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 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, Inc., Amgen Inc., Biogen, Bristol-Myers Squibb Company, Eli Lilly and Company, Genentech, a Member of the Roche Group, Janssen Pharmaceutical R&D, LLC, MedImmune, A member of the AstraZeneca Group, Merck & Co., Inc. 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

CMC STRATEGY FORUM NORTH AMERICA PROGRAM COMMITTEE

Siddharth Advant, Celgene Corporation
Yves Aubin, Health Canada
John Bishop, CBER, FDA
Barry Cherney, Amgen Inc.
JR Dobbins, Eli Lilly and Company
Julia Edwards, Allergan
Sarah Kennett, CDER, FDA
Joseph Kutza, MedImmune, A member of the AstraZeneca Group
Kimberly May, Merck & Co., Inc.
Anthony Mire-Sluis, AstraZeneca
Stefanie Pluschkell, Pfizer, Inc.
Nadine Ritter, Global Biotech Experts, LLC
Dieter Schmalzing, Genentech, a Member of the Roche Group
Timothy Schofield, GlaxoSmithKline
Zahra Shahrokh, ZDev Consulting
Jeffrey Staecker, BioPhia Consulting, Inc.
Andrew Weiskopf, Biogen
Marcel Zocher, Bristol-Myers Squibb Company

CMC STRATEGY FORUM GLOBAL STEERING COMMITTEE

Siddharth Advant, Celgene Corporation, USA
Daniela Cerqueira, ANVISA-Brasilian National Health Surveillance Agency, Brasil
Yasuhiro Kishioka, PMDA-Pharmaceutical and Medical Devices Agency, Japan
Steven Kozlowski, CDER, FDA, USA
Junichi Koga, Daiichi Sankyo Co., Ltd., Japan
Rohin Mhatre, Biogen, USA
Ingrid Markovic, CBER, FDA, USA
Anthony Mire-Sluis, AstraZeneca, USA
Wassim Nashabeh, F. Hoffmann-La Roche Ltd., Switzerland (Chair)
Ilona Reischl, AGES-Austrian Medicines and Medical Devices Agency, Austria
Anthony Ridgway, Health Canada, Canada
Nadine Ritter, Global Biotech Experts, LLC, USA
Thomas Schreitmuller, F. Hoffmann-La Roche Ltd., Switzerland
Mark Schenerman, USA
Karin Sewerin, BioTech Development AB, Sweden
The Scientific Organizing Committee gratefully acknowledges the pharmaceutical and biotechnology industry for their generous support of the CMC Strategy Forum North America series:

<table>
<thead>
<tr>
<th>STRATEGIC DIAMOND PROGRAM PARTNERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genentech, a Member of the Roche Group</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STRATEGIC PLATINUM PROGRAM PARTNERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>AbbVie, Inc.</td>
</tr>
<tr>
<td>Biogen</td>
</tr>
<tr>
<td>MedImmune, A member of the AstraZeneca Group</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STRATEGIC GOLD PROGRAM PARTNERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eli Lilly and Company</td>
</tr>
<tr>
<td>Pfizer, Inc.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STRATEGIC SILVER PROGRAM PARTNER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merck &amp; Co., Inc.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FORUM PROGRAM PARTNERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amgen Inc.</td>
</tr>
<tr>
<td>Bristol-Myers Squibb Company</td>
</tr>
<tr>
<td>Janssen Pharmaceutical R &amp; D, LLC</td>
</tr>
</tbody>
</table>
The Scientific Organizing Committee gratefully acknowledges the following media for their promotional consideration of the CMC Strategy Forum North America July 2017:

<table>
<thead>
<tr>
<th>LEADING MEDIA PARTNERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BioProcess International</td>
</tr>
<tr>
<td>International Pharmaceutical Quality</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MEDIA PARTNERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Laboratory / LabCompare</td>
</tr>
<tr>
<td>American Pharmaceutical Review</td>
</tr>
<tr>
<td>The Analytical Scientist</td>
</tr>
<tr>
<td>BioProcessing Journal</td>
</tr>
<tr>
<td>Genetic Engineering &amp; Biotechnology News</td>
</tr>
<tr>
<td>G.I.T Laboratory Journal</td>
</tr>
<tr>
<td>The Pathologist</td>
</tr>
<tr>
<td>Pharmaceutical Outsourcing</td>
</tr>
<tr>
<td>separationsNOW.com</td>
</tr>
<tr>
<td>Technology Networks</td>
</tr>
</tbody>
</table>
Manufacturing, Quality and Regulatory Considerations for Cell & Gene Therapies

FORUM CO-CHAIRS:
Siddharth Advant, Celgene Corporation
Stefanie Pluschkell, Pfizer, Inc.
Andrew Weiskopf, Biogen

SCIENTIFIC ORGANIZING COMMITTEE:
Kathleen Francissen, Genentech, a Member of the Roche Group
Paul Husak, Amgen Inc.
Steven Oh, CBER, FDA
Cynthia Riggins, Novartis Pharmaceuticals Corporation
Shian-Jiun Shih, Tessa Therapeutics
Bruce Thompson, Fred Hutchinson Cancer Research Center

Cell therapy and gene therapy products stand at the threshold of revolutionizing patient care, offering treatments for unmet medical needs and even the potential to cure some diseases with a single dose. However, the complexities of these advanced therapies pose unique challenges for drug substance and drug product manufacturing, quality and safety, analytical characterization, and supply chains. Elements of manufacturing and controls, including those considered routine for conventional biologics, demand a closer look when developing these products which may be highly perishable, biologically complex, produced with low yield, and in some cases, manufactured for a specific patient. Similarly, regulatory expectations for the CMC of these products are continually evolving, with a degree of nascency not seen since the emergence of recombinant protein biologics in the 1990s. At this CMC Strategy Forum, industry professionals and regulators alike will gather to discuss the many technical, practical, and regulatory aspects and challenges of cell therapy and gene therapy products.
CMC Strategy Forum Program Summary

Manufacturing, Quality and Regulatory Considerations for Cell & Gene Therapies

Monday, July 17, 2017

07:30 – 17:00  Registration in the Washingtonian Ballroom Foyer

07:30 – 08:30  Breakfast in the Washingtonian Ballroom Foyer

08:30 – 08:45  CASSS Welcome and Introductory Comments in Salons D - G
Nadine Ritter, Global Biotech Experts, LLC

CMC Strategy Forum Welcome and Introductory Comments in Salons D - G
Andrew Weiskopf, Biogen

Analytical Methodologies and Specifications
Workshop Session One in Salons D - G
Session Chairs: Bruce Thompson, Fred Hutchinson Cancer Research Center and Andrew Weiskopf, Biogen

08:45 – 09:10  Measurement Assurance for Regenerative Medicine Advanced Therapies
Anne Plant, National Institute of Standards and Technology (NIST), Gaithersburg, MD USA

09:10 – 09:35  Viral Vector Analytical Paradigms, Platforms and Proposed Specifications
Eric Pastor, Sanofi, Framingham, MA USA

09:35 – 10:00  Development of Gene Edited Allogeneic CAR-T Cell Therapy
Julianne Smith, Cellectis, New York, NY USA

10:00 – 10:25  Accelerated CMC Development of Regenerative Medical Products
Yoshiaki Maruyama, Pharmaceuticals and Medical Devices Agency (PMDA), Tokyo, Japan

10:25 – 10:45  Networking Break in the Washingtonian Ballroom Foyer

10:45 – 12:00  PANEL DISCUSSION – Questions and Answers
Svetlana Bergelson, Biogen
Yoshiaki Maruyama, Pharmaceuticals and Medical Devices Agency (PMDA)
Eric Pastor, Sanofi
Anne Plant, National Institute of Standards and Technology (NIST)
Victoria Sluzky, BioMarin Pharmaceutical Inc.
Julianne Smith, Cellectis
Zenobia Taraporewala, CBER, FDA
Monday, July 17 continued…

12:00 – 13:30  **Networking Lunch** in the Washingtonian Ballroom Foyer

<table>
<thead>
<tr>
<th>Time</th>
<th>Session Description</th>
</tr>
</thead>
</table>
| 13:30 – 13:55 | **Comparability of Cell & Gene Therapy Products**  
Workshop Session Two in Salons D - G  
| 13:30 – 13:55 | **Cell Therapy Product Manufacturing Considerations**  
Mohammad Heidaran, *CBER, FDA, Silver Spring, MD USA* |
| 13:55 – 14:20 | **GTx and AAV: Advancing Analytical Characterization to Improve Product Understanding, Control and Comparability Exercises**  
Herbert Runnels, *Pfizer, Inc., Chesterfield, MO USA* |
| 14:20 – 14:45 | **Manufacturing, Development and Comparability Assessments of Cell and Gene Therapy Products for Marketing in Europe**  
Margarida Menezes-Ferreira, *INFARMED, Lisbon, Portugal* |
| 14:45 – 15:10 | **Comparability Studies for Autologous Cell Therapy Processes**  
Christopher Shen, *Kite Pharma, Santa Monica, CA USA* |
| 15:15 – 15:45 | **Networking Break** in the Washingtonian Ballroom Foyer |
| 15:45 – 17:00 | **PANEL DISCUSSION – Questions and Answers**  
Diane Blumenthal, *Spark Therapeutics, Inc.*  
Mohammad Heidaran, *CBER, FDA*  
Margarida Menezes-Ferreira, *INFARMED*  
Herbert Runnels, *Pfizer, Inc.*  
Christopher Shen, *Kite Pharma*  
Christopher Storbeck, *Health Canada* |
| 17:00 – 18:30 | **Networking Reception** in the Washingtonian Ballroom Foyer |
| 18:30 | **Adjourn Day One** |
Tuesday, July 18, 2017

08:00 – 17:00  Registration in the Washingtonian Ballroom Foyer

07:45 – 08:45  Breakfast in the Washingtonian Ballroom Foyer

**Cell & Gene Therapy Manufacturing Strategies**

Workshop Session Three in Salons D - G

Session Chairs: Sid Advant, Celgene Corporation and Shian-Jiun Shih, Tessa Therapeutics

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
</table>
| 08:45 – 09:15 | Regulation of Manufacturing Cell and Gene Therapy Products for Use in Phase 1 Clinical Trials  
Adrian Gee, Baylor College of Medicine, Houston, TX USA |
| 09:15 – 09:45 | Manufacturing Challenges with Cell and Gene Therapy Products: A Health Canada Perspective  
Christopher Storbeck, Health Canada, Ottawa, ON Canada |
| 09:45 – 10:15 | Manufacturing and Commercialization of an Oncolytic Virus Product  
Tia Bush, Amgen Inc., West Greenwich, RI USA |
| 10:15 – 10:45 | Networking Break in the Washingtonian Ballroom Foyer |
| 10:45 – 12:00 | PANEL DISCUSSION – Questions and Answers  
Tia Bush, Amgen Inc.  
Adrian Gee, Baylor College of Medicine  
Mohammad Heidaran, CBER, FDA  
Michael Kelly, Biogen  
Richard Snyder, Brammer Bio, LLC  
Christopher Storbeck, Health Canada |
| 12:00 – 13:30 | Networking Lunch in the Washingtonian Ballroom Foyer |

**Raw Materials Sourcing & Supply Chain**

Workshop Session Four in Salons D - G

Session Chairs: Kathleen Francissen, Genentech, a Member of the Roche Group, Steven Oh, CBER, FDA and Cynthia Riggins, Novartis Pharmaceuticals Corporation

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
</table>
| 13:30 – 14:00 | Standards and Best Practices for Cell, Gene and Tissue-based Therapies  
Rebecca Potts, U.S. Pharmacopeial Convention (USP), Rockville, MD USA |
| 14:00 – 14:30 | A Life Cycle Approach to Raw Material Qualification for Cell and Gene Therapy Products  
Angela Whatley, CBER, FDA, Silver Spring, MD USA |
| 14:30 – 15:00 | Integrated Supply Chain for Cell Therapy  
Bryan Silvey, Kite Pharma, Santa Monica, CA USA |
Tuesday, July 18 continued…

15:00 – 15:30  Networking Break in the Washingtonian Ballroom Foyer

15:30 – 16:45  PANEL DISCUSSION – Questions and Answers
Rebecca Potts, U.S. Pharmacopeial Convention (USP)
Bryan Silvey, Kite Pharma
Christopher Storbeck, Health Canada
Angela Whatley, CBER, FDA
Ran Zheng, Amgen Inc.

16:45 – 17:15  Recap of Program
Summary Slide Presentation
Catherine Anderson, Biogen
Jaclyn Moxham, Pfizer, Inc.

17:15 – 17:30  Invitation to CMC Strategy Forum January 2018

17:30  Adjournment
Session Chairs: Bruce Thompson, *Fred Hutchinson Cancer Research Center* and Andrew Weiskopf, *Biogen*

The varied nature of cell and gene therapy modalities raises unique challenges for analytical method development, assay validation, characterization, and specification setting. This session will feature presentations covering the many facets of analytical methodologies and specifications for cell and gene therapy products. Topics will include perspectives on measurement assurance and assay standardization, gene editing technology and methods for determination of product quality of edited cells, and an overview of current thinking in development of methodology and specifications for viral vectors. Additionally, we will explore the broader view of accelerated CMC development of advanced therapies in Japan, including analytical and manufacturing considerations. Through this session, attendees will gain a better understanding of current issues and potential solutions with respect to development of complex cell and gene therapy products.

NOTES:
Regenerative medicine products are becoming components of many companies’ portfolios, in large part because of the clinical success of CAR-T cell therapies. Fundamental challenges in bringing regenerative medicine products to market include meaningful characterization of these complex products in the absence of good understanding of the mechanism of action, and establishing product characteristics that provide comparability of product through changes in the manufacturing process. NIST works with stakeholders to help provide confidence in measurements for this field through workshops, interlaboratory comparison studies, consortia, standards development, and basic research. Methods for establishing confidence in putative biomarkers is a critical challenge area that is being addressed with new technologies.
Viral Vector Analytical Paradigms, Platforms and Proposed Specifications

Eric Pastor

Sanofi, Framingham, MA USA

It is important to characterize and understand critical quality attributes of viral vector products throughout drug development. Here, we present strategies on how to shape and manage phase-appropriate analytical paradigms, focusing in on specific release tests and method platforms. As the industry aims to accelerate gene therapeutics from pre-clinical to early and late-stage clinical trials, it is also key to discuss phase-appropriate product specifications and to ensure critical quality attributes are properly controlled.

NOTES:
Development of Gene Edited Allogeneic CAR-T Cell Therapy

Juliannne Smith

*Cellectis, New York, NY USA*

Cellectis has developed a platform for generating chimeric antigen receptor (CAR)-redirected T-cells from third-party healthy donors using transcription activator-like effector nucleases (TALEN®). Nuclease mediated inactivation of the TCR alpha abrogates the potential for T-cells bearing alloreactive TCR's to mediate Graft versus Host Disease (GvHD). Additional gene inactivation events can be incorporated, permitting resistance to lymphodepleting or chemotherapeutic agents, resistance to tumor inhibition or suppression of cross T-cell reactions. Such allogeneic “off-the-shelf” CAR T-cell products will permit a wider application of CAR technology and potentially lead to a new paradigm in cancer treatment. The challenges of developing and manufacturing a gene edited cell therapy product will be addressed including considerations for product characterization and specifications.

NOTES:
Accelerated CMC Development of Regenerative Medical Products

Yoshiaki Maruyama

Pharmaceuticals and Medical Devices Agency (PMDA), Tokyo, Japan

The accelerated research on and developments of regenerative medical products, different types of regulations have been in place. In Japan, regulatory reform was carried out to improve access to new therapeutic innovations in regenerative medicine. The Pharmaceuticals and Medical Devices Act (PMD Act) (the revised Pharmaceutical Affairs Law) took effect on November 25, 2014. The PMD Act allows patients early access to promising therapies, using conditional and time-limited approval schemes (as “accelerated approval”) for regenerative medical product review. Quality control strategy should be enriched and developed along with the progress of clinical trials. Accelerated CMC development is extremely important for accelerated approval to promising therapies. Quality control of biotechnological/biological products, which are high molecular compounds with complex structure possessing a low level of homogeneity, are good reference for human cell therapy products (hCTPs) and gene therapy products (GTPs). At present, ICH guidelines for quality of biotechnological/biological products such as Q6B and ICH Q5 series can be applicable for quality control of hCTPs and GTPs.

The presentation will give a short introduction to Japan regulatory framework for regenerative medical products, including gene therapy. And also related guidelines will be given, and the current challenges of quality control of regenerative medicine field will be addressed.

NOTES:
Panel Members:
Svetlana Bergelson, Biogen
Yoshiaki Maruyama, Pharmaceuticals and Medical Devices Agency (PMDA)
Eric Pastor, Sanofi
Anne Plant, National Institute of Standards and Technology (NIST)
Victoria Sluzky, BioMarin Pharmaceutical Inc.
Julianne Smith, Cellectis
Zenobia Taraporewala, CBER, FDA

The following questions will guide the panel discussion:

1. What do phase-appropriate analytical paradigms look like for viral vector gene therapy and cell therapy drug substance/drug product release and characterization?
   a. How do we select what tests are for characterization vs. release?
   b. Is there a point in development beyond which a “report result” specification is no longer acceptable?
   c. How and when is the best time to introduce new and emerging analytical technologies into the characterization paradigm?
   d. What would be the best path forward in scenarios where the mechanism of action is not fully understood at the cellular / molecular level?

2. How do we set phase-appropriate specifications?
   a. What are appropriate early-phase vs. late-phase specifications for dose-defining assays and potency assays?
   b. For viral vectors:
      i. Is a functional assay for expressed protein product absolutely necessary, or can infectivity & expression assays serve as an adequate surrogate?
      ii. What are appropriate specifications and method(s) for vector aggregates and full/empty particles for AAV?
      iii. Is testing for replication-competent virus required for vectors designed in a way that precludes the possibility of recombination?
   c. For cell therapies:
      i. What are acceptable potency assays (e.g., phenotyping or differentiation vs. functional cytokine production vs. cell-killing)?
      ii. What are appropriate purity specifications and how do you best assess “contaminating” cell populations?
      iii. For gene-edited products, what additional attributes (i.e., off-target editing) should be measured for lot release vs. characterization purposes, and how sensitive do these methods need to be?

3. Given the time constraints for releasing cell-based therapies (as well as the potential for vector interference with traditional assays for adventitious agents), what methodologies will be acceptable to assure product safety? E.g., alternatives to traditional sterility and in-vitro virus testing?
4. What characterization tools (in addition to release assays) should be included to demonstrate process and product comparability to support process enhancements, scale-up and/or site changes?
   a. How can standards (reference materials, best practices, reference methods, reporting requirements, etc.) help to push the cell/gene therapy field forward?
   b. What standards would be helpful? What measurements/data/knowledge will be needed to support such standards?

NOTES:
Session Chairs: Paul Husak, Amgen Inc. and Stefanie Pluschkell, Pfizer, Inc.

In this session on the comparability of cell and gene therapy products, we will discuss the unique challenges faced by manufacturers and regulators in conducting and evaluating comparability assessments for advanced medicinal therapies. We will focus on challenges not typically encountered with more established, well-characterized biological molecules due to the lack of substantial prior knowledge from similar therapies to justify the impact of any quality attribute change on safety, immunogenicity or efficacy. This session aims to delineate common challenges in the area of cell and gene therapy products and to identify scientific and technical approaches that can be applied to successfully manage phase-appropriate comparability assessments. Examples will include the difficulties encountered due to typically small batch sizes, limited understanding of the criticality of quality attributes, a still emerging field of applicable robust analytics and biopotency measures, and new challenges in raw or starting/donor material variability. The speaker presentations and Q&A panel discussion are intended to provide opportunities for manufacturers and regulators to further engage in the dialogue to facilitate the advancement of promising cell and gene therapies for the treatment and potential cure of serious or life-threatening illness.

NOTES:
Cell Therapy Product Manufacturing Considerations

Mohammad Heidaran

CBER, FDA, Silver Spring, MD USA

Cellular therapy products are defined as autologous, allogeneic, or xenogeneic cells that have been propagated, expanded, selected, pharmacologically treated, or otherwise altered in biological characteristics ex vivo to be administered to humans and applicable to the prevention, treatment, cure, diagnosis or mitigation of disease or injuries. This definition is broad and encompasses a diverse set of cell based products with many potential applications. While relatively few cell based therapies are currently marketed, others are in late phase clinical development. In addition, the use of cellular therapies in investigational studies has been steadily increasing. Due to the nature of these therapies, they have both great therapeutic potential and manufacturing challenges. Challenges include starting cell variability, lack of reference standards, patient specific and/or small lot sizes, limited material for testing, the need for aseptic processing, and others. Despite these challenges, cell based therapies allow manufacturers to tap into complex and living systems that may be poorly understood but can potentially repair, replace, or restore function in the patient. This talk will focus on providing a few strategies to address common manufacturing challenges by 1) applying principles of Current Good Manufacturing Practices; 2) understanding product’s key Critical Quality Attributes and Critical Process Parameters; and 3) knowing how to deal with process change.

NOTES:
Comparability exercises of gene therapy products are challenged by several aspects, including lack of full understanding of attribute criticality, material availability due to small batch sizes and limitations of standard assays with poor sensitivity and high variability. This presentation will describe attempts to advance analytical capabilities and demonstrate their direct impact to comparability assessment and product characterization. Through the use of a case study, the power of advanced techniques, namely mass spectrometry, RP-HPLC, SEC-HPLC and peptide mapping, to evaluate product consistency and purity will be demonstrated. The implementation of advanced analytical techniques enabled the team to identify and correct the specific process change that was responsible for the product variation(s). It is important to note that this variant was not detected by traditional methods such as SDS-PAGE. In addition, efforts to improve potency functional assay(s) through carefully designed DOEs, to characterize the size of residual host cell DNA and to measure the empty/full particle ratio will be discussed. Though certainly not exhaustive, the collection of these methods will allow teams to better support gene therapy process development, to more fully characterize gene therapy products and to achieve more meaningful comparability exercises.

NOTES:
Changes in the manufacturing process occur during development as product development progresses to full-scale commercial production. These changes are usually introduced before final validation of the process. But changes are almost certainly inevitable also through the life cycle of the product. The most common scenarios relate to changes of the starting materials eg. autologous or limited cell batch size, viral vectors, manufacture improvements, scaling-up, technology transfer …

Appropriate comparability studies should be conducted in order to demonstrate comparability of the pre- and post-change product. The general principles outlined in ICH Topic Q5E for biotechnological/biological products apply. Nevertheless, the comparability approach should respond to the specificities of the different types of ATMP considering (1) the complexity and variability of the starting materials (2); the complexity of the process and (3) the amount of experimental data and/or process knowledge available on the specific process.

The consequences of those changes may have an impact on the quality of the product including effects on its biochemical and biological properties and functionality, and thus have implications on the appropriateness of the non-clinical or clinical data generated. If changes are introduced prior to the start of clinical development it is expected that differences reflect the improvement sought and a better product is expected. In this case the exercise cannot be considered *stricto sensu* as comparability but it should aim at establishing a clear link to the development flow from a prototype to a safe product entering clinical trials. Ensuring filiation of the data means that the safety claims are sustained after the change was introduced. Changes introduced after the start of clinical development where data already accumulated raises higher concerns since clinical data have already been accumulated. A comprehensive comparability exercise is needed to ensure that patients are treated with equivalent products.

At the pivotal trial and beyond into the commercial process changes are also expected. In this context, the comparability should be presented for approval taking into account the variations procedure in the case of authorised ATMPs, or authorisation procedure of a substantial amendment of a clinical trial in the case of investigational ATMPs. For the prospective evaluation of planned changes foreseen to occur post marketing a comparability protocol may be submitted for prior approval and the change introduced is recorded and verified through the pharmaceutical quality system. Such is the case of donor material replacement for limited size batches based on process validation.

Manufacturing process of viral vectors represent a fast changing domain and comparability tools are extremely relevant to enable improvements. Tools are commensurate to the target profile and as such viral entities are easier to address. The exercise is more complex when dealing with cell based medicinal products be it somatic cell therapy, tissue engineering or genetically modified cells. Manufacturing development of genetically modified cells require to integrate not only all aspects related to manufacture and control of the cell intermediate, but also the impact of the differences introduced with changes in the viral/bacterial vector starting materials.

The present talk will discuss the characterisation tools and conditions that are more meaningful to support a comparability claim for viral vectors, cell based products including combined and genetically modified cells.

NOTES:
Comparability Studies for Autologous Cell Therapy Processes

Christopher Shen

*Kite Pharma, Santa Monica, CA USA*

Comparability is a regulatory requirement to demonstrate product equivalence post a process change. Demonstrating product comparability for autologous cell therapy product is particularly challenging because of donor to donor variability. While planning comparability studies it is therefore important to also include process comparability since presently cell therapy products may not be “fully characterized”. Depending on the stage of the manufacturing process and the availability of prior knowledge, different study designs and statistical methods can be used for comparability. Use of split-apheresis approach helps reduce donor related variability. Several comparability studies have been successfully completed at Kite Pharma at different stages of product lifecycle using the split apheresis approach to demonstrate equivalence following process transfer to new manufacturing sites.

NOTES:
Comparability of Cell & Gene Therapy Products
Workshop Session Two

Panel Members:
Diane Blumenthal, Spark Therapeutics, Inc.
Christopher Shen, Kite Pharma
Mohammad Heidaran, CBER, FDA
Margarida Menezes-Ferreira, INFARMED
Herbert Runnels, Pfizer, Inc.
Christopher Storbeck, Health Canada

The following questions will guide the panel discussion:

1. What are suitable **Comparability approaches** for cell or gene therapy products?
   a. Are there any principal differences in approach applied for an advanced therapy as compared to a well-characterized biological?
   b. What process or product changes would require release testing results only, versus more extensive analytical characterization, or pre-clinical and/or clinical data to establish comparability?
   c. How are risk assessments utilized to inform requirements for pre-clinical or clinical studies?
   d. What minor attribute differences between pre- and post-change materials would lead you to conclude that there is no impact on safety or efficacy?
   e. If analytical testing results indicate that products are not comparable for specific parameters and the clinical relevance of the change is unknown, how is the meaningfulness of the difference determined?
   f. Under a circumstance where clinical evaluation may be necessary, what kind of clinical surrogate could be used that would not require a full non-inferiority clinical study?

2. What **quality attributes** should be studied to develop phase-appropriate specifications and comparability criteria?
   a. What are the challenges in identifying CQAs in cell and gene therapy? How can we best manage the current uncertainty of clinical relevance for many quality attributes?
   b. What analytical tools can be used to predict or explain the potential impact of a change to biological activity? How many different potency assays are needed? (For example, for AVV GTx does a robust, single activity assay that measures infectivity and expression suffice?)
   c. What innovative or novel technologies could be used to characterize CQAs and to support comparability assessments?

3. What are the **global expectations for comparability** package content, either pre- or post-licensure?
   a. How and when should comparability plans be communicated to Regulatory Health Authorities?
   b. Are there differences in expectations for analytical comparability content between jurisdictions?
   c. Do comparability assessments utilize summary statistics, statistical tests or historical ranges?
   d. Should forced degradation studies be used in the comparability assessment and how is the data evaluated qualitatively and/or quantitatively?

**NOTES:**
Session Chairs: Sid Advant, *Celgene Corporation* and Shian-Jiun Shih, *Tessa Therapeutics*

Cell and gene therapy products have demonstrated impressive clinical success in recent years, and such products (e.g. gene therapy) have been approved or have been filed with regulatory agencies for market licensure. However, these products have unique challenges in manufacturing processes that are different from typical ones for biologic drugs. Cell and gene products are diverse and complex materials, and these living materials are sensitive to manufacturing conditions. Furthermore, autologous cell therapy products use the starting materials with intrinsic difference and need to be processed in relatively small scales. This session aims to present successful case studies and promote discussion on manufacturing challenges for both cell and gene therapy products.

NOTES:
Regulation of Manufacturing Cell and Gene Therapy Products for Use in Phase 1 Clinical Trials

Adrian Gee

*Baylor College of Medicine, Houston, TX USA*

CAGT manufactures a wide variety of cell and viral vector products for use in Phase 1 clinical trials. Many of these were developed in a basic research laboratory and, therefore, their preparation must be adapted to produce a therapeutic that can be administered to a patient. Under regulations from the Food and Drug Administration (FDA) manufacturing must be performed under current Good Manufacturing Practices (cGMP) as applied to pharmaceuticals. Certain products may fall under the less stringent current Good Tissue Practices (cGTP) based on a low risk designation, due primarily to minimal ex vivo manipulation of the cells and homologous use. The FDA has issued a Guidance1 document that outlines its expectations in terms of the level of cGMP compliance that is expected for products used in Phase I trials. The FDA also recognizes that cellular products and viral vectors differ from small drug pharmaceuticals in many aspects and have issued a Draft Guidance2 that indicates how these differences may be addressed when designing the clinical trial. Additional assistance is provided through two Guidances that provide detailed templates for the CMC section of somatic cell and gene therapy Investigational New Drug (IND) applications. These clearly describe the information that must be included and the formats to be used. Finally, pre-pre- and pre-IND conference calls with the FDA provide an opportunity to clarify the acceptability of specific manufacturing and/or testing procedures prior to submission of the IND application. Through these mechanisms the FDA has provided useful information on what is expected from manufacturers of cell and gene therapy products for use in Phase I clinical trials.

1 Guidance for Industry CGMP for Phase 1 Investigational Drugs U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) Office of Regulatory Affairs (ORA) July 2008 CGMP


NOTES:
Biologic therapies are becoming increasingly prevalent in the sphere of medicine today. In the field of Gene and Cell Therapies (GCT), scientific and technical advances have repositioned this therapeutic classification as an exciting and promising treatment option for a number of challenging disorders and unmet clinical needs. With these advances come challenges with respect to consistent manufacture of high quality product. Novel therapeutics such as CAR T-cells and Oncolytic viruses possess unique characteristics and features that challenge the traditional regulatory models/pathways for biologics. Health Canada’s Biologics and Genetic Therapies Directorate evaluate Clinical Trial Applications (CTAs) for GCT products, primarily for safety in the early developmental stages with increasing expectations as development progresses. With the number of applications increasing come opportunities to work with sponsors to provide guidance as GCT products progress toward marketing applications. While we recognize challenges sponsors face in early development, we encourage a focus on quality with respect to manufacturing processes at the earliest possible stages and capitalization on principles applied to other biologics. Here I will present insight into the Health Canada approach to the review of GCT applications, including our regulatory framework and our approach to CMC challenges surrounding manufacturing of these novel products.

NOTES:
Manufacturing and Commercialization of an Oncolytic Virus Product

Tia Bush

Amgen Inc., West Greenwich, RI USA

Amgen received approval of IMLYGIC in 2016, a first-in-kind live virus oncolytic immunotherapy for the company. IMLYGIC is injected directly into a lesion and has a dual mechanism of action by directly attacking the cancer cells and by helping the immune system to recognize and destroy cancer cells. The live virus manufacturing process and end-to-end supply chain requirements for this product are unique as compared to the more traditional biologics typically produced by Amgen. These unique requirements required the Operations and Commercialization teams to challenge conventional approaches to the manufacture, testing, validation, and distribution of IMLYGIC in order to achieve successful regulatory licensure and launch of this important therapy. This presentation will share the knowledge and experience gained along this journey to bring the innovative medicine to the patients.

NOTES:
Cell & Gene Therapy Manufacturing Strategies
Workshop Session Three

Panel Members:
Tia Bush, Amgen Inc.
Adrian Gee, Baylor College of Medicine
Mohammad Heidaran, CBER, FDA
Michael Kelly, Biogen
Richard Snyder, Brammer Bio, LLC
Christopher Storbeck, Health Canada

The following questions will guide the panel discussion:

1. What manufacturing regulatory guidance can be provided, when manufacturing is more “boutique” with different manufacturing processes?
   a. What are expectations when there are no set precedence/regulations, but manufacturing is being done in “spirit” as opposed to traditional approaches
2. Process changes have/need to be made in the middle of clinical trials. What is the experience and what approaches are being taken? How to keep the comparability in mind while implementing changes?
3. What are the requirements and challenges of region specific manufacturing, for autologous cell therapy products and for gene therapy products?
4. Cell Processing in autologous therapy is still close to art than science- how are these challenges being addressed?
   a. What are the progress in developing processes with automation and/or closed systems?
   b. How long does it take, and how difficult or challenging are, for transition into automation or closed system?
   c. Are there any aspects of the cell therapy processes making them not suitable for moving to automation or closed system?
5. What are the main challenges in the manufacturing of AAV’s?
   a. When would the appropriate time to define the quality attributes of AAV products?
   b. How and when to use critical quality attributes to guide process development?
6. How to transition early stage manufacturing processes to late stage ones? How and when to ensure the tools needed are available to support such transition in an appropriate manner?

NOTES:
In this session, we will discuss raw materials and supply chains for cell and gene therapy products and how we leverage conventional biotech approaches while also addressing the unique aspects. When manufacturing a product on demand for a specific patient, there are unique challenges to the supply chain, including a need for short turnaround times to make product available to patients in a clinically relevant timeframe while maintaining high standards of quality. Furthermore, the products may be highly perishable, and supply chains must be developed and implemented to take this into account and maintain quality of the product. The end-to-end supply chain can extend to and from the clinical sites for personalized products, thus interfacing with Good Clinical Practice (GCP) requirements. The complexities of these time-critical supply chains, including traceability requirements, will be discussed. The processes often define these products, and raw materials are a critical input to the manufacturing processes. For cell, gene, and tissue products, the raw materials may come into direct contact with final products not subjected to filtration or sterilization, hence the risk associated with the use of raw materials is even higher than for conventional products. The session will also include discussion around risk-based approaches for raw materials that may end up in the final formulation.

Example topics include:

- Supply chain management of viral vectors and autologous/allogeneic cell therapies
- Controls, supply continuity, and quality assurance of critical raw materials
  - Risk assessment strategies and qualification programs for raw materials
  - Considerations for human-derived raw materials

NOTES:
**Standards and Best Practices for Cell, Gene and Tissue-based Therapies**

Rebecca Potts

*U.S. Pharmacopeial Convention (USP), Rockville, MD USA*

Cell, gene and tissue-based therapies are a diverse group of medical products that contain human or animal cells. Manufacturers of cell and tissue-based products must ensure that all components used in manufacturing are appropriately qualified. Quality systems including qualification of source cells and tissue, and qualification of components should be incorporated in the manufacturing process. A wide range of analytical methods are used to establish in-process controls and product release criteria for cell and tissue-based products. Gene therapy products are defined by the administration of nucleic acids to modify the genetic material of cells. Manufacturing of gene therapy products include analytical methods for assessing product quality and tests to ensure the safety the product. Ancillary materials used in the manufacturing of cell, gene and tissue-based products may exert an effect on a therapeutic substance but are not intended to be in final formulation. Some ancillary materials are more critical than others. Risk assessment strategies are required to ensure quality of the ancillary materials, to ensure the quality of the final product. Best practices for cell, gene and tissue-based therapies including analytical methods for assessing product quality, and a risk-based approach for qualification of ancillary materials will be presented.

**NOTES:**
A Life Cycle Approach to Raw Material Qualification for Cell and Gene Therapy Products

Angela Whatley

CBER, FDA, Silver Spring, MD USA

Interest in the development of cell and gene therapies continues to grow due to their potential to address a variety of unmet medical needs. As new cell and gene therapy products progress through the phases of clinical trial, there is increased interest among the stakeholders regarding the regulatory requirements applicable to raw materials used in the manufacture of these products. At FDA, we apply a lifecycle approach predicated on increasing levels of scrutiny for all manufacturing components, including raw materials as product development matures. In this session, FDA expectations for qualification of raw materials used to manufacture cell and gene therapy products will be discussed. This session also includes case studies that serve to highlight the importance of raw material quality in the manufacture of cell and gene therapy products.

NOTES:
Integrated Supply Chain for Cell Therapy

Bryan Silvey

*Kite Pharma, Santa Monica, CA USA*

Supply chain processes in personalized immunotherapy products has changed the paradigm in traditional biologics CMC. The ‘One Lot – One Patient’ manufacturing platform and the high level of assurance required that a patient receive back her/his cells drives this emerging industry to think in new terms about the control of both raw materials and drug product. The ability to deliver these products at temperatures well below the ‘cold chain’ requirements of traditional biologics, and with requirements beyond the ‘falsified medicines’ expectations we see today, are the areas this presentation will highlight for cell and gene therapies soon to be realized.

NOTES:
Panel Members:
Rebecca Potts, U.S. Pharmacopeial Convention (USP)
Bryan Silvey, Kite Pharma
Christopher Storbeck, Health Canada
Angela Whatley, CBER, FDA
Ran Zheng, Amgen Inc.

The following questions will guide the panel discussion:

What are special supply chain considerations for made-to-order products that begin and end with the patient (i.e. needle-to-needle or vein-to-vein)?

- These supply chains often require short turnaround time and/or special handling and sensitivity to temperature.
- What are best practices for ensuring the chain of custody, and how do we anticipate that these practices will evolve?
- What are challenges with meeting requirements for FDA Drug Supply Chain Security Act for these products?
- What challenges arise at the interface with clinical sites, such as special training and qualification of clinical sites?

How can regulators and industry come together to ensure batch release works smoothly for individualized products (one batch per patient)?

- Turnaround time for supply includes testing and release time. Are we prepared for the scale out as the number of patients increases?
- What are regulators’ expectations for out of specification/failed lots of personalized medicinal products in clinical development and once commercial?

What are critical Raw Material expectations for cell and gene therapies?

- Design the product with high standards of quality
  - Expectations for “research grade” materials?
  - Expectations for raw materials used in manufacture when there are no purification or sterilization steps of the final product?
  - Incoming testing of raw materials – what is appropriate for cell and gene therapy products

Looking ahead to post-marketing changes for cell and gene therapies:

- Updates to raw materials are a common post-approval change for biopharmaceuticals and are required to ensure continuous supply and high quality. How do you envision these post-approval changes being handled?
- Updates to chain of custody and the practices for tracking ID are anticipated. Such changes shall be performed with proper qualification and validation. How can regulators and industry colleagues work together to enable such changes?

NOTES: