Welcome to the CMC Strategy Forum

We are pleased to welcome you to the CMC Strategy Forum. The purpose of the CMC Strategy Forum is to provide a venue for biotechnology/biological product discussion. The meetings focus on relevant CMC issues throughout the lifecycle of a product and thereby foster collaborative technical and regulatory interactions. The Forum strives to share information with the regulatory agencies to assist them in merging good scientific and regulatory practices. Outcomes of the Forum meetings are published in an appropriate peer-reviewed journal.

Each meeting will focus on a CMC related issue such as product characterization, comparability, specifications, etc. The format of each meeting will consist of case studies and presentations by Industry and/or FDA experts to introduce the topic and the key issues of concern. Breakout sessions will then be conducted to allow for additional discussion on the technical and regulatory details of the topics. It is envisioned that the final outcome of the workshop discussions will be the development of a document to be submitted to the appropriate Regulatory Agency designees for their consideration in developing and/or clarifying good regulatory practice guidelines for biotechnology derived products.

The success of the CMC Strategy Forum will depend on your active participation in discussing and raising issues pertaining to development of biologics. We encourage you to participate wholeheartedly in the workshops that have been designed to stimulate exchange of ideas and information.

We would like to thank the speakers who are giving generously of their time and resources, and to you, for your attendance. We acknowledge the generosity of our program partners: AbbVie, Inc., Amgen Inc., Biogen Idec, Genentech, a Member of the Roche Group, Genzyme Corporation, a Sanofi company, Gilead Sciences, Janssen Pharmaceutical R&D, LLC, MedImmune, A member of the AstraZeneca Group, Merck & Co., Inc., National Institute of Standards and Technology (NIST), Novo Nordisk A/S and Pfizer, Inc. We are grateful for the expert management from CASSS and the audio-visual expertise of Michael Johnstone from MJ Audio-Visual Productions. Their experience and guidance in the preparation of this Forum has been invaluable.
ACKNOWLEDGEMENTS

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Forum Abstract

Combination Products for Biopharmaceuticals: Emerging Trends in Development, GMPs and Regulatory Expectations

FORUM CO-CHAIRS:
Sarah Kennett, CDER, FDA, USA
Andrew Weiskopf, Biogen Idec, USA

SCIENTIFIC ORGANIZING COMMITTEE:
Siddarth Advant, Kemwell Biopharma, USA
Jee Chung, CDER, FDA, USA
Gary Hartman, Amgen Inc., USA
Mark Lee, CBER, FDA, USA
Lana Shiu, CDRH, FDA, USA
John Towns, Eli Lilly and Company, USA

Just as biopharm drug substance and drug product development organizations adhere to practices which ultimately mesh with their companies’ commercial quality management systems, the same is now true for those who develop combination products. In this CMC Strategy Forum, we will cover both regulatory and practical aspects of developing prefilled syringes, autoinjector pens, pumps, and novel drug/device combinations, in order to facilitate the transition from clinical development to licensure and beyond.

Topics will include design controls, design verification and validation, the role of human factors in combination product development strategy, regulatory expectations for combination product reviews and inspections, and best practices in early combination product development vs. post-approval and legacy products.
CMC Strategy Forum Program Summary

Combination Products for Biopharmaceuticals: Emerging Trends in Development, GMPs and Regulatory Expectations

Monday, January 26, 2015

07:30 – 17:00 Registration in the Independence Room, Lower Level

07:30 – 08:30 Breakfast in the Colonial Room, Lower Level

08:30 – 08:45 CASSS Welcome and Introductory Comments in the Colonial Room, Lower Level
Siddharth Advant, Kemwell Biopharma

CMC Strategy Forum Welcome and Introductory Comments in the Colonial Room, Lower Level
Sarah Kennett, CDER, FDA
Andrew Weiskopf, Biogen Idec

Early Development of Combination Products Workshop Session One
In the Colonial Room, Lower Level
Session Chairs: Mark Lee, CBER, FDA and John Towns, Eli Lilly and Company

08:45 – 09:15 Overview of FDA Review Processes: Regulator’s Perspective on General Considerations for Combination Products
Lana Shiu, CDRH, FDA, Silver Spring, MD USA

09:15 – 09:45 Industry Experience: Early Collaboration with FDA on Combination Products
Kristi Kistner, Amgen Inc., Thousand Oaks, CA USA

09:45 – 10:15 Innovative Drug Device Combination Product Development for Rare Diseases
Sujit Basu, Shire, Lexington, MA USA

10:15 – 10:45 AM Break in the Colonial Room, Lower Level

10:45 – 12:15 PANEL DISCUSSION – Questions and Answers
Sujit Basu, Shire, USA
Kristi Kistner, Amgen Inc., USA
Martin Nemec, Health Canada, Canada
Quynh Nguyen, CDER, FDA, USA
Lana Shiu, CDRH, FDA, USA
Molly Story, Sanofi, USA

12:15 – 13:45 Hosted Lunch in the Colonial Room, Lower Level
Monday, January 26 continued…

**Pre-market, Post-approval and Legacy Product cGMP Considerations** Workshop Session Two  
In the Colonial Room, Lower Level  
Session Chairs: Jee Chung, **CDER, FDA** and Gary Hartman, **Amgen Inc.**

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<td><strong>Best Practices for Design Verification and Validation</strong></td>
<td>Steven Badelt, <em>Suttons Creek, Inc., Los Angeles, CA USA</em></td>
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<td>14:15 – 14:45</td>
<td><strong>Compliance with Medical Device Regulations of Combination Products with a Device Constituent Part Already in the Market: CDRH Expectations</strong></td>
<td>M. Isabel Tejero, <em>CDRH, FDA, Silver Spring, MD USA</em></td>
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<td>14:45 – 15:15</td>
<td><strong>How to Avoid Medical Device FDA Observations in 21CFR Part 4</strong></td>
<td>Sean Creighton, <em>ORA, FDA, Ft. Lauderdale, FL USA</em></td>
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<td><strong>PM Break</strong> in the Colonial Room, Lower Level</td>
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<td><strong>PANEL DISCUSSION – Questions and Answers</strong></td>
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<td>17:15 – 17:45</td>
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<td>17:45 – 18:00</td>
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<td><strong>Networking Reception</strong> in the Chinese Room</td>
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Early Development of Combination Products

Session Chairs: Mark Lee, CBER, FDA and John Towns, Eli Lilly and Company

This session will address the early stages of development of combination products (CPs), including novel drug/device combinations and human factors studies. The presentations and discussion will highlight the processes within and expectations of the U.S. FDA and other regulatory authorities, as well as industry experiences with combination product development and working with the regulatory authorities and contract manufacturers.

NOTES:
Overview of FDA Review Processes: Regulator’s Perspective on General Considerations for Combination Products

Lana Shiu

CDRH, FDA, Silver Spring, MD USA

Abstract was not available at the time of printing.

NOTES:
Industry Experience: Early Collaboration with FDA on Combination Products

Kristi Kistner

Amgen Inc., Thousand Oaks, CA USA

This talk will provide an overview of early collaboration opportunities with the Agency for drug/device combination products, directly on a single program and indirectly via coalition/industry groups. Examples of early collaboration topics regarding combination product development will be presented, to include questions from pre-submission meetings with CDRH and Type B/C meetings with CDER. Significant benefits can be associated with early discussions; however, the interactions and communications may be challenging and have varied outcomes. The importance of including the Office of Combination Products in early collaboration meetings with the Centers is highlighted; both positive scenarios/outcomes and dilemmas will be reviewed.

NOTES:
Innovative Drug-Device Combination Product Development for Rare Diseases

Sujit K. Basu

Shire, Lexington, MA USA

Development of therapies for rare diseases presents some unique challenges. This presentation will focus on product development strategies implemented to deal with challenges specific to drug-device combination product development for rare diseases. The complexity of the products and accelerated development timelines demand that we understand the relationship between drug structure, function, manufacturing process, as well as device design requirements, human factor engineering, and drug-device compatibility from early on and continue to learn even after the products have gained licensure.

Combination products hold the promise of innovative solutions to deliver complex therapies. Many rare diseases include significant central nervous system (CNS) manifestations with marked negative impact on patient and caregiver quality of life, as well as high economic costs to families and payors. More than 50% of patients with lysosomal storage disorders (LSDs) suffer from CNS disease. Most biological drug products are macromolecules that do not cross the Blood Brain Barrier (BBB). Direct intrathecal administration may be a novel way to deliver the deficient enzyme to the CNS bypassing the blood brain barrier. Shire is developing combination product therapies for the three most prevalent LSDs that cause devastating CNS disease in children. These include specific and selective sulfatase enzymes delivered through an innovative intrathecal drug delivery device (IDDD). This presentation will discuss practical strategies with case studies on the design and use of preformulation, formulation and device development approaches for combination biopharmaceutical drug products.

NOTES:
The following questions will guide the panel discussion:

1. What are the types of technical changes during development that may impact interpretation of clinical trial data?
   a. Critical considerations for changes within a certain phase of development; Implications of early decisions for later stages
   b. Lessons from the existing CPs on the market
   c. Impact of device and/or the drug/biologic component complexity for development

2. What are some specific challenges being faced by developers of CPs?
   a. Human Factor study results – role in informing revisions to the user interface (e.g., IFU, carton)
   b. ‘Real-life patient handling experience’ studies – issues that are not captured in human factor studies and pharmacokinetic bridging studies (e.g., change from pre-filled syringe to autoinjector delivery system)?
   c. ‘General use’ or ‘general purpose’ device - definition and unique development and submission pathway
   d. Applicability of design controls under 21 CFR 820.30 to CPs under IND and IDE
   e. Submission expectations regarding GMP information at the IND (vs. NDA/BLA)

3. How applicable are the recently published draft and final guidance documents for medical devices to the device constituent of CPs? Are there ways for industry and FDA to harmonize interpretation of the guidance documents for CPs?

4. What is the status of the convergence of global regulation and international standards for medical devices and its implications for combination products?

NOTES:
Pre-market, Post-approval and Legacy Product cGMP Considerations

Session Chairs: Jee Chung, CDER, FDA and Gary Hartman, Amgen Inc.

The afternoon session on combination product development will focus on premarket and post-market activities for successful marketing and compliance to cGMPs and device Quality Systems. The speakers and panelists from industry and regulatory agencies will share their experiences and expectations for design controls for marketing and discuss the current state of legacy combination products and how to bring the legacy products into compliance. As an added perspective for the session, FDA will share some of the common device inspectional observations that biologic combination product developers may find useful to facilitate the development of an effective Quality System (QS).

NOTES:
Best Practices for Design Verification and Validation

Steven Badelt

Suttons Creek, Inc., Los Angeles, CA USA

As combination product development proceeds, manufacturers will need to demonstrate for marketing as well as for post-approval changes to devices, design verification, validation, and a record of design history file. The presentation will provide industry best practices on robust design verification and validation methods and the difference between the two requirements. In addition, provide some real-world experience of what level of detail and information are critical to include and maintain in a Design History File.

NOTES:
Compliance with Medical Device Regulations of Combination Products with a Device Constituent Part Already in the Market: CDRH Expectations

M. Isabel Tejero

CDRH, FDA, Silver Spring, MD USA

This presentation will address the expectations of the Office of Compliance at CDRH regarding compliance with applicable medical device regulations of combination products with a drug PMOA (including biological products) that have a device constituent part and were on the market prior to the implementation of 21 CFR part 4. The presentation will focus on leveraging those requirements to the required part 820 regulatory requirements under 21 CFR part 4.4(b)(1). It will include comments on possible remedial actions to bring a product into compliance with 21 CFR 820.30.

NOTES:
How to Avoid Medical Device FDA Observations in 21CFRpart4

Sean Creighton

ORA, FDA, Ft. Lauderdale, FL USA

I have conducted more than 450 inspections for the FDA, been to more than 70 countries and conducted more than 40 foreign inspectional trips for the FDA. My goal is to provide the audience with clear cut descriptions of how to avoid medical device observations in 21CFRpart4 when their primary quality system in not based on the medical device regulations. The presentation will primarily focus on avoiding design control observations (21CFR820), will include how to avoid CAPA observations (21CFR820.100) and as time permits will include how to avoid purchasing controls (820.50) and management responsibility observations (820.20)

NOTES:
PANEL DISCUSSION – Questions and Answers
Steven Badelt, Suttons Creek, Inc., USA
Sean Creighton, ORA, FDA, USA
Donna French, Genentech, a Member of the Roche Group, USA
Quynh Nguyen, CDER, FDA, USA
Cathy Parker, Health Canada, Canada
M. Isabel Tejero, CDRH, FDA, USA
Anthony Watson, Biogen Idec, USA

The following questions will guide the panel discussion:

1. What is the best practice for handling product complaints and post-market surveillance of user errors to ensure appropriate modifications to design control and QS compliance? How is the need for another round of Human Factors study determined?

2. What types of design control changes would require post-approval submissions? How useful are the current guidances for directing post-approval submission categories? What best practices for initial combination product design and verification can help prevent the need for post-approval changes?

3. How are purchasing controls managed in the global market?

4. How is industry approaching compliance to cGMPs for legacy combination products? What has the reaction of regulatory authorities been to these approaches? What is the perspective of different regulatory agencies with respect to legacy products?

NOTES: