Arbor Biotechnologies Challenges in Developing Gene Editing Medicines

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Arbor Biotechnologies Agenda

Challenges in Gene Editing Drug Development

1. Gene editing drug development from industry perspective
2. Preclinical assessment of benefit/risk using imperfect models
3. CMC investment to meet EU requirements for early clinical
4. Rare and ultra rare indications require global reach- European regulatory vs. ROW
5. Recommendations to make regulatory process more efficient

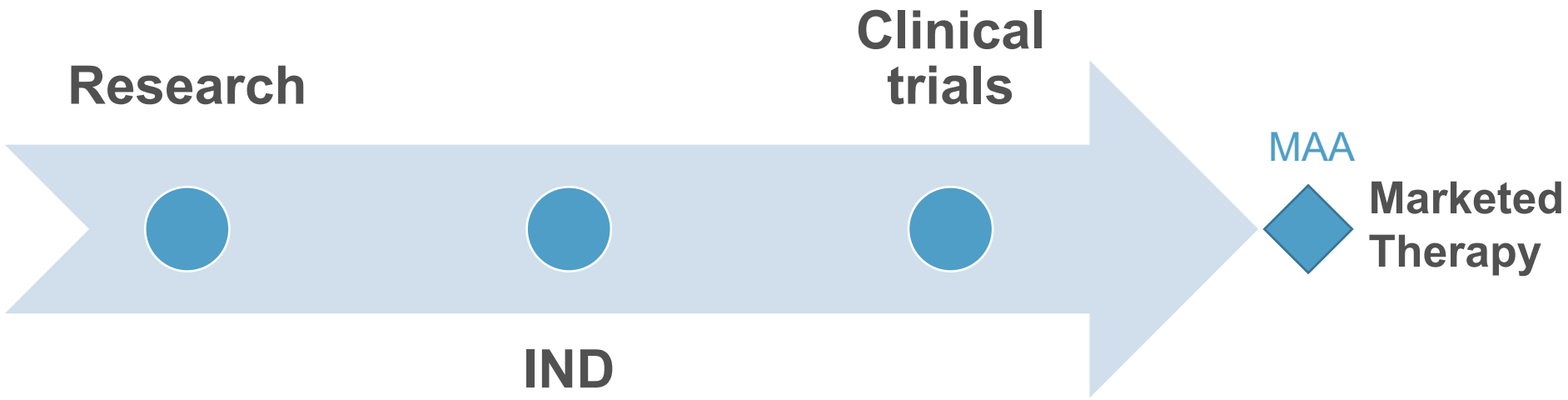
Wholly Owned Programs Enable Therapeutic Application of Arbor's Gene Editing Technologies

Target Organ	Program	Indication (Target)	Technology	Delivery Method	Discovery	Lead Optimization	IND-Enabling	Phase 1/2	Phase 3
Liver	ABO-101	PH1 (HAO1)	Knockdown+	LNP					
	ABO-103	undisclosed	RT Editing	LNP					
CNS	ABO-202	ALS (STMN2)	Nuclease Excision	AAV					
	ABO-203	ALS (undisclosed)	Nuclease Excision	AAV					
	ABO-204	ALS (SOD-1)	Knockdown+	AAV					

Traditional Therapeutics vs. Gene Editing Therapeutic Development

Discovery Stage
Lead Optimization Stage
Fast through discovery due to limited # tiled guides

Phase 1, 2a, 2b, 3
Go directly into patients at a minimally predicted therapeutic dose, ultra rare disease can register on small number of patients in pivotal trial with 2 yr safety, monitor patients for 15 yr



GLP toxicology studies
Biodistribution
CMC- drug production
Clinical trial design

Tox possible to perform in one species
Genotox- off-target editing risk major topic
On-target editing in the unintended tissue risks
CMC close to final product configuration

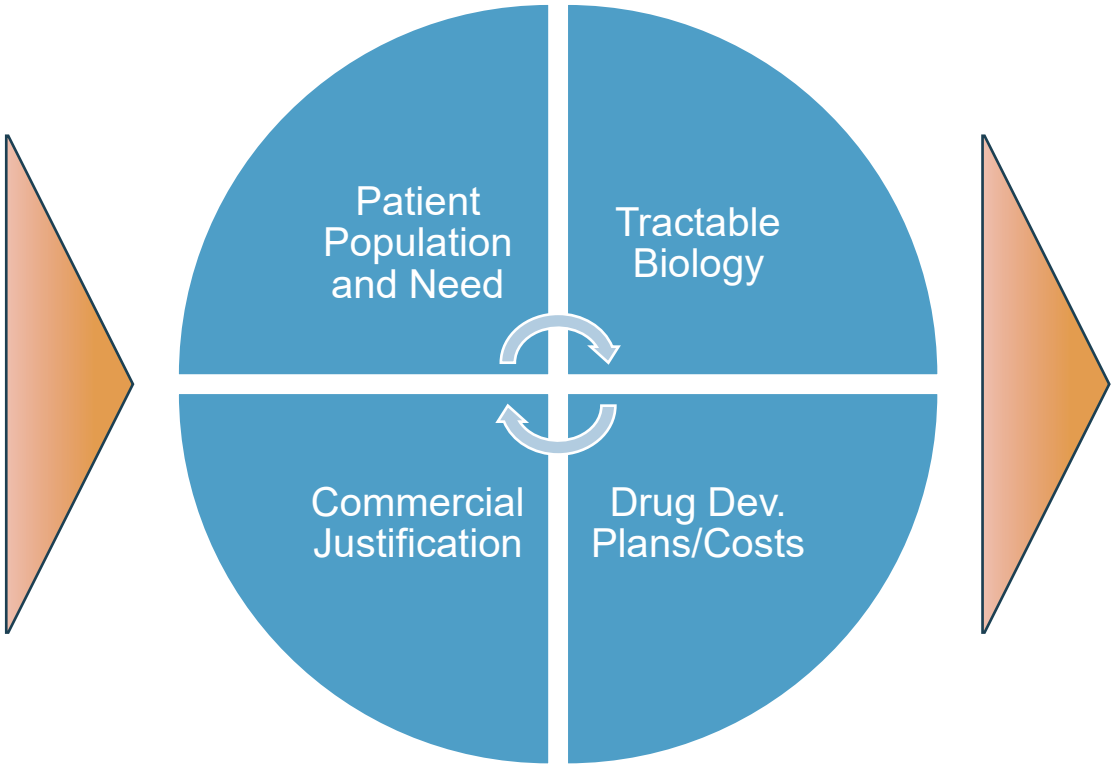
Drug Development in Gene Editing from an Industry Perspective

Investor funding

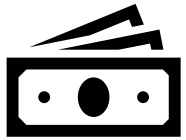
Private companies need to convince investors that their money is spent on meaningful programs that will likely yield positive clinical data to enable the company to;

1. raise more money, or
2. partner asset(s), or
3. get acquired

Program Selection Parameters



Challenges



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Preclinical Methods and Challenges to Assess Benefit of Genetic Medicines

Goal: Demonstrate **benefit** vs. risk for patients in preclinical stage

Regulatory requirement to **initiate clinical trials in patients at a minimally efficacious dose** due to the inferred risk of a gene editing therapeutic

Ways to assess efficacy to support benefit	Challenges of efficacy assessments
• Proof of expected editing using in vitro and in vivo models (can be normal cells or animals in some cases)	• Need an understanding of the level of editing in specific tissue(s) needed to improve human disease- often unknown from literature
• Positively impacting phenotype/ relevant biomarkers in mouse transgenic models	• Mouse models may not exist and are costly/ time-consuming to develop
• Correction of mutation in patient-derived samples (cells, organoids, etc.)	• Mouse transgenic models often have biodistribution translatability issues, while using small # of wild type NHP can be variable and difficult to interpret

Preclinical Methods and Challenges to Assess Risk of Genetic Medicines

Goal: Demonstrate benefit vs. **risk** for patients in preclinical stage

Once undesired edit is detected, the **interpretation of risk is a paper exercise** based on literature of gene function. Sometimes function of gene is unknown or off-target is seen in non-coding region

Ways to assess risk of genetic medicines	Challenges of risk assessment
• Exquisitely sensitive assays to assess undesired off-target editing of human genome (cells, organoids, etc.)	• In general, any off-target editing in human cells is flagged as a risk- what is biologically significant?
• Biodistribution and activity of gene editing cargo have optimized tools for detection	• If on-target editing in a non-target tissue seen - what is biologically significant? • Special consideration given to germ line tissues, with mouse repro models to validate any level of editing
• GLP toxicology to assess pharmacology and toxicity impact of delivery vehicle and cargo	• Human specific adverse findings, such as immunogenicity are not predicted in NHP or mouse model

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CMC for Rare Disease is Very Complex and Expensive

Need to consider scale, process and stability early in development

Illustrative process for LNP

A final LNP Drug Product Batch can cost $7-11M and takes up to 20 months to prepare

- EU has unique requirements for raw/starting materials, impurities, DS/DP release specifications and potency assays that require additional documentation, method development and validation
  - Qualified/ validated release specifications for drug substance and drug product (takes ~12 months and costs >$1M) prior to manufacturing
- Scientific advice meeting is great place to align on specifications, but comes late, any new requests can add substantial time delays to manufacturing.

EU CMC Approval Requires Additional Time and At-Risk Investment Prior to Determining Efficacy in Human

Ph 1/2 IMPD submission	Impact
GMP master cell banks (not required in US for Ph1/2)	Costs of GMP plasmids and MCB >$1.5M
Unique requirements for raw/starting materials that are not in DP (template plasmids for IVT of mRNA) and more specifications for release required compared to US, UK	Frontload assays due risk at filing= time and money
Impurity requirements lead to additional; test methods to quantify, in-process control to enable monitoring, correlate limits to toxicology to justify release specs and risk assessment (not in US, UK for Ph1/2)	Need validation of assays at vendor= time and money
GMP batch required for filing, clinical dose can be 6-9 month later due to regulatory approval process and site contracting	Need to plan time and cost to resupply a year ahead of need
Shelf-life printed on the label, which can change with more real time and modeled data (no expiry on US label)	Relabel frozen drug costs >$100K, need for QP review leads to additional time (weeks to months)

EU CMC Regulatory Approval and QP Release

Post IMPD filing	Impact
Harmonized filing results in receiving requests for additional information from individual countries to the IMPD • IMPD had >60 requests for additional information • UK had 9 additional requests • FDA module 3 had 2 additional requests	Limited time for response (or filing withdrawn), stressful for small company with limited number of employees
Qualified persons' (acting as health agents) requests are not harmonized with each other or with the EMA	Challenging to address with small quality group, leads to delay of release of clinical material (minimum of 2 months)

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Rare Disease Require Global Trials To Reach Patients

Strengths & Challenges of Harmonized EU Regulatory Process

Strengths

Scientific advice

- Input from PEI on our plans early in development was very valuable

Defined timelines for RMS & MSCs

- Predictable timelines for assessments and clock stops helped with internal planning and resource allocation

Clinical trial information system

- Single submission portal and coordinated review reduced duplicative activities and simplified initial application logistics
- Improved transparency through tracking, timeline visualization and document listing

Challenges

Harmonization yielded partial value - Part II

assessment completed before Part I, SM amendment needed to align ICF with updated protocol causing delays to site activation (up to 3 months)

Tight timeline for response to RFIs

- Deadlines are difficult to meet when responses require vendor input, document updates, especially when translations and/or redactions are needed

EU timelines are protracted compared to ROW

Time from Submission to Clearance/Approval

27 days

73 days

119 days

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5. Recommendations to make regulatory process more efficient in future guidance

EU Regulatory Summary

- **EMA input is important to evaluate the preclinical science, manufacturing of complex therapeutics and clinical plans to ensure patient safety**
- **Due to arduous GMP requirements compared to RoW, one needs to carefully consider if EU is essential for clinical enrollment in Ph1/2 trials**
    - If vital, then DP needs to be made to meet EU release requirements, which costs more and takes more time and early planning to enable
- **Harmonized country filings are a good faith effort, but in practice, individual country feedback can differ and can cause substantial time delays for clinical site opening**
- **Regulatory timelines in EU are long, and a small company burns money while waiting for regulatory feedback with no certainty on when clinical studies will start**

Recommendations for EMA Guidance for Gene Editing Medicines from an Industry Perspective

Preclinical/ Clinical	CMC/ Quality	Regulatory Processes
• Develop guidance for germ-line editing analysis and interpretation that does not adversely impact low levels of detection of editing event • Provide guidance on off-tissue editing risk assessment • Enable submission of updated ICFs to align with requested protocol changes during initial review period	• Revise requirements on raw/starting materials that are not in final product • Limit the number of CQAs for early batches • Allow for non-GMP plasmids and MCBs for Ph1/2 studies • Consider filing on engineering run for stability limited ATMP • Streamline or omit QP requirements post CTA authorization • Limit the # of PPQ batches for ultra-rare and rare disease approval	• Align CTA/IMPD review timing to be consistent with US/UK • Promote consistent classification of amendments (SM vs NSM) across member states • Allow concurrent review of amendments to limit time delays