Welcome to the CMC Strategy Forum
The Development of Patient-focused Commercial Specifications through Understanding of Clinical Relevance and Criticality of Quality Attributes

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 regulatory experts to introduce the topic and the key issues of concern. Workshop sessions, which consist of panel discussions and Q&A, 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 Bioresearch Center, Inc.; Amgen Inc., Biogen Celgene Corporation, Eli Lilly and Company, F. Hoffmann-La Roche Ltd., Genentech, a Member of the Roche Group, Jazz Pharmaceuticals; 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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Michael Johnstone, MJ Audio Visual Productions
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<td>International Pharmaceutical Quality</td>
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CASSS Mobile App

Does the printed program look a little bit thinner this year? This year, we are pleased to once again offer the CASSS Mobile App for the CMC Strategy Forum January and WCBP 2019!

Top Ten Reasons You Need to Have the App:
- Connect and network with fellow attendees, speakers, and exhibitors
- View the schedule and create a personalized agenda
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OPTION 1: On your mobile phone, go to the App Store (Apple App Store, Google Play Store) and search "CASSS 365"
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STEP 3: Open the app. It will ask for your username and password. THIS IS THE SAME INFORMATION YOU USE TO REGISTER FOR A CASSS MEETING.

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You now have access to the entire schedule, session abstracts, speaker handouts and bios – as well as the ability to connect with your fellow attendees.

Need Help?
Still not sure how to sign in and get the most out of the mobile app? Don’t miss the Mochas and Mobile Apps: Mobile App Training on Tuesday, January 29 at 10:15 in the Cabinet Room. You can also contact Anna Lingel, CMP, Exhibitor Relations and Technology Specialist by email: alingel@casss.org or stop by the registration office in the Senate Room.
The Development of Patient-focused Commercial Specifications through Understanding of Clinical Relevance and Criticality of Quality Attributes

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Kavita Mistry, Genentech, a Member of the Roche Group
Kavita Ramalingam Iyer, Merck & Co., Inc.

This CMC Forum will include topics covering the definition, identification, control and management of patient focused attributes throughout the lifecycle of biological products including vaccines. The forum will investigate how, along the product development lifecycle to approval, to differentiate what attributes are ‘clinically meaningful’ from those that might be applied for manufacturing capability and/or process consistency. It will explore what attributes have been identified as CQAs, those that have been shown not to have clinical relevance and how it was done, plus develop a lifecycle approach to clinically meaningful specification development. Approaches to establishing CQAs through the use of modelling (e.g. molecular, immunogenicity), prior knowledge, nonclinical and clinical experience will be discussed. CQAs that require specifications - for example, bioburden, sterility (for aseptic products), content/potency etc. versus more product- specific attributes that have been shown to be clinically relevant CQAs will be explored. The forum will not only describe clinically meaningful attributes, but also explore how to set associated acceptance criteria or limits.

Some questions to be answered are as follows:

- Are ‘Clinical Relevance’ and ‘Clinical Exposure’ fundamentally different?
- Based on existing knowledge, are there are some product attributes (modality specific) that can be generally accepted as ‘not clinically relevant’? (e.g., C-terminal lysines for mAbs,) and what level of knowledge is needed to justify?
- Can different approaches be used for specification setting based upon known clinical relevance, or lack thereof?
- What are some considerations related to clinical experience and determining acceptance criteria: multiple batches, number of studies, number of patients, is exposure more than pivotal clinical studies, can PK/PD studies be used?
- How to leverage prior knowledge in establishing CQAs and the associated control strategy.
CMC Strategy Forum Program Summary

The Development of Patient-focused Commercial Specifications through Understanding of Clinical Relevance and Criticality of Quality Attributes

Monday, January 28, 2019

07:30 – 17:00  Registration in the Senate Room

07:30 – 08:30  Breakfast in the Chinese Room / Palm Court Ballroom

08:30 – 08:45  CASSSS Welcome and Introductory Comments in the Grand Ballroom
Nadine Ritter, Global Biotech Experts, LLC

CMC Strategy Forum Welcome and Introductory Comments in the Grand Ballroom
Jason Starkey, Pfizer, Inc.

Data Driven Approaches to Establishing Criticality of Quality Attributes
Workshop Session One in the Grand Ballroom
Session Chairs: Fiona Cornel, Health Canada and JR Dobbins, Eli Lilly and Company

08:45 – 09:10  How to Understand Criticality by in vitro / in vivo Testing
Marisa Joubert, Amgen Inc., Thousand Oaks, CA USA

09:10 – 09:35  How Can Prior Knowledge Support the Justification of Clinical Relevant Specifications?
Jochen Felix Kepert, Roche Diagnostics GmbH, Penzberg, Germany

09:35 – 10:00  Assessing Product Quality Attributes Utilizing Appropriateness Criteria and Efficacy and Safety Inputs to Establish Clinically Relevant Specifications
John Ayres, Pharma Safety Solutions, LLC, Indianapolis, IN USA

10:00 – 10:25  Regulatory Considerations for Setting Patient-focused Specifications
Mats Welin, Medical Products Agency (MPA), Uppsala, Sweden

10:30 – 11:00  Networking Break in the Palm Court Ballroom

11:00 – 12:15  PANEL DISCUSSION – Questions and Answers
John Ayres, Pharma Safety Solutions, LLC, USA
Gerald Gellermann, Novartis Pharma AG, Switzerland
Marisa Joubert, Amgen Inc., USA
Jochen Felix Kepert, Roche Diagnostics GmbH, Germany
Anthony Ridgway, Health Canada, Canada
Mats Welin, Medical Products Agency (MPA), Sweden
Monday, January 28 continued…

12:15 – 13:45  **Networking Lunch** in the Chinese Room / Palm Court Ballroom

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<tr>
<th>Time</th>
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<tr>
<td>13:45 – 13:50</td>
<td><strong>Introduction</strong></td>
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<tr>
<td>13:50 – 14:15</td>
<td><strong>Best Practices for Setting Patient-focused Commercial Specifications</strong></td>
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<td></td>
<td>Darrin Cowley, AstraZeneca, Gaithersburg, MD USA</td>
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<td>14:15 – 14:40</td>
<td><strong>Justification of Specifications Compared using Traditional versus a Risk-based Approach</strong></td>
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<td>Gerald Gellermann, Novartis Pharma AG, Basel, Switzerland</td>
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<td>14:40 – 15:05</td>
<td><strong>IQ Consortium Biologies Working Group on Specification Setting Strategies</strong></td>
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<td>Juliana Kretsinger, Eli Lilly and Company, Indianapolis, IN USA</td>
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<td>15:05 – 15:30</td>
<td><strong>Clinically Relevant Specifications: Case Study and Summary of Discussion at the BioPhorum Development Group Meeting</strong></td>
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<td>Taro Fujimori, AbbVie Bioresearch Center, Inc., Worcester, MA USA</td>
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<td>15:30 – 16:00</td>
<td><strong>Networking Break</strong> in the Palm Court Ballroom</td>
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<td><strong>PANEL DISCUSSION – Questions and Answers</strong></td>
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<td>Barry Cherney, Amgen Inc., USA</td>
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<td>Kavita Ramalingam Iyer, Merck &amp; Co., Inc., USA</td>
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<td>17:15 – 17:30</td>
<td><strong>Closing Remarks and Invitation to the CMC Strategy Forum July 2019</strong></td>
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<td>“Practical Aspects of ICH Q12 Implementation”</td>
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<td>Anthony Mire-Sluis, AstraZeneca</td>
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<td>17:30</td>
<td><strong>Adjournment</strong></td>
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<td>17:45 – 19:00</td>
<td><strong>Networking Reception</strong> in the Chinese Room / Palm Court Ballroom</td>
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Understanding the critical quality attributes of a biopharmaceutical and the potential risk to patients is foundational to establishing patient focused specifications. This session will discuss approaches to leveraging product-specific and prior knowledge to inform the assessment of Criticality of Quality Attributes. The discussion will begin with the use of *in vitro / in vivo* model systems to evaluate attribute severity and the potential impact on safety and efficacy of the product. The appropriate use of prior knowledge in justifying specifications will then be presented. Next, clinical considerations, including the use of appropriateness criteria, efficacy and safety inputs to explore criticality and define clinical relevant specifications, will be explored. Finally, the session will be rounded out with the regulatory perspective on Attribute Criticality and setting patient-focused specifications.

NOTES:
How to Understand Criticality by \textit{in vitro} / \textit{in vivo} Testing

Marisa Joubert

\textit{Amgen Inc., Thousand Oaks, CA USA}

Abstract was not available at the time of printing.

NOTES:
How Can Prior Knowledge Support the Justification of Clinical Relevant Specifications?

Jochen Felix Kepert

Roche Diagnostics GmbH, Penzberg, Germany

The application of ICHQ8/9/10 and 11 give guidance on how to define product quality with respect to critical quality attributes (CQA) and the use of quality risk assessment tools. Adoption of the principles described in these guidelines may enable alternative approaches in setting the specification as described in ICHQ6B. The presentation will discuss how knowledge from similar products may be leveraged during CQA assessment and how this information can then be translated into setting of specifications. While some knowledge may be applicable across molecules, some other mechanistics may not and need to be assessed product specifically. During the presentation examples will be discussed that illustrate the opportunities, as well as limitations is use of prior knowledge in supporting clinical relevant specifications.

NOTES:
Assessing Product Quality Attributes Utilizing Appropriateness Criteria and Efficacy and Safety Inputs to Establish Clinically Relevant Specifications

John Ayres

Pharma Safety Solutions, LLC, Indianapolis, IN USA

The impetus to adopt “Clinically-Relevant Specifications” is not a new concept and dates to the early 2000’s when FDA embarked upon the “Pharmaceutical Quality for 21st Century Initiative.” The development and adoption of ICH Q8-11 provided a structured way to define product critical quality attributes (CQAs), design space, the manufacturing process and the control strategy for establishing specifications tied to the Quality Target Product Profile (QTPP). While progress has been made, limitations persist that have stymied the realization of establishing registered specifications limited to direct clinical impact.

This presentation will look at some of the impediments faced in achieving the goal of risk-based and clinically relevant specifications and the utility and shortcomings of clinical inputs to establish relevant acceptance criteria. This will include examining the effect of institutional/cultural normative behavior, risk aversion, the impact of uncertainty and economic drivers impacting innovator/industry and regulatory interaction. A paradigm to assess drug substance and drug product batches with CQAs that fall outside pivotal clinical trial exposure levels but within the inherent variability of a capable and well-controlled manufacturing process will be presented.

NOTES:
Regulatory Considerations for Setting Patient-focused Specifications

Mats Welin

*Medical Products Agency (MPA), Uppsala, Sweden*

ICH Q6B states that since specifications are chosen to confirm the quality rather than to characterize the product, the manufacturer should provide the rationale and justification for including and/or excluding testing for specific quality attributes. In addition, it is written that “specifications should be based on data obtained for lots used in pre-clinical and clinical studies. The quality of the material made at commercial scale should be representative of the lots used in preclinical and clinical studies”. The outcome of the 2011 EMA-Industry workshop was in line with this, stating that clinical qualification is considered the most important aspect when setting acceptance criteria. Having said that, the principles of setting acceptance criteria will depend on the nature of the tests. Acceptance criteria for tests of critical product specific attributes are expected to be based on clinical justification.

The talk will cover common issues identified in assessing biological medicinal products including both the selection of attributes to test for and how to set acceptance criteria.

The criticality of the attributes will for obvious reasons have impact on the need to control them batch wise. Prior knowledge may be taken into account when assigning criticality, but its applicability should be justified. Alternatives to testing at Drug substance and Drug product level have been accepted in the past.

As regards the acceptance criteria applied, it is frequently claimed by applicants that clinical results are considered in justifying these criteria but in the end the limits are claimed without any justification from a clinical point of view but rather set based on statistical calculation from all batches. It is acknowledged that it may be difficult to set limits based on results from batches used in clinical trials since often very few batches are involved and these may not mirror the normal variability seen in production. The talk will touch upon certain measures we have seen in the past how clinically justified limits can extended beyond the actual levels seen in batches used for clinical trials. This includes making use of prior knowledge, understanding of structure-function relationships, making use of dose finding studies etc.

**NOTES:**
Data Driven Approaches to Establishing Criticality of Quality Attributes
Workshop Session One

Panel Members:
John Ayres, Pharma Safety Solutions, LLC, USA
Gerald Gellermann, Novartis Pharma AG, Switzerland
Marisa Joubert, Amgen Inc., USA
Jochen Felix Kepert, Roche Diagnostics GmbH, Germany
Anthony Ridgway, Health Canada, Canada
Mats Welin, Medical Products Agency (MPA), Sweden

The following questions will guide the panel discussion:

1. How is clinical data being leveraged to understand CQA impact?
2. What type and amount of data is needed to demonstrate that a specification is safe?
3. Is cross-product knowledge valuable for determining product-specific attribute impact?
4. What are some examples of how to vary and/or broaden attribute ranges of clinical materials?
5. Are there some attributes which we can all agree are not clinically relevant and if so, how should these be presented in regulatory filings?

NOTES:
Developing Patient-focused Specifications
Session Two

Session Chairs: William Egan, GSK Vaccines and Anthony Ridgway, Health Canada

Having determined the necessary product attributes for ensuring the continued safety and efficacy of the drug product (vaccine or therapeutic protein), the difficult task then arises to establish clinically meaningful specifications for those attributes. Clearly, the range of values explored in clinical trials become acceptable ranges for those specifications. Oftentimes, however, due to a well-controlled and consistent manufacturing process, the investigated range of attributes may be rather narrow and, as a result, overly narrow (relative to what might be clinically needed) specifications may be set. Following licensure, over time, the need for expanded specifications may become apparent, along with the realization that they might have been set too narrow. This Forum intends to explore those strategies that might be employed during clinical development to arrive at a set of clinically meaningful specifications not strictly bounded by manufacturing consistency.

NOTES:
Best Practices for Setting Patient-focused Commercial Specifications

Darrin Cowley

AstraZeneca, Gaithersburg, MD USA

A specification, according to ICH Q6, “should focus on those molecular and biological characteristics found to be useful in ensuring the safety and efficacy of the product”. Historically, clinical manufacturing was not as reproducible or productive often resulting in significant variability in final product attribute levels throughout the history of a clinical program. This enabled commercial specifications to be established that were both based on “clinical exposure” and product specific clinical manufacturing history. But over time manufacturing has become more consistent, bioreactor productivity has increased, and accelerated approval pathways have significantly limited the number of batches manufactured and used in the clinic, which all have subsequently minimized the product specific attribute variability introduced into the clinic. Unfortunately, the commercial specification setting philosophy hasn’t evolved to address this new reality and continues to have a strong foundation in process consistency. Today, we must incorporate elements of ICH Q8-11 to make informed risk- and science-based decisions when setting specifications to overcome this unintended consequence of manufacturing advances. Industry and regulators alike must leverage the vast amounts of prior knowledge available to better understand the impact of attribute levels on potency, immunogenicity, etc. Once a common understanding of attribute risk is realized, then specification setting can shift from clinical experience/process variability to an attribute centric specification focused on safety and efficacy.

NOTES:
Justification of Specifications Compared using a Traditional versus a Risk-based Approach

Gerald Gellermann

Novartis Pharma AG, Basel, Switzerland

In this presentation we compare traditional assessment with an advanced and risk-based approach for definition and justification of specifications. The putative impact(s) on manufacturing process and lifecycle management are discussed. While the traditional approach focusses on consistency, the advanced approach provides opportunities to utilize present understanding of structural-function relationships for the analyte molecule. This enables definition of limits which may extend outside those determined by clinical experience. Where indicated, this is required to incorporate more worst-case assessments as the basis to predict future manufacturing variability. These scenarios are the basis for designing a robust commercial manufacturing process and, further, facilitate an efficient product life-cycle management.

NOTES:
IQ Consortium Biologics Working Group on Specification Setting Strategies

Juliana Kretsinger

Eli Lilly and Company, Indianapolis, IN USA

The International Consortium for Innovation and Quality in Pharmaceutical Development (IQ) is a technically-focused organization of pharmaceutical and biotechnology companies with a mission of advancing science and technology to augment the capability of member companies to develop transformational solutions that benefit patients, regulators and the broader R&D community. In 2017 the Biologics leadership group within IQ initiated a working group to discuss strategies for phase appropriate specifications. The first effort from this working group focused on early phase specification practices. Responses from a survey among IQ member companies to understand the current practices were integrated into a manuscript that was recently accepted for publication in the Journal of Pharmaceutical Sciences. This publication provides guidance on strategies for defining early phase specifications, including platform specification examples. The second focus is to develop an industry aligned view on commercial specification setting best practices, with an emphasis to define patient-focused commercial specifications. The IQ working group includes members that represent a broad range of companies working on biologics, enabling preparation of guidance that addresses a wide range of questions and concerns. Highlights of the current thinking will be shared to support the discussion on specification setting strategies.

NOTES:
Clinically Relevant Specifications: Case Study and Summary of Discussion at the BioPhorum Development Group Meeting

Taro Fujimori

AbbVie Bioresearch Center, Inc., Worcester, MA USA

The talk will focus on the expectations for a company to establish and utilize clinically relevant specifications. A case study on clinically relevant specifications will be presented. This case study was discussed at the BioPhorum Development Group Meeting and a summary of those discussions will also be presented. The mission of the BioPhorum Development Group is to connect process development biopharmaceutical organizations, provide an effective environment for the community to collaborate on shared issues and accelerate improvement across the biopharmaceutical development arena. There are twenty-four-member companies in the BioPhorum Development Group.

NOTES:
Panel Members:
Barry Cherney, Amgen Inc., USA
Fiona Cornel, Health Canada, Canada
Darrin Cowley, AstraZeneca, USA
Taro Fujimori, AbbVie Bioresearch Center, Inc., USA
Gerald Gellermann, Novartis Pharma AG, Switzerland
Juliana Kretsinger, Eli Lilly and Company, USA
Kavita Ramalingam Iyer, Merck & Co., Inc., USA

The following questions will guide the panel discussion:

1. What is the role, if any, of data garnered in dose ranging studies in setting specification ranges for either safety or efficacy?
2. Specifications must be met throughout the products shelf life. Are clinical studies carried out at the end of the intended product shelf life useful in setting specifications. If so, in what manner.
3. How can you widen the specification after commercial approval if the expectation is that once approved, clinical trial material should meet the requirements of commercial material?
4. Is there any apatite by regulators to accelerate product degradation in a control process to be able to introduce product with higher levels of specific CQA into the clinic?

NOTES: