Implementing the Principles of Quality by Design for Early Stage Gene Therapy Products

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Gene Therapy Development

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Overview

- Gene Therapy V’s Protein Biologics
- Development of Gene Therapy Technology
- Gene Therapy Development at Genzyme
- Drug Development at Genzyme
- Drug Development Lifecycle
- Design for Manufacturability-Gene Therapy Products
- Adopting QbD to Gene Therapy Development
- Critical Success Factors for Implementing QbD
Gene Therapy V’s Protein Biologics

- Unlike protein therapeutics, conventional Gene Therapy products exploits the biology of viruses to transfer the genetic sequence encoding for a therapeutic to target cells.
- The therapeutic protein is expressed by the cell from the gene under the control of a promoter, following transduction.
- The period of expression of the transgene can vary, depending on the biology of the transducing vector, from weeks (e.g. Ad) to years (e.g. AAV) as long as the transduced cell is metabolically maintained.
- A single administration of a Gene Therapy product is potentially feasible, compared to multiple administrations of therapeutic proteins to treat genetic disease.
Development of Gene Therapy Technology

- Gene Therapy, as a therapeutic strategy has been in R&D since the early ‘70’s with the first clinical trial initiated 1990, but has yet to result in an approved product.

- During that time, a broad range of clinical indications, vector types, routes of administration and therapeutic transgenes have been evaluated.

- The number of manufacturing platforms to generate clinical vector has also been diverse:
  - e.g. Transfection, packaging cell line, producer cell lines.

- Multiple administration strategies for gene therapy have been investigated:
  - Direct transduction of cells in localized targets
    - e.g. Brain (Parkinson’s), Eye (LCA2, AMD)
  - Direct transduction of target cells through systemic administration
    - e.g. Liver transduction by I.V administration (Hemophilia)
  - Transduction of cells ex-vivo prior to administration
    - e.g. Stem cell transduction, cancer vaccines
Development of Gene Therapy Technology

- Gene therapy enjoyed a period of growth in the “90’s, but following clinical setbacks (Jesse Gelsinger, 1999), gene therapy stalled and many of the gene therapy companies failed to survive.
- Much of the research in gene therapy has “gone back” to academia, and much progress has been made quietly.
- Recent advances and successes in the clinic has given new hope for gene therapy as a viable therapeutic platform,
  - e.g. LCA2, SCID-ADA, X-linked SCID, Parkinson’s, Adrenoleukodystrophy
- The key will be to ensure that the processes used to manufacture and characterize the products are robust and reliable and approvable.
**Development of Gene Therapy Technology**

- Much of the early research and development work in gene therapy has been focused on improving vector design to enhance safety/potency and capability e.g. target cell tropism, tissue specific expression and control of immunogenicity.

- Less work has been done to develop manufacturing methods.

- Many investigational products in the gene therapy space are manufactured from “enhanced” research laboratory protocols, executed under GMP.

- Large amount of clinical manufacturing performed in boutique CMO’s and academic-based GMP environments.

- Many investigational gene therapy vectors have historically been manufactured and characterized based on Quality by Testing (QbT) strategies.

- Over the years, many improvements to manufacturing and product characterization infrastructure have been realized, but challenges still remain to reliably support commercial demands and modern BLA requirements for gene therapy products.
Gene Therapy Development at Genzyme

- Genzyme have been involved in the development of Gene Therapy products since the early 1990’s and feel we have a leadership position in the field.
- We support our own internal programs and support smaller companies/academic investigators in a variety of ways.
- We believe that Gene Therapy has the potential to make significant contributions to the development of novel transformative therapeutics for serious diseases.
- We have made a tremendous investment to build our Gene Therapy capability in Science, Engineering and Clinical disciplines.
- We want to use our knowledge/experience/lessons from the protein manufacturing environment to advance gene therapy development and manufacturing capability to world class status.
- We will leverage/adopt best practices and tools available to support or product development ambitions from corporate infrastructure.
Design for Manufacturability-Gene Therapy Products

- We are working to establish a long term strategy that can adequately support supply of gene therapy products
- Based on developing “modern” processes that support “manufacturability”
  - Scalable platform-based manufacturing processes with well established in-process controls and characterization capability
  - Consistent lot to lot performance and quality
  - Processes based on well understood unit operations
  - Animal-derived component-free
  - Portable (can be transferred to different manufacturing sites/locations)
  - Based on single-use disposable infrastructure (multi-product)
  - Cost effective

- We expect that incorporating QbD to our development strategies will be a important step in helping us realize out ambitions!
Drug Development at Genzyme

- At Genzyme, we have experienced significant product supply challenges in our commercial protein therapeutics businesses, as a result of process, operational and quality issues.

- To address those issues, we have revised our operating requirements for biologics. We are establishing a series of Corporate Standards to ensure the implementation of best practices for biologics manufacturing, including the drug development process.

- Quality by Design is a critical cornerstone of the revised operating strategy to improve our drug development process.

- Currently establishing an infrastructure and expertise to support incorporation of QbD to R&D functions.
Drug Development Lifecycle at Genzyme

- In accordance with Genzyme’s Corporate Standard on Drug Development, the product lifecycle structure has been established using an eight stage model.

Stage 1: Therapeutic Candidate Identification
Stage 2: Process Investigation
Stage 3: Process Definition
Stage 4: Process Optimization
Stage 5: Process Installation
Stage 6: Commercial Start-up
Stage 7: On-going Commercial Manufacturing and Continuous Improvement
Stage 8: Product Discontinuation

- Stage 4 is the transition point between early and late stage process development.
Idealized Timeline for Drug Development, showing stages and relevant milestones.

- **Therapeutic Candidate Identification Stage 1**
- **Early Process Development**
  - Process Definition Stage 3
  - Process Installation Stage 5
- **Quality by Design**
  - pCOA established by RA
  - QbD Design Space
- **Process Investigation Stage 2**
- **Process Optimization Stage 4**
- **Commercial Start-up Stage 6**
- **Product Discontinuation Stage 8**
- **On-going Manufacturing Stage 7**

Stages:
- Stage 1: Therapeutic Candidate Identification
- Stage 2: Process Investigation
- Stage 3: Process Definition
- Stage 4: Process Optimization
- Stage 5: Process Installation
- Stage 6: Commercial Start-up
- Stage 7: On-going Manufacturing
- Stage 8: Product Discontinuation
What is QbD?

- “A systematic approach to development that begins with pre-defined objectives and emphasizes product and process understanding and process control” (ICH Q8)

- “A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight”
  
  - Janet Woodcock, CDER
Adopting QbD to GT development?

- Gene therapy vectors are complex biologics!
- Gene therapy products are manufactured by complex biological manufacturing processes!
- Gene therapy products are characterized by complex analytical methods!

**Question:** How do we start to implement QbD for Gene Therapy?

**Answer:** In the same way we implement QbD for protein biologics!
Steps in adopting QbD for drug development

- QbD lifecycle well defined for Biologics
- At Genzyme, we are developing a road map, based on established principles
  - Quality Target Product Profile (QTPP)
  - Identify Preliminary Critical Quality Attributes (pCQAs)
  - Preliminary Process Control Strategy
  - Develop/understand process control parameters (CPPs, kPPs, nkPPs)
  - Design Space
  - Continually refine within product lifecycle for continuous improvement!

- Early stage development focuses on preliminary CQA’s, PCS and CPP’s
- Towards late stage development (Stage 4) and beyond the Design Space, lifecycle management and continuous improvement are more in play!
Establish a QbD team

- Establish a strong collaborative cross-functional team, including
  - Technical and Business leads
  - Cell culture scientists
  - Downstream/purification scientists
  - Formulation/fill and finish scientists
  - Analytical scientists
  - Process engineers
  - Statisticians
  - Project managers
  - Risk assessment SMEs
  - QbD SMEs

- Train the team on principles of QbD and Risk Management!
Quality Target Product Profile (QTPP)

“A QTPP is a prospective summary of the quality characteristics of a drug (biologic) product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug (biologic) product” ICH Q8

- Basis of design for development of product, includes...
  - Intended use (clinical setting, route of administration, dosage form, delivery system)
  - Dosage strength
  - Container closure system
  - Therapeutic delivery and attribute affecting pharmacokinetic characterization (e.g. vector, transgene expression and biological function)
  - Drug product quality criteria appropriate for intended marketed product (e.g. sterility, purity)

- The QTPP is the highest order of hierarchy in the QbD model and is critical in the establishment of all lower order components
Critical Quality Attributes (CQAs)

“A CQA is a physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality”. (ICH Q8)

- Preliminary CQAs are defined early in stage 3 of the drug development lifecycle using Risk Assessments.
- pCQA’s are further investigated using DOE/process experience and will be refined during the early phase of the development lifecycle based on enhanced product knowledge and early clinical experience.
- Serve as the basis to identify Critical Process Parameters and facilitate development of the Design Space (Stage 4).
Factors to consider in the determination of CQA’s for GT products include:

- Vector Type
- Production Platform
- Route of administration
- Dose
- Process and product knowledge
- Process and analytical capability
- Product variants
- Process contaminants
Critical Quality Attributes (CQAs)

Typical list of potential CQA’s considered for GT products

<table>
<thead>
<tr>
<th>Process Impurities</th>
<th>Safety</th>
<th>General Quality</th>
<th>Product variants</th>
<th>Potency</th>
<th>Purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residual Benzonase</td>
<td>Endotoxin</td>
<td>Appearance</td>
<td>Empty Capsids</td>
<td>Gene Expression</td>
<td>Host cell protein</td>
</tr>
<tr>
<td>Residual Resin</td>
<td>Mycoplasma</td>
<td>Osmolality</td>
<td>rcVector</td>
<td>Transgene function</td>
<td>Host cell DNA</td>
</tr>
<tr>
<td>Ligand</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leachables</td>
<td>Bioburden</td>
<td>Conductivity</td>
<td>Aggregation</td>
<td>Infectivity</td>
<td></td>
</tr>
<tr>
<td>Buffer salts</td>
<td>Sterility</td>
<td>pH</td>
<td></td>
<td>Concentration</td>
<td></td>
</tr>
<tr>
<td>Adventitious Agents</td>
<td>Identity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Particulates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Residual Benzonase
- Endotoxin
- Appearance
- Empty Capsids
- Gene Expression
- Host cell protein
- Mycoplasma
- Osmolality
- rcVector
- Transgene function
- Host cell DNA
- Bioburden
- Conductivity
- Aggregation
- Infectivity
- Concentration
- Identity
- Particulates
- Residual helper virus
- Residual HV DNA
- Residual HV Protein
Critical Quality Attributes (CQAs)

Risk Assessment Model
Following a review of the various Risk Assessment tools available, we have decided to use a numerical Risk Ranking tool for CQA assessment. This process is being incorporated into a software tool, currently being piloted in a number of development programs.

\[
\text{Risk} = \text{Criticality} \\
\text{Criticality} = \text{Impact} \times \text{Uncertainty}
\]

We establish a list of possible CQAs based on knowledge and experience using a standard risk ranking, we evaluate criticality of each attribute on Safety, Efficacy, PK/PD and Immunogenicity.

In general for early stage products, most attributes are expected to score as critical, in large part due to a high level of uncertainty. For early stage process development, CQAs are ranked and DOE studies are performed to better understand impact and reduce uncertainty to acceptable level.
## Risk Ranking - Impact on Safety

<table>
<thead>
<tr>
<th>Score</th>
<th>Ranking</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Very Low</td>
<td>attribute would not result in any Adverse Events (AEs)</td>
</tr>
<tr>
<td>4</td>
<td>Low</td>
<td>attribute has the potential to result in minor, transient AEs</td>
</tr>
<tr>
<td>12</td>
<td>Medium</td>
<td>attribute has the potential to result in manageable AEs</td>
</tr>
<tr>
<td>16</td>
<td>High</td>
<td>attribute has the potential to result in reversible AEs</td>
</tr>
<tr>
<td>20</td>
<td>Very High</td>
<td>attribute has the potential to result in irreversible AEs</td>
</tr>
</tbody>
</table>
## Risk Ranking-Impact on Efficacy

<table>
<thead>
<tr>
<th>Score</th>
<th>Ranking</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Very Low</td>
<td>attribute would not change product efficacy/biological activity</td>
</tr>
<tr>
<td>4</td>
<td>Low</td>
<td>attribute has the potential to result in a slight change/decrease in</td>
</tr>
<tr>
<td></td>
<td></td>
<td>efficacy/biological activity</td>
</tr>
<tr>
<td>12</td>
<td>Medium</td>
<td>attribute has the potential to result in a moderate change/decrease in</td>
</tr>
<tr>
<td></td>
<td></td>
<td>efficacy/biological activity</td>
</tr>
<tr>
<td>16</td>
<td>High</td>
<td>attribute has the potential to result in a significant change/decrease in</td>
</tr>
<tr>
<td></td>
<td></td>
<td>efficacy/biological activity</td>
</tr>
<tr>
<td>20</td>
<td>Very High</td>
<td>attribute has the potential to result in a very significant change/complete</td>
</tr>
<tr>
<td></td>
<td></td>
<td>loss in efficacy/biological activity</td>
</tr>
</tbody>
</table>
## Risk Ranking-Impact on PK/PD

<table>
<thead>
<tr>
<th>Score</th>
<th>Ranking</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Very Low</td>
<td>attribute would not impact PK or PD</td>
</tr>
<tr>
<td>4</td>
<td>Low</td>
<td>attribute has the potential to result in a slight change with no impact on PD</td>
</tr>
<tr>
<td>12</td>
<td>Medium</td>
<td>attribute has the potential to result in a moderate change with no impact on PD</td>
</tr>
<tr>
<td>16</td>
<td>High</td>
<td>attribute has the potential to result in a moderate change with an impact on PD</td>
</tr>
<tr>
<td>20</td>
<td>Very High</td>
<td>attribute has the potential to result in a significant change with an impact on PK</td>
</tr>
<tr>
<td>Score</td>
<td>Ranking</td>
<td>Criteria</td>
</tr>
<tr>
<td>-------</td>
<td>--------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>2</td>
<td>Very Low</td>
<td>Anti-Therapeutic Antibody (ATA) not detected for this product attribute or ATA detected with no relevant in vivo effect</td>
</tr>
<tr>
<td>4</td>
<td>Low</td>
<td>ATA detected for this product attribute with a minimal in vivo effect</td>
</tr>
<tr>
<td>12</td>
<td>Medium</td>
<td>ATA detected for this product attribute with an in vivo effect that can be managed</td>
</tr>
<tr>
<td>16</td>
<td>High</td>
<td>ATA detected for this product attribute and confers limits on efficacy</td>
</tr>
<tr>
<td>20</td>
<td>Very High</td>
<td>ATA detected for this product attribute and confers limits on safety</td>
</tr>
</tbody>
</table>
## Risk Ranking-Uncertainty

<table>
<thead>
<tr>
<th>Score</th>
<th>Ranking</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Variants and Host-Related Impurities</td>
</tr>
<tr>
<td>1</td>
<td>Very Low</td>
<td>Impact of specific variant established in Clinical Studies with this molecule</td>
</tr>
<tr>
<td>2</td>
<td>Low</td>
<td>Variant has been present in material used in clinical trials</td>
</tr>
<tr>
<td>3</td>
<td>Medium</td>
<td>Nondclinical or in vitro data with this molecule. Data (nondclinical, in vitro or clinical) from a similar class of molecule</td>
</tr>
<tr>
<td>5</td>
<td>High</td>
<td>Published external literature for variant in related molecule</td>
</tr>
<tr>
<td>7</td>
<td>Very High</td>
<td>No information (new variant)</td>
</tr>
</tbody>
</table>
## Risk Ranking Matrix

<table>
<thead>
<tr>
<th>Uncertainty</th>
<th>Impact 2</th>
<th>Impact 4</th>
<th>Impact 12</th>
<th>Impact 16</th>
<th>Impact 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>14</td>
<td>28</td>
<td>84</td>
<td>112</td>
<td>140</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>20</td>
<td>60</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>12</td>
<td>36</td>
<td>48</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>6</td>
<td>24</td>
<td>32</td>
<td>40</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>12</td>
<td>16</td>
<td>20</td>
</tr>
</tbody>
</table>

**CQA Limit = 12**

Red = CQA, Green = Not CQA
Process Control Strategy (PCS)

“A control strategy is designed to ensure that a product of required quality will be produced consistently…These controls should be based on product, formulation and process understanding and should include, at a minimum, control of the critical process parameters and material attributes”. (ICH Q8)

- A process control strategy is dynamic and evolving with the product development lifecycle and based on various elements including but not limited to, the following:
  - Environmental controls
  - In-process controls
  - Process and analytical capability
  - Raw material controls
  - Drug substance and drug product specifications
  - Demonstrated product stability
  - Process monitoring controls
  - Product comparability studies
  - Process validation
Process Control Strategy (PCS)

- Implementation of a PCS in early development
  - A PCS team is established for a new investigational product
  - An initial PCS is developed at **Stage 3** of the product development lifecycle from various sources of knowledge, including:
    - Quality Target Product Profile/pCQAs
    - Pre-clinical research information
    - Relevant literature references
    - Prior clinical knowledge
    - Process investigation data (derived from Stage 2)
    - Any available specification information from toxicology batches or clinical batches
Process Control Strategy (PCS)

- iPCS at a minimum will include
  - pCQA’s and pCPPs
  - A description of the preliminary process flow with a defined purpose for each unit operation
  - Preliminary process control elements
  - Raw materials and process intermediates w/specifications
  - Intermediate specifications and/or in-process controls
  - Proposed drug substance and drug product specifications

- The PCS will be further refined throughout Stage 4 of the drug development lifecycle and beyond
QbD: Hierarchy of Parameters

- QTPP
- Specifications
- Intermediate Specifications
- In-Process Controls
- Critical Process Parameters
- Key and non-key Process Parameters, Process/Consistency Indicators
- Process Control Strategy
- More CQAs
- Less Regulatory/Quality Importance and/or Compliance Significance
Process Parameters (cPP, kPP, nkPP)

“CRITICAL PROCESS PARAMETER (CPP): A process parameter whose variability has an impact on a Critical Quality Attribute and therefore should be monitored or controlled to ensure the process produces the desired Quality”. (ICH Q8)

“KEY PROCESS PARAMETER (KPP): A Process Control Element whose variability has an impact on process attributes, such as yield, cycle time, etc., where these attributes are associated with a robust and reproducible process, and are not associated with CQAs, specifications, and/or IPCs, and therefore should be monitored and controlled to ensure the aforementioned robustness and reproducibility of the process. A PP should be operated within an acceptable range”.

“NON-KEY PROCESS PARAMETER (NKPP): A parameter that is neither critical nor key that requires data be gathered and operated within acceptable ranges. A nKPP does not impact robustness, reproducibility of the process or CQAs.
Process Parameters

- Developed initially by mapping CQAs to manufacturing process and performing risk assessments
- Determine impact of process parameters to *quality* or *manufacturability* of product
  - Establish critical, key or non-key classification
- Established and refined throughout the process development lifecycle
# Process Parameter Categorization

<table>
<thead>
<tr>
<th>Parameter Type</th>
<th>Quality</th>
<th>Process</th>
<th>Controllability</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPP</td>
<td>Critical</td>
<td>N/A</td>
<td>Difficult</td>
</tr>
<tr>
<td>kPP</td>
<td>Non-critical</td>
<td>N/A</td>
<td>Easy</td>
</tr>
<tr>
<td>nkPP</td>
<td>Non-critical</td>
<td>Non-critical</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Design Space

DESIGN SPACE: The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of product quality. (ICH Q8)

- The Design Space is established based on process characterization/DOE studies using a qualified scale-down model of the manufacturing process.
- Links multivariate interactions of product attributes to process performance and control parameters.
- Used to evaluate all unit operations with complex interactions/control dynamics and establish demonstrated process performance limits and operating, control and investigated ranges for process.
- Limited use in early process development to date (Stage 3), see Design Space as a critical tool to establish basis for process validation and process improvement (Stage 4).
The Design Space

- The Process Design Space is developed from process characterization
- Establishes “Safe” operating range
Critical success factors for implementing QbD

- Implementing QbD in process development groups who typically practice QbT requires a “paradigm shift”, it will take time to re-skill/re-tool.
- The probability of success of implementation efforts of QbD will be significantly increased if facilitated by QbD SMEs.
- Training of all team members in principles/practices of QbD is critical to achieving adoption/understanding.
- Diverse team membership is essential.
- Complete sponsor, stakeholder and team commitment.
- The philosophy of QbD is well established, practical implementation of the activities may be more challenging.
Acknowledgements

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Nathan Jones

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Ken Karey

QbD
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Bob Mattaliano
Thank you for your attention!