Gene Therapy for Rare Diseases

Gene Therapy Clinical Development Considerations

Food and Drug Law Institute

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Regulation of Gene Therapy

- Traditionally, the domain of academic medicine
- Recent increase in interest by large pharmaceutical companies and academic spinoffs
- To get this right from the beginning:
  - get buy-in from rare disease patient network
  - obtain early advice from different regulatory authorities
  - plan for global trials for a reasonable enrollment rate
  - collaborate

Gene Therapy - Challenges

- Manufacturing and delivery of the product
- One dose can have prolonged or permanent effect
  - subject with rare disease cannot try multiple products and/or can try only few different doses
- Immunogenicity to vector (e.g., AAV capsid), transgene or the protein expressed can also be prolonged or permanent.

Gene Therapy- Challenges (Continued)

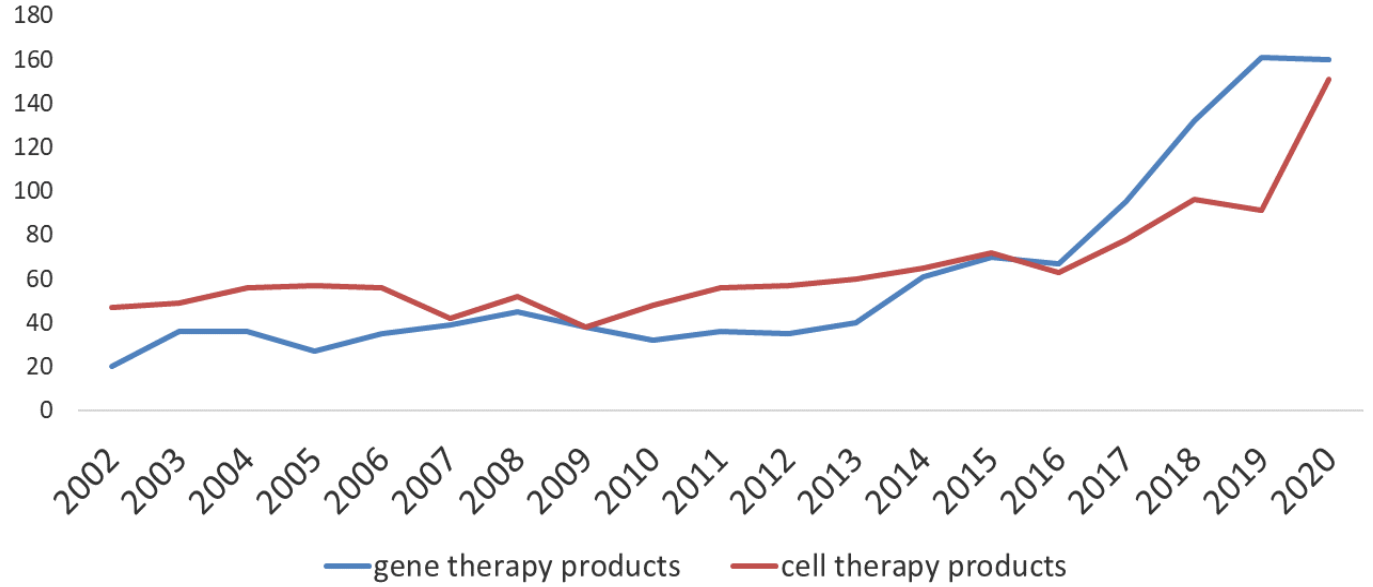
- Tweaking the product is very common during development
  - comparability issues
- Dose exploration is limited by cost and manufacturing capability
- Often delivery through invasive methods
  - intra-cerebral
  - intracardiac

Gene Therapy- Development Considerations

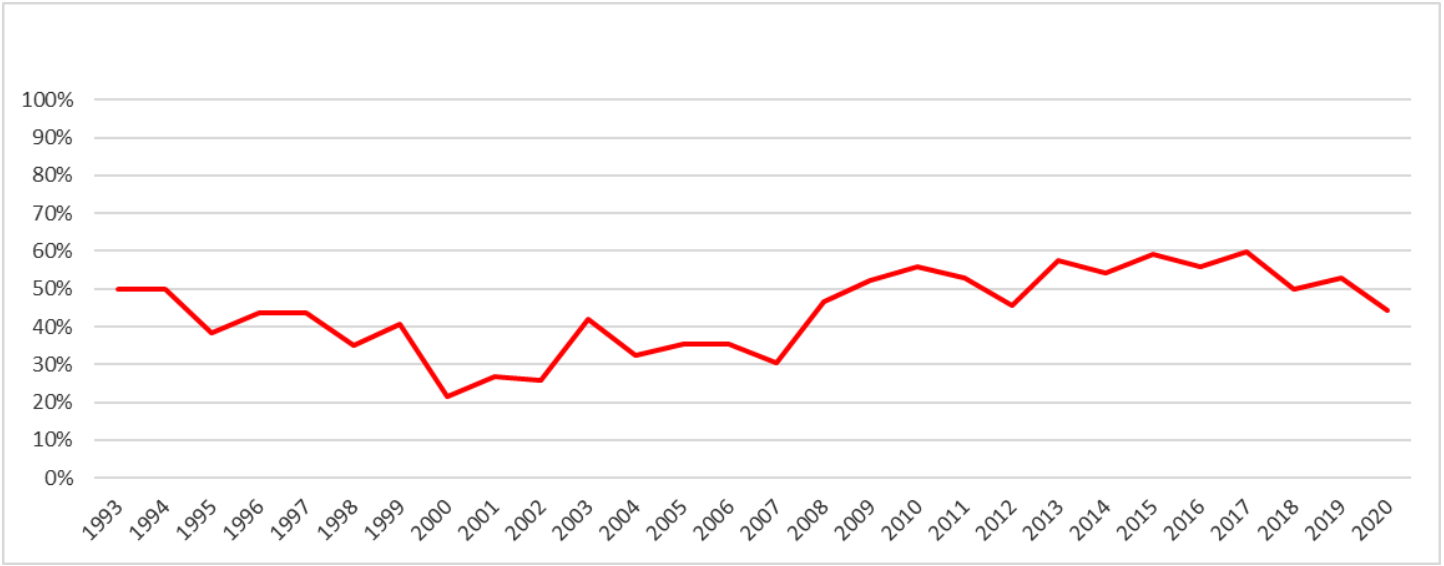
- Traditional phases (e.g., Phase 1, 2, 3) are commonly blended into early phases versus late phases (more like learning and confirming)
- Prolonged or permanent effect: a subject in early phase can be followed for years and contribute good long-term efficacy and safety data
- Compared to small molecular drugs or therapeutic proteins, more critical to have early randomized controlled trials, even in first-in-human trials

CBER's Regulatory Toolbox for Rare Diseases

Cell and Gene Therapies: Research INDs 2002 – 2020



Research INDs for Rare Diseases (percent per year)



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FDA Headquarters

- **OTAT Learn Webinar Series:**

  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

- **CBER website:** www.fda.gov/BiologicsBloodVaccines/default.htm
- **Phone:** 1-800-835-4709 or 240-402-8010
- **Consumer Affairs Branch**: ocod@fda.hhs.gov
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Thank you

Facilitating End-to-End Development of Individualized (Bespoke) Gene Therapies

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Food and Drug Law Institute (FDLI)
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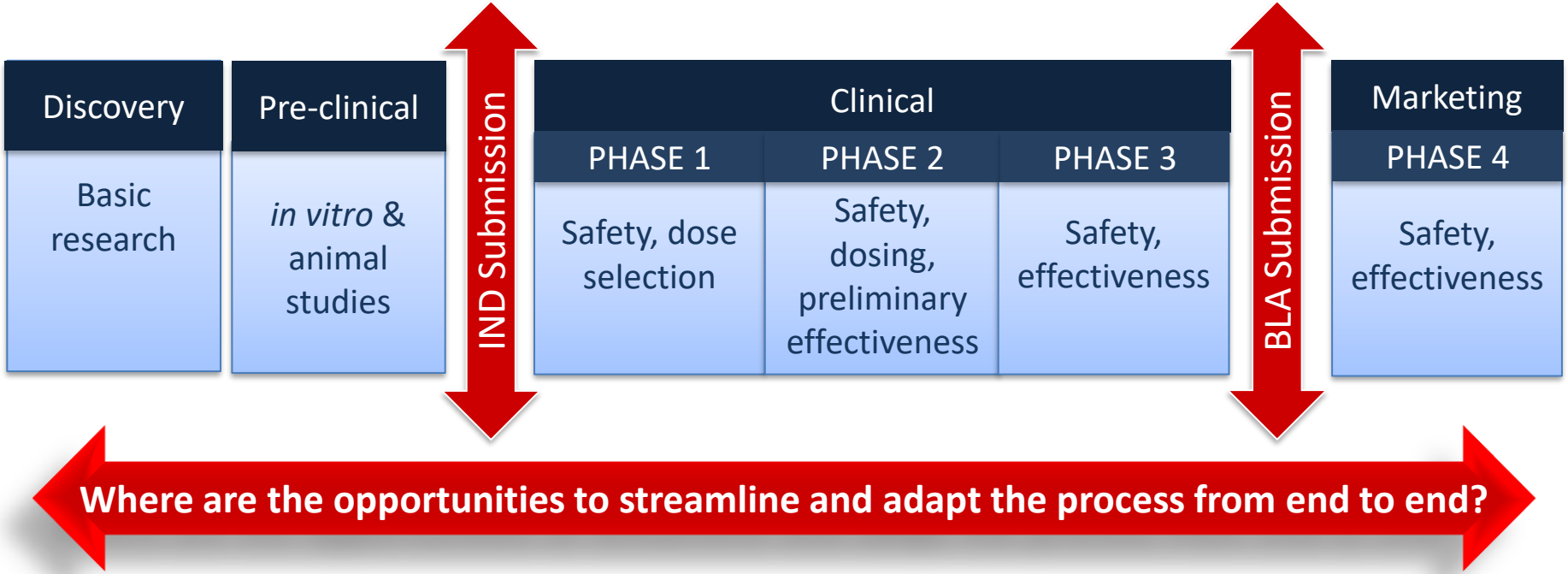
Facilitate Development of Individualized Therapeutics



Challenges of Individualized Gene Therapies

Current manufacturing constraints present a “Goldilocks” phenomenon -- viable commercial solutions are not available for very small or large populations but do exist for mid-size indications.

Individualized Therapies: Challenges and Potential Solutions

- NIH, FDA, other stakeholders investigated major challenges to manufacturing and access to gene therapies and explored potential opportunities
  - Facilitate through a precompetitive public-private partnership?
    - ✓ Bespoke Gene Therapy Consortium (BGTC)
  - Regulatory streamlining to support product development and licensure?
  - Other innovations?

Accelerating Medicines Partnership: Bespoke Gene Therapy Consortium

Collaboration between

FNIH, NIH/NCATS & FDA/CBER

AMP-BGTC: Partnerships

Strategic and Programmatic leadership:

- Foundation for the National Institutes of Health (FNIH)
- National Center for Advancing Translational Sciences (NIH/NCATS)
- Center for Biologics Evaluation and Research (FDA/CBER)

Other significant partners:

- Multiple NIH Institutes
- Industry organizations
- Academic investigators
- Patient advocacy groups

Funding for AMP-BGTC:

- National Institutes of Health
- Industry partners

BGTC “Proof of Principle” Pilot Program

- Strategic objective: Use **common set of procedures** in a pre-competitive environment to **drive innovation** and **promote access** to individualized therapies
- Pilot focuses on clinical trials for **disorders that have such low prevalence** (~ 1 – 100 patients in the U.S.) **that there is no commercial interest** currently in product development
- Anticipate program will have broader impact as the **technologies, paradigms, and information gained can be applied** to rare & common disorders with higher prevalence

Bespoke Gene Therapy Consortium (Non-profit umbrella organization)

Gene therapy target for rare disease

Vector Generation

Standard vector menu:
- Suite of vectors
- Instructions for use
- Tropism
- Non-proprietary tools

Manufacture of therapeutic

Standard process menu:
- Known safety database
- Leverage manufacturing expertise & experience
- Facilitate preclinical testing

Clinical treatment of patients

Standard delivery menu:
- Known safety for non-proprietary vectors
- Standard clinical protocols (templates)
- Standard delivery protocols

Therapies for patients

FDA to streamline regulatory requirements to facilitate product development
e.g., Establish Master File(s) for standard vector(s); leverage data, where appropriate

All results from treatments are reported back to the consortium for iterative learning

BGTC – Mfg/Analytics Process

Vector Producer A1

Vector Producer A2

Vector Producer I1

Vector Producer I2

CoA

Supplemental testing component

Toxicology testing component

Pre - Clinical core

NIH CoA

Clinical Coordination Core

IRB

Regulatory Core

IND

Clinical sites

outcomes SAEs

Data Management and Analysis Core

BGTC Coordination Center

A= academic, I= industry

= clinical AAV vector

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Summary of BGTC Pilot Program Design (early stages; work-in-progress)

- Leverage existing manufacturing capacity & experience
- Standardize testing where possible (e.g., vector quantification)
- Roles and responsibilities
  - Commercial manufacturing partners will produce gene therapy product (in-kind) for clinical trials
  - NIH will be the IND holder; coordinate & manage the clinical trials
- Studies will be run sequentially so learnings and new information, including from AAV biology research, can be incorporated; enhance and refine the process

BGTC Pilot: Role of FDA

- Early engagement with FDA for feedback on specific issues e.g., testing requirements for AAV-based gene therapy products
  - Focus on principles so feedback is generally applicable (not product-specific)
- Establish Master Files
- Explore streamlining regulatory requirements – examples:
  - Leveraging pre-clinical and CMC data based on past experience with vector or similar gene therapy product, if scientifically justified, to reduce testing of future iterations of a similar product
  - Innovative clinical trial design for bespoke products
- Full spectrum of formal FDA meetings to support product development
  - e.g., CATT, INTERACT, pre-IND etc.

Regulatory Streamlining to Facilitate Development of Bespoke Gene Therapies

Important Considerations for Individualized Therapeutics

- Determining the quantity of supportive preclinical evidence needed prior to patient treatment
- Understanding the relevant disease-specific clinical information that should be captured when patients are treated
- Manufacturing quality product that is fit-for-purpose
- Finding sustainable ways to deliver individualized therapeutics to patients if the products show clinical benefit

Potential for Regulatory Streamlining

- Master Files
- Leveraging data (based on past experience with vector or similar gene therapy product)
- Pathway to licensure?

Master Files

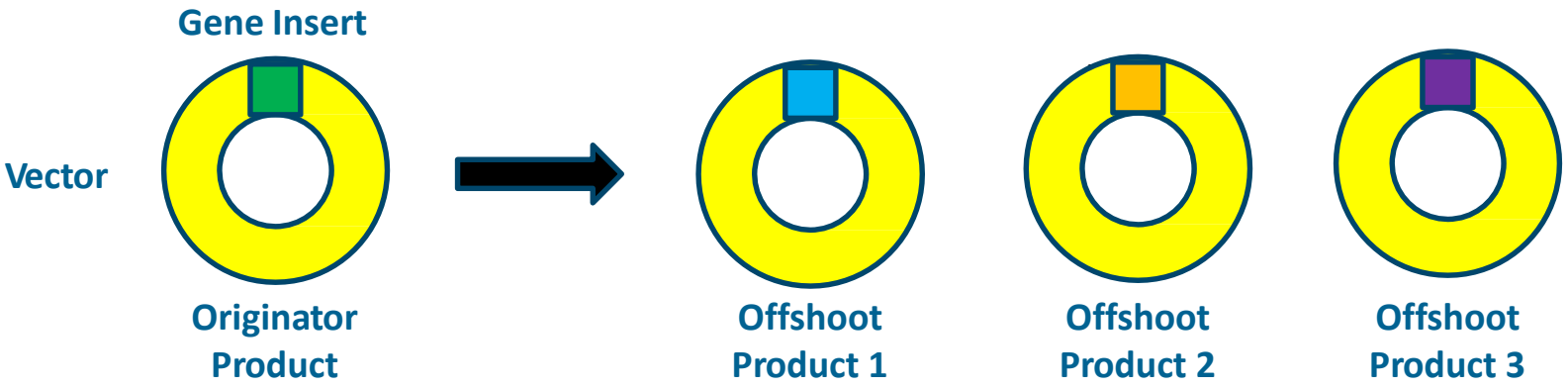
BGTC could be a repository for suite of standard AAV vectors for investigators interested in developing gene therapy products

- Conduct full breadth of characterization and testing on the standard AAV vectors
- Submit CMC data to FDA in a Master File
- Investigators developing individualized gene therapies using standard vectors can cross reference the relevant Master File
- May allow streamlining of testing for the product

Treating Diseases with Current Gene Therapy Technology

- Many gene therapies for rare disorders are produced as “one-offs” in academic laboratories or small corporate entities
- Current regulatory process does not leverage information to expedite the production of potentially transformative treatments
- A **regulatory program that allows leveraging non-clinical and manufacturing data from one application for another** can facilitate product development and promote access
  - **Concept of originator product and offshoot products**

Advancing the Development of Bespoke Therapies will Benefit the Larger Gene Therapy Ecosystem



Collaborative effort by FDA with relevant stakeholders, including industry partners, to **develop the regulatory framework to leverage existing knowledge** to advance development of bespoke gene therapies

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Thank You!