

Common Challenges in the Development of Gene Therapy Products

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- You've finished exploratory trials
- You have some promising clinical data

Are you ready for pivotal trials?

Only if your product is characterized

Overview

- What is product characterization?
- Examples of specific tests.
How to use them to show product consistency
- How having good characterization can aid your product development

Product characterization

- *Potency*
- *Identity*
- *Stability*
- Sequencing
- Other purity / consistency tests:
 - pH, conductivity, osmolality, particulates, host cell DNA or protein
- Assay validation, process validation

Why is product characterization important?

- To demonstrate lot-to-lot consistency
- To show comparability after manufacturing changes
- To generate solid clinical data
- If you don't characterize your product:
 - Difficulty attracting partners & investors
 - Pivotal trials may be placed on hold

Product characterization costs money: how can we afford to do this?

- How can you afford *not* to do this?
 - Better to uncover problems sooner rather than later
 - Transition to pivotal trials and commercialization will be easier
 - A poorly-characterized product may lead to uninterpretable clinical results
 - The expense of product characterization is small when compared to the expense of re-running clinical trials

Specific tests

Potency
Identity
Stability

Potency

- Measures the biological function of the product
- Unique assay for your product
- Qualify assay before phase III trials
- Validate assay before licensure

Potency

- May be *in vitro* or *in vivo* assay
- Ideally a quantitative measure of the bioactivity
- We will also accept a quantitative physical assay along with a qualitative bioassay
- Examples:
 - An oncolytic adenovirus:
 - measure cytopathic effect or viral replication
 - A cytokine-producing vector:
 - ELISA to measure cytokine quantitatively, and
 - cellular proliferation assay for cytokine activity

Identity

- Verification that vial contents match the label
 - Develop identity assay specific for the product
 - Multiple active components in product?
The test methods should identify all of them
 - Distinguish the final product from other products made in the same facility

Stability

- Stability should be tested throughout all phases
 - Results will determine expiration dating, and shipping and storage conditions
- Stability testing should encompass:
 - Concentration
 - Potency
 - Integrity
 - Sterility (limited testing)
 - Stability during:
 - Manufacturing holding steps
 - Shipping / transport
 - Loading into delivery devices

Unique issues with genetically modified cell therapies

- Some cell/gene therapies are tailored for each patient:
 - Dendritic cells
 - T cells
 - Tumor cell vaccines
 - Transduced bone marrow cells
- Identity is particularly important when there are multiple active cell types
- What is an appropriate potency assay?

Unique issues with genetically modified cell therapies

- For individualized products, each single-patient lot must be tested prior to release
- Limitations:
 - Waiting for test results may affect viability, potency
 - Only small amounts of product for testing
- Solutions:
 - Some flexibility in how/when testing is done and availability of results
 - In-process testing
 - Encourage development of rapid test methods

Having good product characterization
can aid your product development

Need for product consistency

- Biological products are very complex
- There are theories about how they work, but often it is not known for sure
- Minor components or contaminants might be important
- Small changes in manufacturing might cause unpredictable changes in:
 - Safety
 - Efficacy
 - Antigenicity
 - Pharmacokinetics / biodistribution
 - Stability

Manufacturing changes can affect consistency

- Manufacturing changes are common and unavoidable:
 - Scale-up
 - Formulation/concentration changes
 - Changes in manufacturing site
 - Manufacturing or processing changes
 - Serum-containing medium → serum-free
 - Cells grown in flasks → cells in bioreactors
 - Purification: ultracentrifugation → chromatography

Early product development is an opportunity to learn

- How do manufacturing process changes affect the product?
- Which types of process changes lead to major product changes?
- When is a product no longer comparable?

Major changes in manufacturing require comparability testing

- Recommend complete characterization of three lots produced with old methods and three with new methods
- Major manufacturing changes *may* require bridging studies:
 - Comparability tests in animals
 - New studies in patients
- Try to avoid major changes while in phase III

Product characterization: how to succeed

- From the start, design your product and manufacturing process with an eye to consistency
- Don't neglect your product - start product characterization early
 - Potency assay development and qualification
 - Identity
 - Stability

Additional sources of information

- <http://www.fda.gov/cber/guidelines.htm>

- Manufacturers assistance:

MATT@CBER.FDA.gov

- For specific product questions:

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