Regulatory Landscape in the US

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Gene Therapy

Advantages

- Generally administration of only one dose is required
- High possibility of success based on design
- Many different diseases can be addressed
- Long-term disease benefit or even cure possible

Disadvantages

- Complexity and cost of manufacture
- Potential for irreversible side effects
- Special expertise required for administration
- Presents challenges of a new business model

U.S. Approved Gene Therapies

- Kymriah (2017)
- Yescarta (2017)
- Luxturna (2017)
- Zolgensma (2019)
- Tecartus (2020)
- Breyanzi (2021)
- Abecma (2021)
- Carvykti (2022)
- Zynteglo (2022)
- Skysona (2022)
- Hemgenix (2022)
- Adstiladrin (2022)

Product Development Ecosystem

- FDA is responsible for ensuring that human medical products are safe and that they meet a legal standard for efficacy
  - Involved in the process of product development from concept through clinical investigation in humans to post-market surveillance

https://www.fda.gov/patients/learn-about-drug-and-device-approvals/drug-development-process

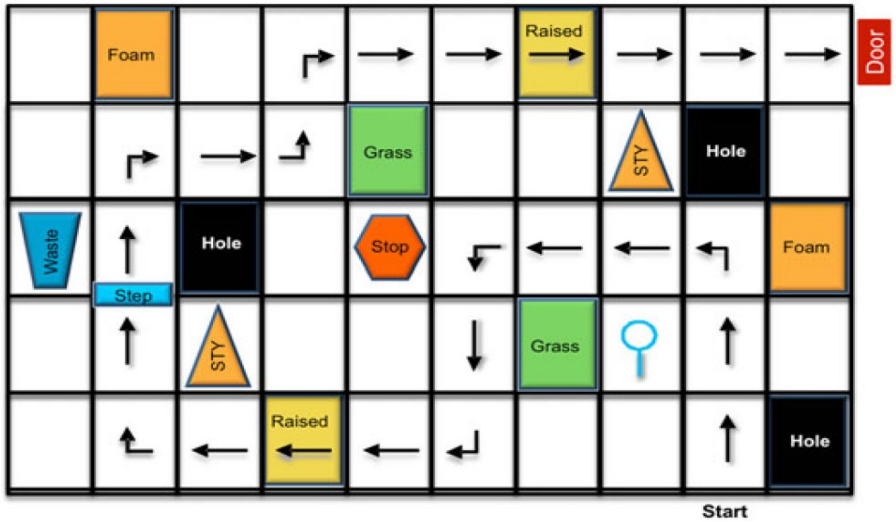
Expedited Development Programs

- Fast Track
- Priority Review
- Accelerated Approval
- Breakthrough Therapy
- Regenerative Medicine Advanced Therapy

These programs may be applicable to drugs or biologics intended to treat serious conditions

Multi-Luminance Mobility Test

Negotiating a path with obstacles at different light levels



Scoring based on time and accuracy

Illuminance (lux)	Luminance (cd/m^2)	Corresponding environment
1	0.32 mesopic vision	Moonless summer night; or indoor nightlight
4	1.3 mesopic vision	Cloudless summer night with half moon; or outdoor parking lot at night
10	3.2 mesopic vision	60 min after sunset in a city setting; or a bus stop at night
50	15.9 photopic vision	Outdoor train station at night; or inside of illuminated office building stairwell
125†	39.8 photopic vision	30 min before cloudless sunrise; or interior of shopping mall, train or bus at night
250‡	79.6 photopic vision	Interior of elevator, library or office hallway
400	127.3 photopic vision	Office environment; or food court

Chung DC et al., Clin Exp Ophthalmol, 20182018; 46:247–259

Potential Rare Disease Therapeutics

- Small molecules
- Protein therapeutics
- Antisense oligonucleotides
- Gene therapy

Importance of Therapies for Rare Disorders

- Gene therapy has the potential to address rare disorders affecting from one to thousands of individuals around the globe
- The ability to address defects though gene therapy may also reduce some more common diseases to very rare diseases

Current Challenges

- Gene therapy is at a critical juncture at this time due to a combination of factors
  - Manufacturing challenges
  - Clinical development timelines
  - Different global regulatory requirements

Gene Therapy Commercial Viability in 2023

Little progress in commercial viability over the past 5 years

Approximate Treatment Population Per Year	1-100	>100-10,000	>10,000

Possible Future of Manufacturing

The optimal small batch gene therapy manufacturing platform of the future may be a device

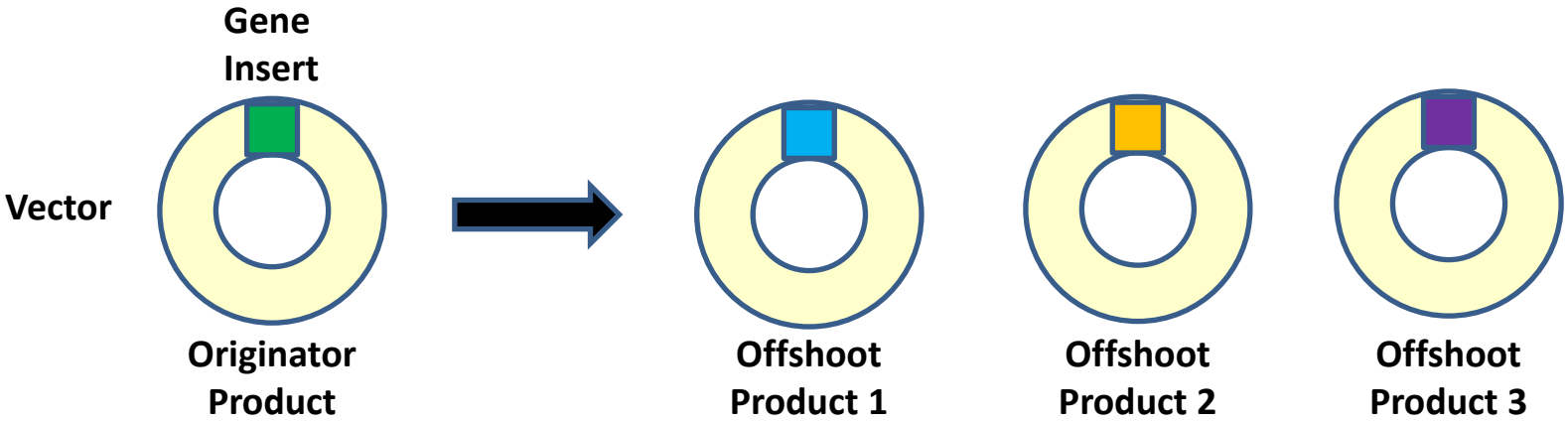
Actions at Center for Biologics

- Advancing manufacturing technologies for cell and gene therapy through research
- Work to more clearly define the use of accelerated approval for gene therapy
- Exploring concurrent submission and product review with other regulatory authorities
- Operation Warp Speed for Rare Diseases communication pilot

Concepts in Development

- "Cookbook" for the development and manufacturing of bespoke therapeutics
- Leveraging of nonclinical and manufacturing data from one application to another
  - Concept of originator and offshoot products leveraging information on file and focusing on distinguishing attributes of offshoot products

Bespoke Therapies



Premise

- In appropriate situations, non-clinical data and manufacturing information from one product may be able to be leveraged to another

Leveraging Accelerated Approval

- The science inherent in the development of many gene therapies potentially facilitates the use of biomarkers as endpoints that are *reasonably likely* to predict clinical outcomes
  - Enzyme activity levels, structural protein levels can be measured and correlated with clinical endpoints in model systems or even in humans

Global Regulatory Convergence: High Income Countries

- Robust commercial viability currently requires ≈100 to 200 gene therapy treatments per year
- Any one country may not have enough patients to make many products commercially viable
- However, marketing across high income countries could result in commercial viability

Global Cooperation

- Produce document on potential regulatory framework for cell and gene therapies for low- and middle-income countries (ongoing at WHO)
- Convergence of regulatory approach in high income countries (? harmonization in the future)
- Discussion of concurrent collaborative review process for gene therapy (Project ORBIS model)

Communications Pilot

(Operation Warp Speed for Rare Diseases)

- Background: experience with COVID-19 product development indicated the potential benefits of frequent communication
- Purpose: further accelerate the pace of development of therapeutics for small populations with high medical need
- Products eligible: products for life-threating rare genetic diseases showing promising efficacy early in development
- Procedures: initial meeting followed by ongoing informal interactions via email or live meetings on an as needed basis

Gene Therapy Development

- FDA is committed to advancing the timely development and availability of gene therapy
  - Helping to individualize product development
  - Defining development and approval pathways
  - Advancing manufacturing technologies
  - Working toward global regulatory convergence

Summary

- Though the smallest of the human medical product centers at FDA, CBER oversees the development and approval of a remarkable group of cutting edge products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