CQAs and Strategies to Accelerate the Development of Gene Therapies

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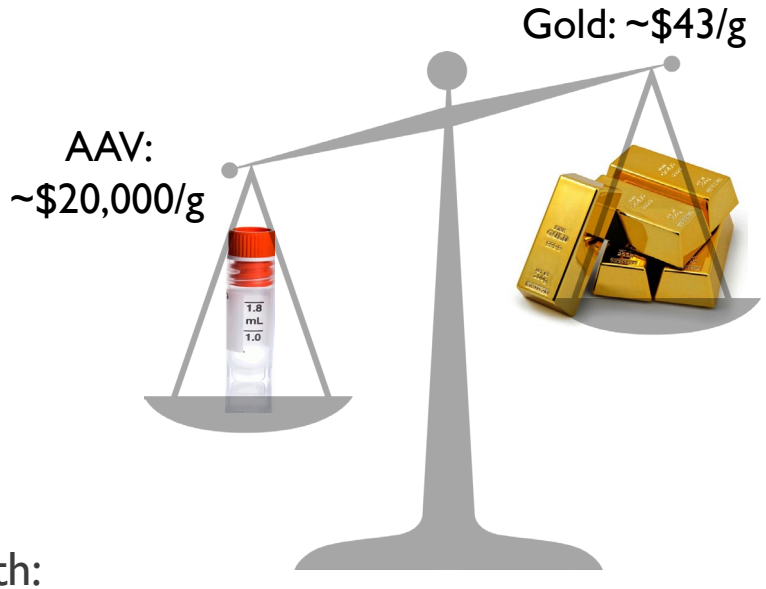
Agenda

- Introduction
- CMC Challenges
- How to Identify CQAs
- Example Quality Attribute Risk Assessment and Rankings
- CMC and regulatory strategies to accelerate development of gene therapies

Introduction

CHALLENGES OF NEW EMERGING TECHNOLOGIES

- AAV gene therapies are relatively new
- Gene therapy development is challenging:
  - Lengthy development timelines
  - Occurs one product at a time
  - Small patient populations (often monogenic, rare diseases)
  - Costly: R&D, preclinical, CMC, IND-enabling and clinical studies
  - Product and process knowledge is limited, CMC activities often on critical path:
    - Fewer literature references or databases, less cumulative expertise/talent pool
    - No (or few) established quality standards or testing/compendial standards
    - No well-established processes and process controls

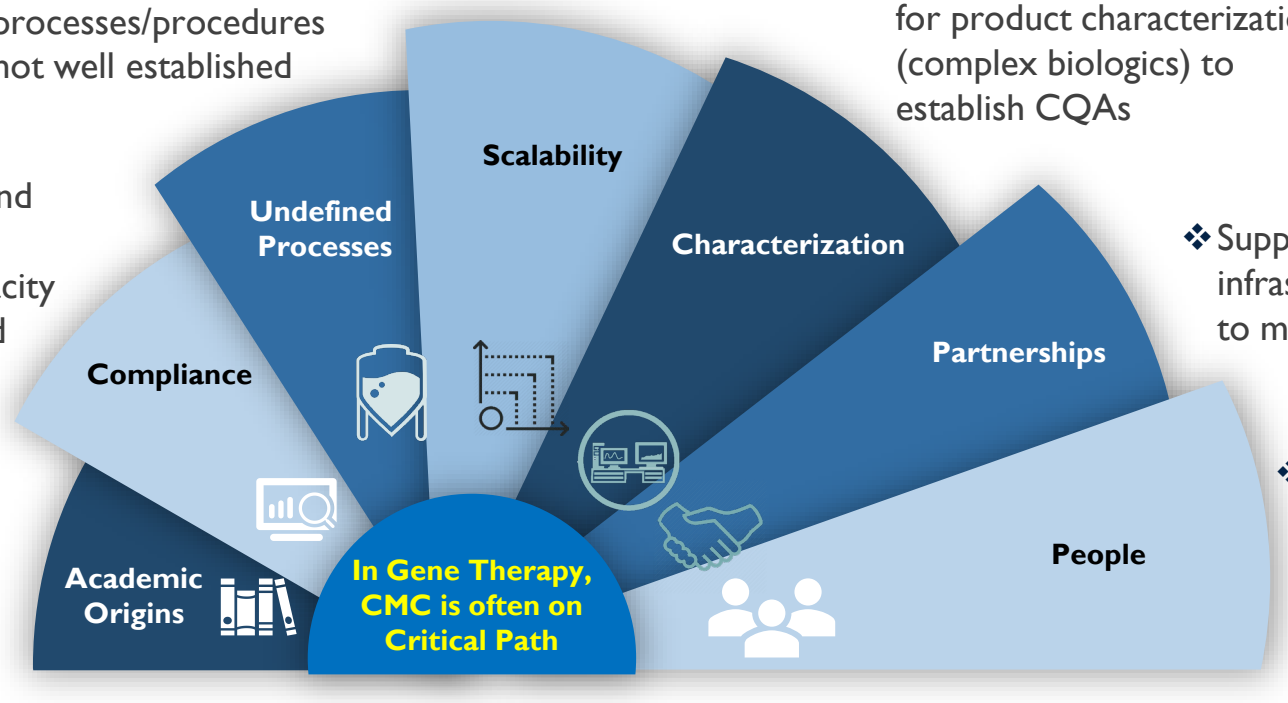


- Need for streamlined development and accelerating time to market
- Gene therapies present a unique opportunity to leverage "platform" approach

CMC Challenges for Gene Therapies

Various challenges on the CMC side can be on critical path

- Manufacturing scale up to meet clinical trials and process/product characterization demand
- Manufacturing and analytical processes/procedures not well established
- Difficult to characterize process to establish CPPs
- Difficult to develop analytics for product characterization (complex biologics) to establish CQAs
- Inadequate manufacturing and critical material production capacity to meet demand
- Supportive industry infrastructure needs to mature
- Generally, academic programs lead discovery and often suffer from GMP compliance issues
- Finding and recruiting talent to build a world class workforce



How to Solve CMC Challenges

QUALITY BY DESIGN – ICH Q8

The process determines the product
Control of the process = control of CQAs

- Product Profile
- CQAs
- Risk Assessment
- Design Space
- Control Strategy
- Continual Improvement

- Quality Target Product Profile (QTPP)
- Determine "potential" critical quality attributes (CQAs)
- Link raw materials attributes and process parameters to CQAs and perform risk assessment
- Develop a design space (optional)
- Design and implement a control strategy
- Manage product lifecycle, including continual improvement

Approaches to Identify CQAs

- Start with QTPP:
  - Consider all drug product attributes
  - Conduct a risk assessment (refer to ICH Q9):
    - Identify based on the severity of harm to a subject (both safety and efficacy) that could result from the failure to meet that quality attribute
- CQAs are further refined with experiments (DOE), process experience and clinical data
- Discuss approach with regulatory agencies prior to pivotal studies
  - Preliminary CQAs should be defined early in Phase 1 stage of clinical development, and refined by late-stage development to facilitate development of the design space
  - Adequate process controls should be established prior to pivotal studies
- Can be challenging in the case of accelerated development

Quality Attribute Rankings

Summary of Severity Risk Rankings

Level	Description	
1	Low	Variability in attribute has minor or negligible potential for decreased safety/efficacy. Negligible or minor transient adverse effects are expected based on historical experience
3	Medium	Variability in attribute may have moderate potential for decreased safety or efficacy within the clinical history of the product. Attribute may result in manageable adverse effect seen historically but no new adverse effects
10	High	Variability in attribute may have potential for severe effect on patient. Potential significant change in safety/efficacy or risk/benefit profiles. May result in a serious (reversible or irreversible) adverse effect.

X

Summary of Uncertainty Rankings

Level	Description	
1	Low	Well characterized effect based on extensive data (in vitro, in vivo, or clinical). Large body of knowledge in the literature
2	Medium	External published literature available. Well characterized effect known. Internal data (in vitro, in vivo, or clinical) from this or similar class products.
3	High	Limited or no published external scientific literature and no internal data from this or similar class products.

A-Gene - Alliance for Regenerative Medicine: https://alliancerm.org/manufacturing/a-gene-2021

Final Criticality Rankings

	Uncertainty 3 (High)	Uncertainty 2 (Medium)	Uncertainty 1 (low)
Severity 10 (High)	30 (CQA)	20 (CQA)	10 (CQA)
Severity 3 (Medium)	9 (KQA)	6 (KQA)	3 (KQA)
Severity 1 (Low)	3 (KQA)	2 (QA)	1 (QA)

Drug Product Quality Attributes

- Example of assessment of DP quality attributes and their criticality
- This assessment is refined as additional clinical and manufacturing data becomes available

Attribute	Severity score	Uncertainty score	Attribute Criticality	Comments
Appearance	10	3	30 CQA	Could be indicative of other quality issues
pH	1	1	1 QA	Well-controlled, within defined limits and no impact on biological activity or stability
Subvisible Particles	3	3	9 KQA	Potential immunogenicity of particles, but mitigated by filter needle prior to injection. Minor risk of titer decrease if particles form from drug product and are removed on filter
Genomic Titer	10	3	30 CQA	Potential for delivering sub-optimal dose or overdose (safety impact)

Strategies to Accelerate Product Development

4DMT Platform Approaches

- 4DMT uses platform approaches at all development stages:
  - Vector and promoter optimization
  - Formulation development
  - Manufacturing and analytical testing
  - Nonclinical development
  - Clinical development

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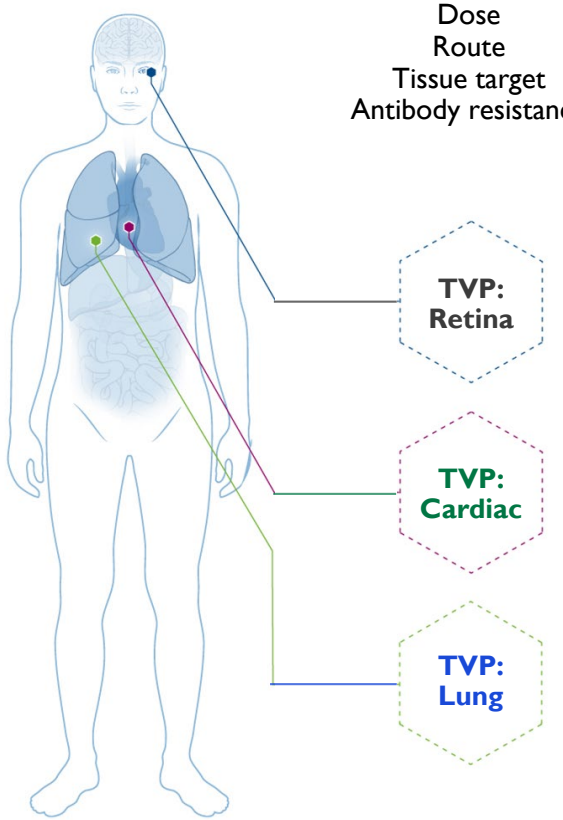
Platform Solution: Therapeutic Vector Evolution

COMPETITIVE SELECTION FOR TARGET VECTOR PROFILE FITNESS

IDENTIFY DISEASE TARGET(S)

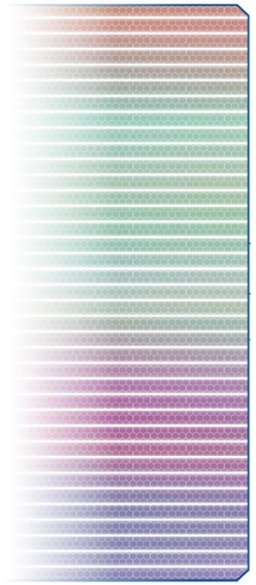
DESIGN ORGAN-SPECIFIC TARGET VECTOR PROFILE

Dose
Route
Tissue target
Antibody resistance



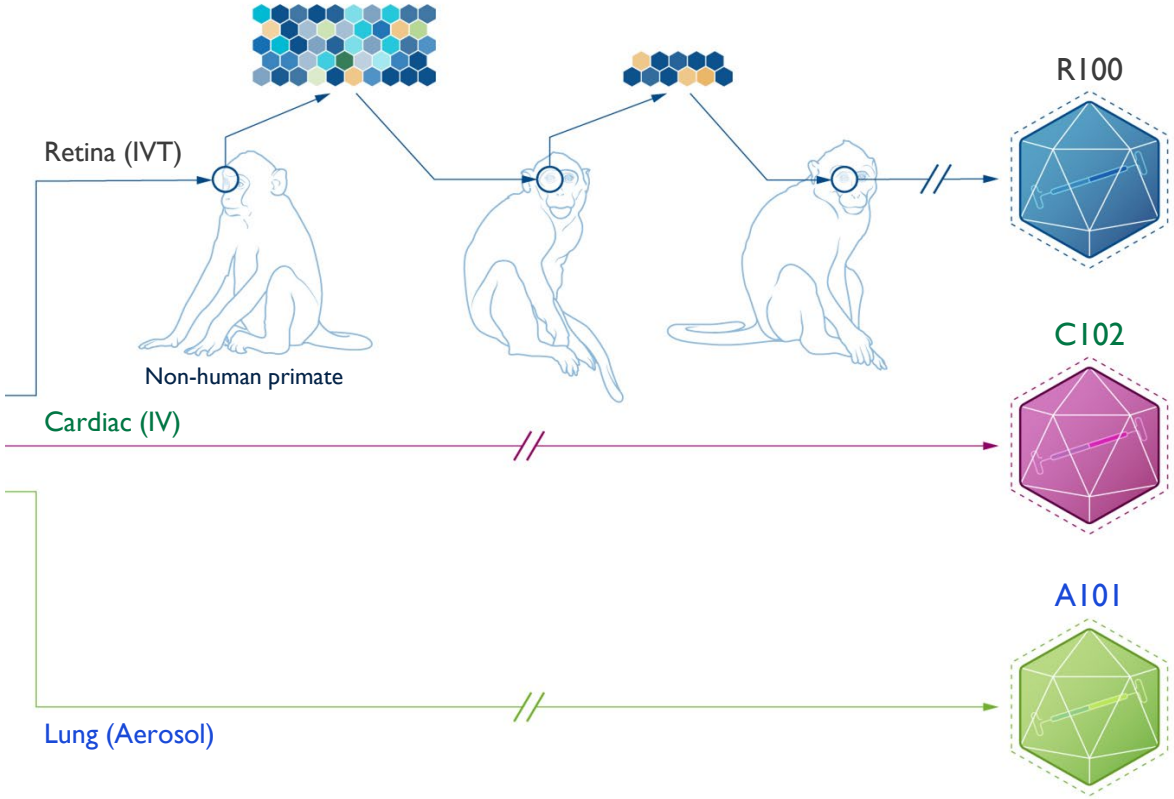
PACKAGE 4DMT AAV LIBRARIES

From **~1 BILLION** synthetic AAV capsid sequences in 40 distinct libraries



ADMINISTER 4DMT AAV LIBRARIES

COMPETITIVE SELECTION* TARGET VECTOR PROFILE FITNESS



LEAD VECTORS

*Capsid library placed under varying selective pressures. // Actual number of selection rounds varies by target.

Vector Modularity

BROAD APPLICATION ACROSS MULTIPLE RETINAL DISEASES

R100

Candidate	Transgene	Promotor	Target Indication
4D-150	Aflibercept VEGF-C miRNA	Ubiquitous	Wet AMD, DME
4D-110	*CHM*	Ubiquitous	Choroideremia
4D-125	*RPGR*	Photoreceptor-specific	X-linked retinitis pigmentosa
4D-175	*sCFH*	Ubiquitous	Geographic atrophy

- Therapeutic vector profile supports modular design of retinal gene therapy candidates

Pipeline

VECTOR/ DELIVERY	PRODUCT CANDIDATE	INDICATION	RESEARCH CANDIDATE	IND-ENABLING	PHASE 1/2	PHASE 3	PRODUCT RIGHTS
OPHTHALMOLOGY R100 Intravitreal	4D-150	Wet AMD					4DMT
		DME					
	4D-125	XLRP					4DMT
	4D-110	Choroideremia					4DMT
	4D-175	Geographic Atrophy					4DMT
	Undisclosed *Vector licensed to Astellas*	Undisclosed Rare Disease					astellas
PULMONOLOGY A101 Aerosol	4D-710	CF Lung Disease (monotherapy)					4DMT
		CF Lung Disease (combo w/ mods)					
	4D-725	A1ATD Lung Disease					4DMT
CARDIOLOGY C102 IV	4D-310	Fabry Disease Cardiomyopathy					4DMT
CNS B Series Multiple	Unnamed *Led by Arbor*	Amyotrophic Lateral Sclerosis					arbor biotech 50/50 WW

Strategies to Accelerate Development

Process Control Strategies

- Leverage process knowledge from other products in the same family:
  - Leverage raw materials criticality assessments and controls
  - Leverage hold time data: products with similar formulation and capsid are likely to display similar stability, particularly in early-stage development
  - Implement similar process controls and in-process testing:
    - CPPs identified for one product/process often applicable to other products/processes
    - Early stage in-process testing can focus on safety assays with wide acceptance criteria (ie "report results")
    - Later-stage in-process testing should narrow-in on process performance, with tighter acceptance criteria established based on manufacturing experience and identification of CQAs and CPPs.

Strategies to Accelerate Development

CMC Strategies

- Leverage stability data:
  - If formulated in same buffer, can leverage previous stability and forced degradation studies
    - Capsid stability will generally stay consistent for products that use the same capsid
    - Transgene or payload evaluation may be needed to confirm stability
  - Establish a shelf life based on another product, to be confirmed with real-time data (or extrapolation, where allowed per ICH Q1A)
  - Enables improved supply chain and logistics, and reduces product waste
- Leverage drug-CCS and drug-device compatibility data:
  - Regulatory agencies often concerned with product adsorption onto container closure system and compatibility with drug administration devices
  - Regulatory agencies also concerned about CO_2 ingress and absorption onto glass walls of the CCS during shipments on dry ice.
  - Leveraging data from another product using the same CCS, capsid and formulation to avoid duplicating studies

Strategies to Accelerate Development

CMC Strategies

- Leverage pre-IND feedback from other programs
- Leverage manufacturing experience from one product to another
  - For products that use the same capsid, likely no/minimal change needed in manufacturing process
  - Process development, optimization and scale-up can be leveraged for multiple products
- Leverage analytical assays from one product to another:
  - Almost all assays can use a platform approach (ie. no customization required)
  - For genomic titer: can use same ddPCR primers if using ITR (or common promoter/terminator) region
    - Validation of genomic titer assay can be leveraged if using identical primers for different products that use the same capsid
    - Also allows consistency of dosing across different programs
  - Exception to platforming: potency assay for late phase

Strategies to Accelerate Development

CMC Strategies

- Potency assay:
  - Measure of biological activity based on the mechanism of action of the product
  - Stage-based development: qualitative or semi-quantitative for early-stage clinical studies (Phase 1)
  - Transgene (protein) expression only for early-stage clinical studies:
    - This can be platform for a single capsid, and used as a starting point (ie, cell line, MOIs, and RT-ddPCR detection based on ddPCR primers) for multiple assets using different capsids
  - Infectivity, expression and biological activity usually required for late-stage development (Phase 3)
  - Validated and quantitative assays generally required prior to pivotal studies

Regulatory Strategies to Accelerate Development

Regulatory Submission Strategies

- Explore creative strategies!
- Pre-IND interaction with FDA is a great opportunity to explore novel approaches
- Evaluate accelerated pathways (RMAT, PRIME, etc.)
- Cross-reference to similar products in previously submitted INDs / MFs
- Peter Marks comments[1]:

"There are certain pieces of gene therapies that are not like your typical small molecule drug because they're reused repeatedly. Provided you don't either under- or over-stuff [AAVs], you can probably get a similar result when putting a similar type of insert that produces a similar type of either secreted or membrane protein. If we could get this paradigm to work, rather than having a manufacturer go back and do all of the preclinical toxicology and give us all the manufacturing information each time they submit something, they would just cross reference. That would allow us to focus on innovation that's going to bring benefit to people."

[1] https://www.genengnews.com/gen-edge/peter-marks-outlines-fdas-commitment-to-advancing-gene-therapies/

Thank You

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