Biologics Development

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PRODUCT UNDERSTANDING: CONNECTING THE DOTS
Drug Development Approaches

Two Drug Substance Development Approaches Described in ICH Q11

**Traditional:**
Process set points and ranges are defined; the control strategy is based on process reproducibility and testing to meet acceptance criteria.

**Enhanced:**
Extensive use of risk management and scientific knowledge to understand process parameters that impact CQAs and to develop process control strategies, including design space. Quality by Design (QbD)

These approaches are not mutually exclusive and companies can use either the traditional or enhanced approaches or a combination.
Process & Process Understanding: Keys to Product Quality

- Process developed with clinical importance in mind
- More clinically relevant specifications and comparability criteria

A-MAb:A Case Study in Bioprocess Development
Critical Quality Attributes & The Patient

Uncertainty

?  ×  Impact

Safety
Immunogenicity
Potency/Efficacy
PK/PD
Potential to cause adverse events?

Critical Quality Attributes

Safety e.g. Bioburden
Product Variants e.g. glycosylation
Purity e.g. Half antibody
Potency
Strength
Process Residuals e.g. HCP
Identity

- Decrease uncertainty with improved attribute understanding
Reducing Uncertainty & Predicting Patient Outcomes

- Product attributes sciences and non clinical data are key to predicting patient outcomes
  - In vitro cell based data
  - Serum studies to understand impact in vivo
  - Non clinical data to understand impacts on PK/PD
  - Clinical prior knowledge with similar molecule
  - Clinical knowledge with molecule

- Therapeutic products are complex
  - Quality attributes (QA) are often interlinked
  - QA inverse relationships with each other
  - Studying one attribute at a time clinically can be challenging

- Dosing patients with higher than expected levels carries considerable patient risk
CASE STUDY 1: TUMOR DERIVED OR TUMORGENIC PHENOTYPES IN GENE THERAPY PRODUCTS
Rigorous Confirmation of Patient Safety needed

**CMC Information for Human Gene Therapy INDs**

“If you are using cells that are tumor-derived or with tumorigenic phenotypes or other characteristics that give rise to special concerns, more stringent limitations of residual DNA quantities may be needed to assure product safety.”

**Case Study**

- DNA sequences from master cell bank were found to be encapsidated in DS
- Assays monitoring the presence of these sequences are included as part of characterization testing
- Results confirmed full length sequences were present

Due to high impact of safety concerns uncertainty needs to be removed.
Can DNA be transcribed/translated into oncogenic protein?

INVESTIGATION PATH: IS AAV-X SAFE FOR PATIENTS?

IN VITRO CELL BASED

A biologically relevant cell line was infected with Product X at three different multiplicities of infection (MOIs) and infection times

- mRNA transcription by RT-PCR
- Protein translation by Western Blot

NON CLINICAL DATA

Serum from Toxicology study examined for mRNA

- mRNA transcription by RT-PCR
• Product X transgene mRNA increased with infection time
• No encapsidated DNA impurity mRNA was detected under any infection condition
• No encapsidated DNA impurity mRNA detected in Tox samples
• No impurity protein detected

PRODUCT SAFETY CONFIRMED
DNA impurity promoter likely not encapsidated
POTENCY & EFFICACY

CONNECTING THE DOTS TO PROPOSE CLINICAL RELEVANT SPECIFICATION
Using Product Knowledge to Setting Clinical Relevant Specifications

- **Product Y P3 vs P2 comparability**
  - Product Y activity was found to be slight lower in P3 vs P2
  - All other attributes found to comparable

- **How should the P3 specifications be justified, if confirmed comparable?**

- **What information can be gathered?**
  - Cell based potency vs activity
  - Non clinical data in efficacy model
  - Clinical experience
Product Y Activity & In Vitro and In Vivo Data

- Product Y samples generated with high and low activity levels
- Samples studied in in vitro potency assay and non clinical efficacy model

- *In vitro* potency & non clinical data illustrate differences are normalized in the *in vivo* animal model and cell based potency assay
Proposing a clinical relevant specification

- Difficult to dose samples at the edge of the clinical specifications and cover the whole range
- Generate additional non clinical data to cover the range
  - Can material be made at lower activity levels?
  - Can we understand the in vivo relevance of the in vitro activity data?
- Qualify the animal model and potency with clinical data
CASE STUDY 2: EVALUATING IMMUNOGENCITY FOR NEW HCPS
Case Study: New HCP Detected After Process Changes

**Background**

- Intensified cell culture process developed as P2 process
- Lower HCP levels by HCP ELISA in P2 vs P1 process
- MS-HCP profiling from P1 vs P2
  - Moderate changes in HCP1
  - HCP2 present above QL

**Considerations**

- Potential risk of HCPs to the patient
  - Immunogenicity
  - Toxicity
  - Adverse impact on the efficacy of the therapeutic
- Limited guidance on the quantities of HCPs that are acceptable
- Risk-based approach
### One HCP Risk-Assessment Tool – Factors to Consider

<table>
<thead>
<tr>
<th>Impact</th>
<th>Identity of HCP</th>
<th>Exposure to HCP</th>
<th>Clinical Indication</th>
<th>Therapeutic MOA</th>
<th>Phase of Devpt</th>
<th>Route of Admin</th>
<th>Duration of Treat</th>
<th>Dose Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very High</td>
<td>Not homologous with human</td>
<td>No experience</td>
<td>Autoimmune, Pediatric</td>
<td>Immune activating</td>
<td>Phase III</td>
<td>Interderm, IM, Inhale, Ocular</td>
<td>Chronic</td>
<td>Intermittent</td>
</tr>
<tr>
<td>High</td>
<td>Homologous with human</td>
<td></td>
<td>Immunology</td>
<td></td>
<td>Phase II</td>
<td></td>
<td>Daily/Weekly</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>Non-clinical experience</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Human homolog is inaccessible</td>
<td>Clinical experience</td>
<td>Oncology, Elderly</td>
<td>Immune suppressing</td>
<td>Phase I or Pre-clinical</td>
<td>Single dose</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- The identification of these risks forms the “basis for cross-functional discussion” and informs process development and decision-making.
- It is wise to comprehensively assess HCP profiles early to facilitate a strategy for mitigating changes in HCPs.
Human homology & In silico Antigenicity Profiling

Results
HCP1 = low risk
HCP2 = high risk

Identify HCP

Obtain corresponding CHO proteins and human sequences from public database

Multiple alignment to identify homology to human proteome

Check for non-human high binding T cell epitopes using IEDB algorithm

Evaluate potential T cell epitopes using EpiMatrix algorithm and obtain immunogenicity score

Evaluate T cell content and CHO specific T cell epitopes using CHOPPI algorithm

Antigenicity/immunogenicity risk

Rate Immunogenicity Risk using EpiMatrix Immunogenicity scale

Linking it to patient outcomes

- Leverage using clinical adverse event information
- Use clinical experience from multiple products to understand safe limits for high risk HCPs?
PRIOR KNOWLEDGE MANAGEMENT

PRODUCT UNDERSTANDING: CONNECTING THE DOTS
Prior Knowledge Management

Challenges
- Lots of information from multiple sources
- Collecting information across projects & function groups can be challenging & time consuming
- Project often re-invent the wheel

Mitigation
- Data lake generation
- Information database development with advanced data analytical apps
  - Quality attribute driven
  - Different from data sources

Any regulatory concerns for using data for specification and control strategy justifications?
Conclusions

- Product attribute sciences are important for building understanding of CQAs
  - Easier to study single attributes at a time
  - Need to be bridge to clinical and non clinical studies to ensure relevance

- Prior knowledge is powerful,
  - Study relationships between attributes
  - Link clinical data across projects e.g HCPs to understand impact at a larger scale
  - Well organized, searchable & secure

- Understanding is imperative to providing well controlled products
  - Enhancing holistic control strategy & relevant specifications
Acknowledgments

- Analytical Development
- Characterization
- Upstream Development
- Downstream Development
- Clinical Development
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Thankyou