SCIENTIFIC PROGRAM

CASSS
Bay Area Discussion Group

Co-chairs:
Malou Gemeniano, *Audentes Therapeutics, Inc.*
Shelley Suggett, *Bayer*

South San Francisco Conference Center
Thursday, June 1, 2017
# Table of Contents

Conference Program Partners.........................................................................................3  
Acknowledgements........................................................................................................4  
General Information.......................................................................................................6  
Scientific Program Summary..........................................................................................8  
Program and Speaker Abstracts......................................................................................9  
Career Development Luncheon Roundtable.................................................................12  
Roundtable Discussion Point Sheets.............................................................................13  
Note Paper....................................................................................................................30
The Organizing Committee gratefully acknowledges the Conference Program Partners for their generous support of this Bay Area Discussion Group Program

Program Partners

Agilent Technologies

BioMarin Pharmaceutical, Inc.

Genentech, a Member of the Roche Group

Thermo Fisher Scientific

Waters Corporation
Acknowledgements

Special Thanks to all the Program Committee Members Who Helped Develop this Bay Area Discussion Group

Program Committee
Greg Cantin, *Five Prime Therapeutics*
Jenny Chen, *Nektar Therapeutics*
Judy Chou, *Bayer*
Kathleen Francissen, *Genentech, a Member of the Roche Group*
Michelle Frazier, *Coherus BioSciences*
Malou Gemeniano, *Audentes Therapeutics, Inc.*
Nomalie Jaya, *Seattle Genentics*
Guifeng Jiang, *Boehringer Ingelheim*
Vinaya Kapoor, *Johnson & Johnson*
Rob McCombie, *Genentech, a Member of the Roche Group*
David Passmore, *Bristol-Myers Squibb Company*
Joanne Severs, *Bayer*
Bryan Silvey, *Kite Pharma, Inc.*
Shelley Suggett, *Bayer*
Trevor Swartz, *Genentech, a Member of the Roche Group*
Lance Wong, *Strand Bio*
Min Young, *Ultragenyx Pharmaceutical*
Christopher Yu, *Genentech, a Member of the Roche Group*
Eike Zimmermann, *Boehringer Ingelheim*
Fengrong Zuo, *Pfizer, Inc.*

Roundtable Facilitators
Sara Linda Amaden, *Boehringer Ingelheim*
Lori Boville, *Genentech, a Member of the Roche Group*
BJ Bruce, *Bayer*
Duane Brumm, *Bayer*
Andrea Challand, *Genentech, a Member of the Roche Group*
Lisette Coye, *Seattle Genetics*
Heather Flores, *Genentech, a Member of the Roche Group*
Feny Gunawan, *Genentech, a Member of the Roche Group*
Scott Henry, *Seattle Genetics*
Pratik Jaluria, *Five Prime Therapeutics*
Eva Kras, *Coherus BioSciences*
Ying Liu, *Johnson & Johnson*
Ekta Mahajan, *Genentech, a Member of the Roche Group*
Robert McCombie, *Genentech, a Member of the Roche Group*
Rafi Mohammad, *Bayer*
Charles Morgan, *Genentech, a Member of the Roche Group*
Lal Ninan, *Genentech, a Member of the Roche Group*
Roma Panjwani, *Boehringer Ingelheim*
Elaine Peters, *Bayer*
Elijah Tan, *Coherus Biosoines*
Acknowledgements - Continued

Roundtable Facilitators - Continued
Kanti Thirumooorthy, Kite Pharma, Inc.

Sara Wright, Boehringer Ingelheim
Yunzhi (Sophie) Xiao, BioMarin Pharmaceutical, Inc.
Nathalie Yanze, Coherus BioSciences

Roundtable Scribes
Kris Antonsen, BioMarin Pharmaceuticals
Greg Cantin, Five Prime Therapeutics
Judy Chou, Bayer
Michelle Frazier, Coherus Biosciences
Malou Gemeniano, Audentes Therapeutics, Inc.
Nomalie Jaya, Settle Genentics
Rob McCombie, Genentech, a Member of the Roche Group
Karen Miller, Coherus Biosciences
David Passmore, Bristol-Myers Squibb Company
Melissa Schwartz, Boehringer Ingelheim
Trevor Swartz, Genentech, a Member of the Roche Group
Julia Yeh, Boehringer Ingelheim

Audio Visual
Michael Johnstone, MJ Audio-Visual Productions

CASSS Staff
Stephanie L. Flores, CAE, Executive Director
Julie Fowle, Meeting Coordinator
Linda Mansouria, CMP, CMM, Program Manager
General Information

Name Badges
Please wear your name badge throughout the day.

Registration
The registration desk will be open from 8:00 a.m. to 3:45 p.m. We will accept walk-in registrations.

Roundtable Session
There are 12 roundtable topics for you to choose from. The roundtable summary portion of the program will all be held in Salon F. The goal is for these roundtables to be active discussions, not presentations or lectures. The table topics are listed below.

Table Topic 1: How do you define the appropriate level for Insulin, Protein A and Table Antifoam for Early Development Stages (Phase 1-2)
Table Topic 2: How do you define the appropriate level for insulin, Protein A and Antifoam for Late Life Cycle States (Phase 3 and Beyond)
Table Topic 3: HCP Discussion (Phase 1-2)
Table Topic 4: HCP Discussion (Phase 3 and Beyond)
Table Topic 5: Metals Analysis
Table Topic 6: Leachables/Extractables coming from Disposable Technologies
Table Topic 7: Approaches to Controlling and Assessing Risk for Residuals or Unknown Impurities
Table Topic 8: What approaches have been found useful to meet regulators expectations that Impurity Acceptance Criteria/Limits be Supported by Clinical Experience
Table Topic 9: Development of Assays for Process-related Impurities
Table Topic 10: How Companies Deal with Variability of Raw Materials in Process Related Impurities
Table Topic 11: Cell and Gene Based Therapies
Table Topic 12: Control of Impurities Through Multi-Attribute Methods
Tables are set with 11 seats each. **Table topics are on a first come, first serve basis.** These roundtables will include two facilitators, whose role is to help assist the discussion and ensure a lively exchange, and a scribe, whose role is to make general, anonymous notes about the discussion so others can have a chance to view the main discussion points even if they could not participate. The roundtable discussion notes will be shared with all attendees during the session summary at the end of the program, and the notes will also be posted on the CASSS website after the program concludes.

**Career Development Luncheon Roundtable**
Successful career progression requires planning. This is particularly the case in the Biopharmaceutical industry where career advancement typically occurs over long time frames. Young scientists may not have a complete understanding of how to plan for a typical career progression, while experienced scientists may be seeking knowledge of how to achieve a mid-career transition. If you are seeking information about career development in Biotech/Biopharma, then please join the CASSS Career Development roundtable session which will be held during lunch. This table topic will be facilitated by Rob McCombie, *Genentech, a Member of the Roche Group* and David Passmore, *Bristol-Myers Squibb Company*. Refer to Page 11 for additional information.
Scientific Program Summary

Thursday, June 1, 2017

08:00 – 15:45    Registration

08:00 – 09:00    Continental Breakfast in Salon F

09:00 – 09:30    CASSS Welcome and Introductory Comments in Salon F
                 David Passmore, Bristol-Myers Squibb Company

09:30 – 10:15    Christopher Downey, CDER, FDA

10:15 – 10:30    AM Break in Salon F

10:30 – 11:00    Sara Parker, Genentech, a Member of the Roche Group

11:00 – 11:30    Kanti Thirumoorthy, Kite Pharma, Inc.

11:30 – 12:15    Panel Discussion Moderated by: Shelley Suggett, Bayer

                   Panel Members:
                   Christopher Downing, CDER, FDA
                   Sara Parker, Genentech, a Member of the Roche Group
                   Mimi Roy, BioMarin Pharmaceutical, Inc.
                   Kanti Thirumoorthy, Kite Pharma, Inc.

12:15 – 13:15    Networking Lunch in Salon E

13:15 – 14:00    Roundtable Discussions in Salon F

14:00 – 14:30    PM Break and Creation of Roundtable Summaries Salon F

14:30 – 15:30    Summary of Roundtable Discussions by Table Facilitators in Salon F

15:30 – 15:45    Closing Remarks by Vinaya Kapoor, Johnson and Johnson and Trevor Swartz, Genentech, a Member of the Roche Group
Impurities in biological drug products are typically classified as either product- or process-related impurities. ICH Q6B defines process-related impurities as those that are derived from the manufacturing process, i.e. cell substrates, cell culture, or downstream processing, and exclude molecular variants of the product. Examples of process-related impurities include: host cell proteins, DNA, media and buffer components, added oxidizing and/or reducing agents, inorganic salts and metals, and extractables/leachables from column resins, equipment, and containers. The majority of process-related impurities are almost entirely removed during the downstream purification process; however, residual levels of these agents may be left within the bulk drug substance and, subsequently, the drug product.

Global regulatory health authorities require that the control process-related impurities are addressed in regulatory dossiers, and that the risk to patient safety of residual amounts of process-related impurities be evaluated. Expectations and the type of management of process-related impurities may vary, and typically evolve throughout the product lifecycle (beginning with first in human studies) of the product.

We will discuss strategies for evaluating process related impurities, assessing their risk and setting up appropriate control strategies to enable potential efficient and cost-effective development, production, and availability of safe and beneficial new products.
A Regulatory Perspective on Characterization and Control of Process-Related Impurities
Christopher Downey, CDER, FDA

The manufacture and testing process of biotechnology products must provide sufficient control process-related impurities and process contaminants. ICH Q6B broadly categorizes these impurities as cell substrate-derived, cell culture-derived, and downstream-derived. Process-related impurities or contaminants may pose a risk to patient safety or may affect the activity or stability of drug products. Consequently, these impurities need to be well controlled for the drug substance and drug product manufacturing processes and in some cases controlled with in-process or release tests. The control strategy for process-related impurities should be risk-based and will evolve over the course of clinical development and throughout post-approval lifecycle management. Dr. Downey will discuss regulatory experience and expectations related to control of these substances, including case studies. This will include not only discussions of the challenges of detecting and controlling host cell protein impurities, but will also provide examples of cell-culture and downstream-derived impurities.

Controlling Process-Related Impurities for Ocular Indications
Sara Parker, Genentech, a Member of the Roche Group

Control of process-related impurities in products intended for intravitreal administration requires special considerations compared to products intended for other routes of administration. This is due to the unique nature of the eye as well as minimal health authority guidance and publications on the subject. Here we present the risk assessment and control strategy for beta glucans as a case study for controlling process-related impurities in ocular drug products.

Impurities in Autologous Cell Therapies
Kanti Thirumoorthy, Kite Pharma, Inc.

Impurities in autologous cell therapies can be divided into two categories broadly. Those that are similar to other therapies – impurities like host cell protein, host cell DNA, upstream media components or processing aids. Then there are impurities from the subject’s apheresis material, a key raw material for the process. The challenges in the personalized subject raw material are unique to this therapy. We find the apheresis material to be highly variable depending on the type and disease stage of the subject, the types of previous treatments, and individual blood phenotype. The variability of this apheresis material from subject to subject plays an important role in critical quality attributes of the final product. The methods that can be typically used to assess these impurities are unique to the therapy. Measurement of live cells requires use of flow cytometry. Flow cytometry which employs use of staining of distinct cell surface markers and detection gets complicated when multiple cell types are being quantitated. Apheresis material, in-process and final product are characterized for B-cells, NK cells, different T cell phenotypes. Multiple gating
strategies, complex analysis methods and lack of proper reference standards create challenges for qualification of the methods. Understanding the effect of any process changes and their results on these impurities and their decrease or clearance necessitate studying a huge number of lots due to the inherent variability already present in the starting material. The number of subjects in the studies, the accelerated pathways due to breakthrough designation and pivotal phase 2 followed by BLA makes the timelines of CMC activities very constrained. Establishing a characterization program in this therapy area creates challenges that the industry is trying to address in collaboration with regulatory agencies.
Career Development Luncheon Roundtable

Two tables will be set aside during the networking lunch to discuss career development. The volunteer facilitators for these tables are Rob McCombie, Genentech, a Member of the Roche Group and David Passmore, Bristol-Myers Squibb Company. There will be a total of 20 seats available for this career development discussion - 10 seats per table. Seating will be on a FIRST COME, FIRST SERVE basis. The discussion points are listed below.

TOPIC: Career Development – Transferable Skills

FACILITATORS: Rob McCombie, Genentech, a Member of the Roche Group
David Passmore, Bristol-Myers Squibb Company

SCOPE:
We will be discussing career development within the Biotech and Pharma Industries. We will explore myths regarding the numbers of years one has to acquire to attain a desired position of different area or discipline in the industry. And we will discuss transferable skills, management experience and strategic skills sets.

DISCUSSION POINTS:

1) Is important to have a degree in the field that you are pursuing?
   a. For example, if the goal is to be a Director of Analytic, does one need degree in chemistry, Biology. Does one require a PhD?
   b. Is this the case for all careers? For example, does this hold true for Regulatory affairs or project management?

2) How does one move from technical jobs to Regulatory affairs, project management, Quality assurance, and vice versa etc.?
   a. What are transferable skills in the industry?
   b. How can start thinking more cross-functionally?
   c. How can you think more strategically?

3) Is it better to have a more diverse background or focus on one field for many years to be successful?
   a. How can one gain more experience in one discipline yet still stay in their current position?
TABLE 1

TOPIC: How Do You Define the Appropriate Level for Insulin, Protein A, and Antifoam for Early Development Stages (non-pivotal Phase 1-2 studies)

FACILITATORS: Pratik Jaluria, Five Prime Therapeutics
             Jenny Chen, Nektar Therapeutics

SCRIBE: Greg Cantin, Five Prime Therapeutics

SCOPE:
ICH Q6B [1] defines specifications as follows: “a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance, drug product or materials at other stages of its manufacture should conform to be considered acceptable for its intended use”, and “…found to be useful in ensuring the safety and efficacy of the product”.

WHO guideline on rDNA-based biotherapeutics [2] states “… impurities need to be tested and evaluated on a case-by-case basis using a risk-assessment and risk-management approach. In the case of a potential impact on the safety of the product, the removal of such impurities to acceptably low levels during downstream purification may need to be validated or end-product testing and specification limits established.

This table will examine aspects that might be considered in setting appropriate limits (levels) for insulin, protein A, and antifoam in biologics that are in the non-pivotal Phase 1-2 clinical stage.

BULLET POINTS FOR DISCUSSION:

1. Information used in setting appropriate levels (acceptance criteria) for contaminants in Phase 1-2
   a. Nonclinical data
      i. Predicted process capability/variability
      ii. Predicted analytical capability/variability
   b. Clinical data
   c. Prior knowledge / Platform experience (also see flow chart below)
      i. Acceptance criteria used for similar products/indications that have been accepted by regulatory agencies
         1. Examples where specific guidance is available:
            a. Residual DNA – 10 ng/dose [3]
            b. Endotoxin – 5 EU/kg·hr (IV administration) [4]
         2. Example where specific guidance is limited, but expectations are well-known:
            a. Host cell protein – < 100 ppm [5, 6]
d. Risk assessment (also see flow chart below)
   i. Example where toxicity has been tested in animal models:
      1. Monitor process for specific impurities (e.g. dimethicone – active ingredient in antifoam) by pulling samples from at-scale runs and testing for impurities
      2. Identifying a relevant IC50 level and including a safety margin/factor (~ 1000X)
      3. Calculating the level of the impurity in BDS assuming it co-eluates with protein to determine the worst-case level being administered

2. Are statistical methods needed to set expected range or acceptance criteria in Phase 1-2?
   a. If so, what methods can/should be used?
      i. Target level: < expected level + 1-3 Std. Dev. of the variability of process and/or analytical method

3. Testing not needed for release, if:
   a. Development work showed that sufficient removal is achieved?
   b. Non-qualified in-process testing carried out?
      i. If qualified in-process testing carried out, it would be considered a release assay?
   c. Removal (Validation) Studies carried out
      i. Typically done in Phase 2?

4. Participants asked to provide examples of acceptance criteria used in the past for Phase 1-2
   a. Insulin:
   b. Protein A:
   c. Antifoam:

REFERENCES:

5. USP <1132> Residual host cell protein measurement in biopharmaceuticals

Flow chart: Setting acceptance criteria
Impurity 1

Any prior regulatory guidance/criteria from similar biological products?

Yes
Follow the guidance

No
Criteria learned/measured in process development

Additional modification of Criteria while the program revolves; especially when additional tox/clinical data is available
TABLE 2

TOPIC: How Do You Define the Appropriate Level for Insulin, Protein A and Antifoam for Late Life Cycle States (Phase 3 and Beyond)

FACILITATORS: Sara Wright, Boehringer Ingelheim
Lisette Coye, Seattle Genetics

SCRIBE: Trevor Swartz, Genentech, a Member of the Roche Group

SCOPE:
This table will discuss the acceptable level of process related impurities in products in late phase. This discussion will focus on insulin, Protein A and anti-foam but discussion could also extend to other process related impurities. Table members are encouraged to discuss the safety concerns for these impurities and how this factors into what is deemed an acceptable level.

BULLET POINTS FOR DISCUSSION:
1. What is the safety concern for each of these impurities?
2. What level of each impurity could be impactful to patients?
3. What are the regulatory guidance if any for acceptable levels?
4. Does anyone have experience in which they had detectable levels of these impurities for products in late life cycle states?
5. What is the overall success rate to validate out these type of process related impurities? If there has been success, share your strategy.
6. Which impurity should remain on release? If so why?
**TABLE 3**

**TOPIC:** HCP Discussion (Phase 1-2)

**FACILITATORS:** Andrea Challand, *Genentech, A Member of the Roche Group*  
Elaine Peters, *Bayer*

**SCRIBE:** Melissa Schwartz, *Boehringer Ingelheim*

**SCOPE:**  
This table will discuss the topic of Host Cell Proteins (HCPs) for Phase 1-2. The discussion will focus on method development challenges and successful examples, e.g. the topic of coverage, robustness and regulatory expectations for Phase 1-2.

**BULLET POINTS FOR DISCUSSION:**

1. What type of assay is used for Phase 1-2; e.g. a generic kit or a platform assay?  
   - What are regulatory expectations?  
   - When do you switch to a cell line specific assay? What needs to be considered if switched (Phase 1-2 appropriate)?

2. What is phase appropriate method development for Phase 1-2?  
   - How are process changes addressed in method development?

3. Is coverage assessed for Phase 1-2?  
   - If yes, how is it assessed? What coverage is acceptable to move forward?  
   - If poor coverage exists, are cell line specific HCPs being identified; or are common immunogenic HCPs targeted for evaluation?  
   - If using a generic kit, do you have assays for specific HCPs?  
   - What is the experience with health authorities?

4. What are acceptable Phase appropriate limits/specifications; numeric values expectations?  
   Regulatory expectations?

5. Is Mass Spec Analysis used for HCP analysis in Phase 1-2?
**TABLE 4**

**TOPIC:**  
HCP Discussion (Phase 3 and Beyond)

**FACILITATORS:**  
Feny Gunawan, *Genentech, a Member of the Roche Group*  

**SCRIBE:**  
Julia Yeh, *Boehringer Ingelheim*

**SCOPE:**  
This table will discuss HCP strategies and characterization for Phase 3 and beyond.

**BULLET POINTS FOR DISCUSSION:**

1. **HCP ELISA:**
   a. What type of HCP ELISA do you think is suitable for use on Phase 3 and beyond (Platform, Process Specific, or Generic)? How do you establish suitability of use? If process specific ELISA is recommended, what should be used to generate the HCP antibodies for the process utilizing affinity chromatography as the capture chromatography?
   b. What is your control strategy for HCP ELISA (CoA testing or In Process testing or characterization testing or no testing)?
   c. How do you establish HCP specification (limits) for Phase 3 and beyond? Do you account for process changes (e.g. changes to the purification process for Phase 3)?

2. **Method Comparability:** If a different HCP ELISA is used on Phase 3 and beyond, how do you establish method comparability to the HCP ELISA use in the earlier phases?

3. **Do you employ orthogonal methods to your HCP ELISA?** If so:
   a. What type of orthogonal method(s)?
   b. Is the orthogonal method part of the control system or characterization only?
   c. When do you use the orthogonal method?
   d. Which samples are tested orthogonally? Clinical or Development or Material representative of the clinical process?
TABLE 5

TOPIC: Metals Analysis

FACILITATORS: Charles Morgan, Genentech, a Member of the Roche Group
BJ Bruce, Bayer

SCRIBE: David Passmore, Bristol-Myers Squibb Company

SCOPE
This table will discuss the approach to metals analysis and elemental impurities. Contributors to the roundtable discussion are expected to provide input based upon their experience, interactions with contract manufacturers, vendors and health authorities (HA).

BACKGROUND & RESOURCES
Elemental impurities in drug products may arise from various sources: intentional ones e.g. carry-over of metals (synthesis catalysts), or unintentional impurities (coming from equipment or containers). Since elemental impurities do not provide any therapeutic benefit to the patient, levels should be controlled within acceptable limits.
Core guidance, ICH Q3D, reached Step 4 in November 2014, the final step (5) is implementation by regulatory bodies, e.g. EMA expected new marketing authorization applications (MAA) to adhere to ICH Q3D starting from July 2016 (authorized medicinal products due December 2017); for Health Canada new applications starting January 1, 2017.

- ICH Q3D document (www.ich.org) - suggested pre-read
- USP Elemental Impurities (www.usp.org/usp-nf/key-issues/elemental-impurities)

BULLET POINTS FOR DISCUSSION:

1. General approaches
   a. evaluate potential elemental impurities;
   b. establish Permitted Daily Exposure (PDE);
   c. apply a risk based approach to control.
2. Which levers are most helpful?
   a. sources / removal of impurities
   b. multi-product / platform experience
3. Analytics - role of compendial methods e.g. USP <232>
   a. which samples are submitted for testing?
   b. internal testing or contract labs?
4. Reporting to HA
   a. where to place the information? Drug Substance and Drug Product CTD sections.
   b. at what level of detail to report?
   c. HA expectations and differences
TABLE 6

TOPIC: Leachables/Extractables Coming from Disposable Technologies

FACILITATORS: Ekta Mahajan, Genentech, a Member of the Roche Group
Nathalie Yanze, Coherus Biosciences

SCRIBE: Rob McCombie, Genentech, a Member of the Roche Group

SCOPE
This table will discuss different approaches to assess extractables and leachables form Single-use manufacturing Technology (SUT). Contributors to the roundtable discussion are expected to provide input based upon their experience during process design/characterization, process qualification/verification, continued process verification, and interactions with their suppliers, vendors and health authorities.

BULLET POINTS FOR DISCUSSION:

Strategy/ Company Position
5. Do you conduct an E/L assessment to implement Single-use Technology?
6. Do you rely only on vendor data?
7. Do you rely on CMOs performing the studies?
8. Do you have an approach based on risk and distance from bulk?
9. Do you assume clearance?
10. Do you only do an assessment of the leachable making it through to DP (i.e. ADE/EDI calcs)
11. Do you assess product quality impact and/or performance impact from leachables?
12. Do you agree with the bracketing approach for extractables?
13. Have you heard of BPOG and attempts to harmonize E/L packages and data from vendors?
14. Are you aware of USP 663.1/USP 665? If so are you actively commenting?

Change Management – Vendor Management – Reportability
1. Are back-up vendors typically qualified?
2. Are agreements in place with vendors to communicate changes to SUT (e.g material, manufacturing process)?
3. Are all vendors treated equally?
   a. If not, what criteria are in place to determine higher risk vendors?
   b. Are audits conducted more frequently on higher risk vendors?
4. How are raw materials used for SUT controlled with third party manufacturers?
5. Does your company rely on third parties to test incoming SUT?
6. Have companies had third parties have issues in handling/testing their SUT?
Strategy During Development Phase

1. Do you do anything differently for each phase of development, e.g. phase I through PIII to commercial
2. Do you report in IND/IMPD your use of SUT?
3. Do you rely on CMOs performing the studies?
4. How do you report, if at all, changes in SUT materials during clin dev / commercial manufacture?
TABLE 7

TOPIC: Approaches to Controlling and Assessing Risk for Residuals or New Impurities

FACILITATORS: Lori-Anne Boville, Genentech, a Member of the Roche Group  
               Elijah Tan, Coherus Biosciences

SCRIBE: Nomalie Jaya, Settle Genentics

SCOPE:
This table will discuss best approaches to control and assess risk for residuals or new process-related impurities (e.g. HCP, Protein A, glucans, antifoam, triton, leachables, etc.) for biologics. Table members will provide input based upon their experience with process validation (encompassing process design/characterization, process qualification/verification and continued process verification), control systems, and interactions with health authorities. Participants will discuss the following key questions in their area.

BULLET POINTS FOR DISCUSSION:

• How are qualification limits or safety thresholds for process-related impurities established in each of the situations below? (e.g. new potential leachable, cell culture media component, potential process contaminant, etc.)
  o Process-impurity clearance validation
  o Clinical control system (e.g. DS or DP in-process or release specifications)
  o Commercial control system (e.g. DS or DP in-process or release specifications)
  o Comparability studies
  o Post-approval monitoring
  o Novel or non-standard route of administration e.g. intravitreal, inhalation, intrathecal, etc. (for which there is a lack of published safety information or regulatory limits)

• How are new impurities identified during routine QC testing? What actions are taken by the company if new impurities are identified?

• What questions or information requests have you received from health authorities (e.g. FDA, EMA, Health Canada) regarding risk assessment or control of residual/unknown impurities?
  o Are there any surprises with these information requests that may suggest evolving regulatory expectations?

• What measures have your company taken to comply with ICH Q3D Elemental Impurities and regional guidance or regulations pertaining to elemental impurities?

• There is an expectation that extractables and leachables evaluation and risk assessment extend beyond evaluation of primary container closures.
o How does your company address process-related extractables and leachables (e.g. from process equipment having product contact, tubing, water system, etc.)?

o Is a risk based approach (paper-based exercise) taken for these process-contact components, and if so, what does the risk based approach entail? Is the risk assessment supplemented with further studies?
TABLE 8

TOPIC: What Approaches Have Been Found Useful to Meet Regulators Expectations that Impurity Acceptance Criteria/Limits be Supported by Clinical Experience

FACILITATORS: Ying Liu, Johnson & Johnson
Rafi Mohammad, Bayer

SCRIBE: Judy Chou, Bayer

SCOPE:
This table will describe various approaches and challenges to meet the regulatory expectations that impurity acceptance criteria supported by clinical experience. Table members will share their experiences based on their skills in regulatory, research and development areas. Participants will focus on the best practices in the industry.

BULLET POINTS FOR DISCUSSION:

1. Current regulatory requirements: Impurity acceptance criteria supported by clinical experience
   a. Challenges
   b. What are the different approaches used by different biotech companies
   c. Are there any differences small versus large molecules

2. Prior knowledge for claiming clinical justification.
   a. Impurities, glycosylation and their impact on Immunogenicity with biotechnology products
   b. Dose finding studies

3. Use of statistical methods
   a. Relevance of statistical methods
   b. Advantages and pitfalls of using statistical methods

4. How can regulatory agencies and industry can work together to address the challenges in the acceptance criteria be supported by clinical experience.
TABLE 9

TOPIC: Development of Assays for Process-related Impurities

FACILITATORS: Sara Linda Amaden, Boehringer Ingelheim
Duane Brumm, Bayer

SCRIBE: Karen Miller, Coherus Biosciences

BULLET POINTS FOR DISCUSSION:

Define what are ‘Process Related Impurities Assays’:
• For Drug Substance (process limitations) vs Drug Product (excipient)
• For SMOL
  o Catalysts, Enzymes
  o Ligands (free conjugates, (free PEG))
• For Biologics
  o Cellular host DNA, Intercellular material (viral, proteins)
  o Unreacted ADC, PEG

The need for process-related impurity testing:
• Should it be done with every GMP batch or only during process validation?
• How many in-process steps are necessary?
• Is it necessary for supporting comparability studies between phases?
• Is testing required for process development of in-process steps?

Development strategies:
• Limit test or quantitative test? Related to PDE?
• Should methods be qualified or validated? What are the intent, process development (pre-GMP) vs Quality managed development (Tox / GMP)?
• Mass Spec in HCP development – when/how are we using mass spec, how is it going?
• Is anything better than ELISAs for routine screening of protein impurities? Considering sensitivity and throughput.
TABLE 10

TOPIC: How Companies Deal with Variability of Raw Materials in Process Related Impurities

FACILITATORS: Lal Ninan, Genentech, a Member of the Roche Group
Heather Flores, Genentech, a Member of the Roche Group

SCRIBE: Michelle Frazier, Coherus Biosciences

SCOPE:
ICH Q7 defines a raw material as a general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or APIs. While there is no standardized classification system for raw materials, they can be considered based on their origin (ie, biologically or chemically derived, physical raw materials) or when and how they are used in a process. Regardless of their classification, it is important that raw materials are appropriately qualified, tested and stored to ensure their identity, purity, quality and safety. Many firms utilize risk-based approaches for establishment of their raw materials programs. This discussion will focus on best practices for raw materials qualification.

BULLET POINTS FOR DISCUSSION:

1. Why should we care about raw materials? What are potential safety concerns for raw materials? What are the ideal raw material characteristics? Do companies develop impurity profiles for some or all raw materials? How do compendial standards for raw materials help with their characterization?

2. How do companies qualify raw materials for early stage clinical development programs? Does the qualification strategy change in rigor and requirements for late-stage or commercial requirements?

3. Raw material suppliers may change over time and/or suppliers may change components. How are these changes communicated to pharmaceutical/biotech companies and how are these changes evaluated? What can go wrong if there is a breakdown in communication or evaluation? What best practices are used to manage suppliers who provide critical raw materials, but whose business footprint in pharma/biotech is relatively smaller compared to other industries (such as food)?

4. Many companies utilize a risk-based approach for establishing raw materials programs. What are best practices for developing a risk-based raw materials program? How are risk assessment tools used to identify critical raw material attributes? How is the impact of raw material variability characterized?

5. Changing of raw materials components, sources – especially critical raw materials - for commercial products often requires approval by global health authorities. What studies are executed to assure comparability of the raw material from the new supplier to that
6. purchased from the original supplier? What are some strategies that companies can employ to reduce the need for these post-approval submissions that ensure consistent raw material quality and continued global supply of product? For those raw material changes that require global health authority approval, what are best regulatory and quality practices in order to expedite introduction of the change?
TABLE 11

TOPIC: Control of Process Related Impurities of Cell and Gene Therapies

FACILITATORS: Eva Kras, Coherus Biosciences
Roma Panjwani, Boehringer-Ingelheim

SCRIBE: Malou Gemeniano, Audentes Therapeutics

SCOPE:
This table will discuss the unique challenges associated with controlling and characterizing process related impurities of Cell and Gene Therapies

BULLET POINTS FOR DISCUSSION:

1) What are the unique challenges in controlling or characterizing process related impurities?
   a. Process challenges
   b. Method challenges
   c. Raw material
2) What are the different types of cell and gene therapy products existing?
   a. What are the similarities?
   b. What are the differences?
   c. What are the similarities that we can draw from the more platform modalities – eg. Monoclonals?
   d. What are the similarities that we can draw from vaccine products?
3) What are examples of the process related impurities for cell and gene therapy? (eg. Helper viruses, residual plasmids)
   a. What are possible mechanism of control?
   b. What are the unique considerations when performing risk assessments?
4) What are control strategy examples for cell and gene therapy products?
   a. Raw material qualifications
TABLE 12

TOPIC: Control of Impurities Through Multi-attribute Methods

FACILITATORS: Scott Henry, Seattle Genetics
Kanti Thirumoorthy, Kite Pharma

SCRIBE: Kris Antonsen, BioMarin Pharmaceutical, Inc.

SCOPE:
This table will discuss the analytical challenges and opportunities associated with the development of multi-attribute/MS methods for process impurity control.

BULLET POINTS FOR DISCUSSION:

1. Does MAM offer advantages to traditional methods for control of process impurities, and for which impurities are you applying MAM methods?
2. What are the major analytical challenges for the development of MS impurity methods?
   - Sensitivity (esp. compared to ELISA)
   - Analyte diversity (eg. HCP)
   - Quantitation (eg, label free, isotopic standards specialized data acquisition methods)
3. Does MAM have value in release testing or is it primarily a tool to support process development?
4. Do you employ or are you developing MAM/MS methods for HCP testing?
5. What software solutions have you found useful to support MAM methods and are there limitations with regard to compliance or validation?
6. What unique challenges are presented in qualification of MAM impurity methods?
7. What challenges have you experienced in transfer of MAM impurity methods?
8. What regulatory challenges are you facing in comparison to traditional analytical modalities?
9. Is there a role for MAM or other MS methods for testing non-proteinaceous impurities (eg, glucan, DNA)?
NOTES: