization
    - Better understanding of form and function
  - More relevant tests
    - Relating to excipient CMAs and product CQAs
  - Analytical methods applicable to continuous manufacturing
  - To maintain product quality and patient safety

Excipient characterization

- Excipients for the emerging complex lipid formulations (e.g. liposomes)
- FDA is working to better understand the issues concerning generic equivalence of such products.
  - Characterization of lipid and lipid-derived excipients from different manufacturers and different sources.
  - What is the impact on the formulation?
  - What further regulatory constraints are required for parenteral use?
  - Example excipients include: cholesterol, phosphatidyl choline, oleic acid, etc.

Session IV

Emerging Topics with respect to Excipients

Presentation Summaries

Excipient Composition and the Formulation of Biotechnology Drugs

Thiago Carvalho, Ph.D., Member, USP Excipient Monographs 1 EC

- Excipient composition may impact the critical quality attributes of biologics drug products and bring challenges to the excipient monograph Up-to-Date Initiative. USP aims to work closely with FDA and industry stakeholders in identifying a pathway for novel excipients not yet in approved drug products.

Presentation Summaries

HCP Mediated Degradation and Potential Mitigation Strategies

Y. John Wang, Ph.D., Genentech

- Research on PS 20 and PS 80 degradation shows that the enzymatic hydrolysis of PS 20 and PS 80 is linked to precipitating particles in drug products. Removal of long-chain fatty acids could mitigate this concern. PS 20 made from greater than 99% lauric acid exhibited no or minimal particles of insoluble fatty acids. Although it was made and used prior to 2004, this material now requires FDA approval prior to inclusion in an NF monograph.

Pathways for Development and Approval of Novel Excipients

Keith Horspool, Ph.D., Boehringer Ingelheim Pharmaceuticals

- Pharmaceutical companies and excipient developers are working together to engage FDA in discussions on potential opportunities for a qualification process to encourage sustained innovation in novel excipients. This process would also stimulate their use in creating more effective, convenient, and cost-effective products for patients.

Workshop Summary/Conclusions

- Excipients are a hot topic for several reasons
  - Potential for adulteration
  - Issues with Excipient Composition and the Formulation of Biotechnology Drug Products
    - *e.g.*, formation of aggregates in protein therapeutics
  - Use in Complex Drug Products
  - Excipients for Parenteral Drug Products
- Other Workshop topics not covered in this presentation include:
  - Equivalence of Topical Drug Formulations
  - Excipients for Inhalation Drug Products
- Lack of an approval mechanism for new chemical excipients is a barrier to innovation in drug delivery

USP Asks

- USP wants to work with the FDA and sponsors to develop new and update existing monographs that the FDA and industry can support.
  - New monographs: USP would also like to 'fill in the gaps' – to develop monographs for excipients currently in use, but without a monograph, for example:
    - Poly (dl-lactic-co-glycolic acid) (50:50 m.w. 46,000)
    - Posted on the USP website in the Priority New Monographs (*http://www.usp.org/get-involved/partner/modernization-priority-new-monograph-lists*)
  - Up-to-Date initiative:
    - List of official monographs posted on the USP website in the Modernization list (*http://www.usp.org/get-involved/partner/modernization-priority-new-monograph-lists*)

USP Asks

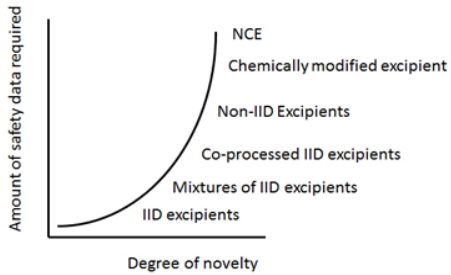
Challenges to developing Novel Excipients:

- New excipients evaluated only in the context of NDA/BLA
- No independent evaluation procedure
- Entire application could be rejected if excipient is unacceptable to FDA
- Barrier to development of new excipients/new delivery systems (e.g., Biologics)
- Adds uncertainty to the drug application process
- Excipient is only permitted for use at the level used in that drug and for that particular route of administration.

Patient/Public health impact:

- Potential new classes of APIs that can treat as yet untreated diseases and meet unmet patient needs are being identified.
- The drug products that use these APIs will only reach the marketplace if novel excipients designed to overcome undesirable physical and/or chemical properties are available to enable their effective delivery

What do we mean by novel?



IPEC-Americas Co-processed excipients guide, in press

FDA/USP Workshop, Feb 27-28, 2017 – Videos

- Videos from most of the sessions are available on the USP Excipients website:

Questions

Empowering a healthy tomorrow

Thank You

Empowering a healthy tomorrow