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The Journey to Commercialization

CASSS 2024

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Introduction

It really is a Journey

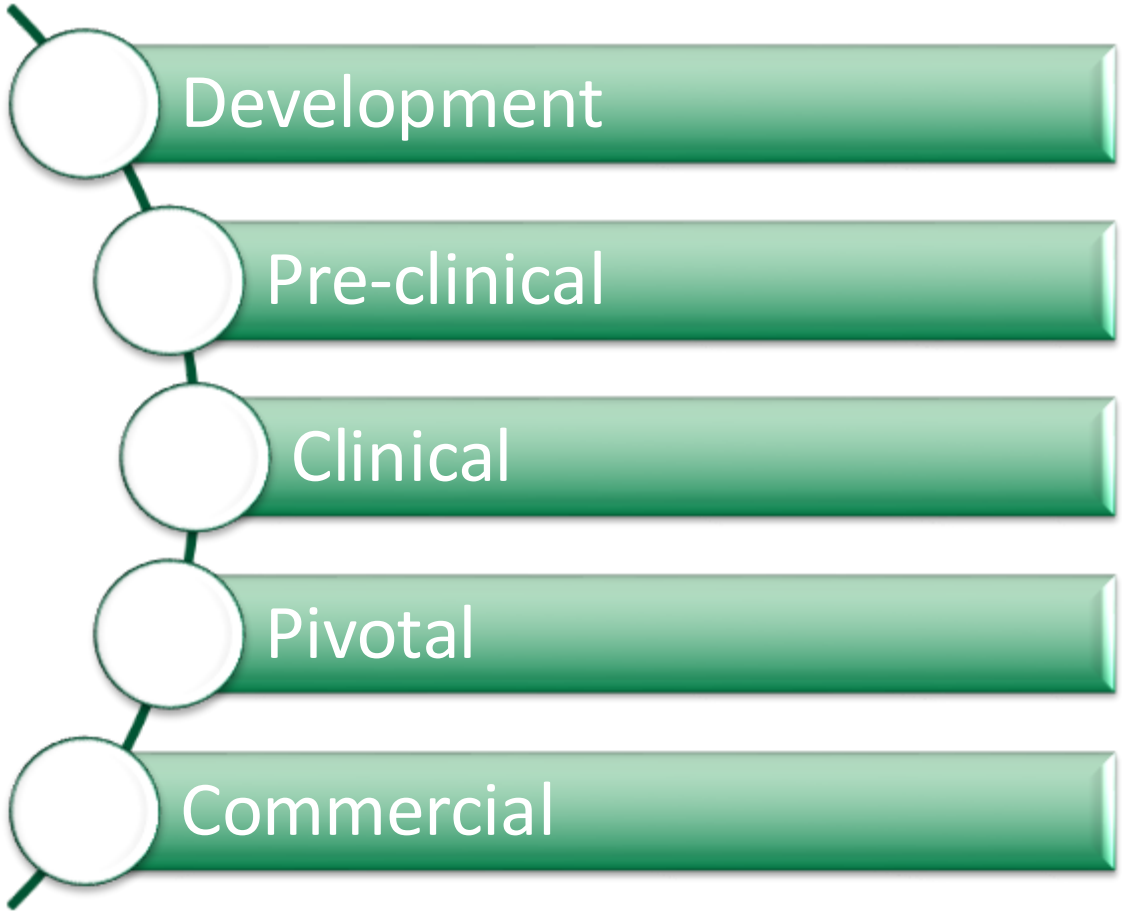
- ATMPs require unique manufacturing strategies and are often fast tracked, leading to numerous hurdles which need to be surmounted during a product's life cycle

- Identifying manufacturing, testing and regulatory strategies early in a products life-cycle, as well as planning for success and understanding risk, can greatly improve the ease, timeline, and expense associated with bringing CGT products to market

- At a high level, this talk will focus on identifying strategies to help navigate a product's lifecycle

Early Stage Product Life-Cycle: Points to Consider

- Early stage
  - Plan for success
  - Have an end goal in mind when weighing decisions
  - Take a phase-appropriate approach and understand upfront vs. long-term regulatory, cost and timeline risks
- Platform and scale
  - Decide your platform early (e.g., viral vectors: suspension vs. adherent; cell therapies: open or closed, automated or manual)
  - Understand the expected data and information to support comparability if platforms need to change in later stages
- Raw materials
  - Use highest quality raw materials. Ensure their manufacturing and testing is appropriate and acceptable.
- Manufacturing
  - External vs. Internal
    - Do you plan to move the program in house at some point?
    - Comparability and clinical considerations if manufacturing changes are made
    - Raw materials (e.g., plasmids and cell banks)
      - If you need to move the manufacturing, will you be able to take the plasmids and cell bank?
    - IP – Is there any IP that would need to be shared with a new manufacturer?



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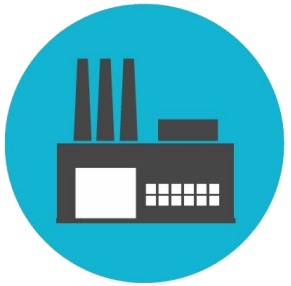
Timelines and Expenses

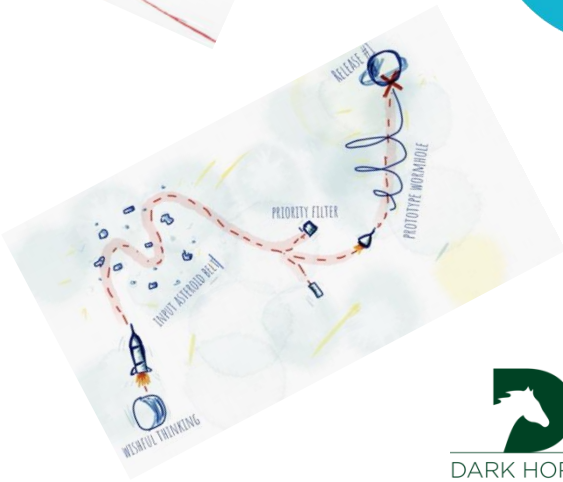
Time is money. Considerations that help can help save on both.

- Set manufacturing, analytical, and regulatory strategies early on
  - Funding and timelines may dictate strategy
  - Setting strategy early can speed up timelines and save on costs
- Internal vs. external manufacturing
  - External manufacturing can be the fastest way to get into clinic
  - Leverages external expertise, systems, and infrastructure
- Comparability considerations
  - Early financial limitations can greatly influence a products path
    - Understand the implications of manufacturing changes
- Tolerance for risk
  - All companies have differing tolerances for risk
  - Timelines can be improved by taking on more risk
  - Understand your tolerance for risk and take an appropriate risk-based approach to your strategy planning

Early-Stage Product Suggestions

- Create a Target Product Profile (TPP)
  - Living document
  - Puts everyone is on the same page
- Considerations for internal or external development and manufacturing
  - Early stage vs. late stage
  - Comparability challenges
- Importance of Master Service Agreements (external manufacturing)
  - These contracts set the stage for how and when your product is made
  - MSAs should not be one sided. Don't be afraid to negotiate
  - Can give you recourse should you need it
  - Legal, technical and quality aspects to consider
- Roadmaps – Plan out timelines, considerations, and expenses
  - Develop a roadmap early on to detail planned activities and estimated costs
  - Can be used with a Gantt to evaluate project progress
  - Can help to identify where risks can be taken to improve timelines
- Risk appetite and strategies
  - Define your appetite for risk





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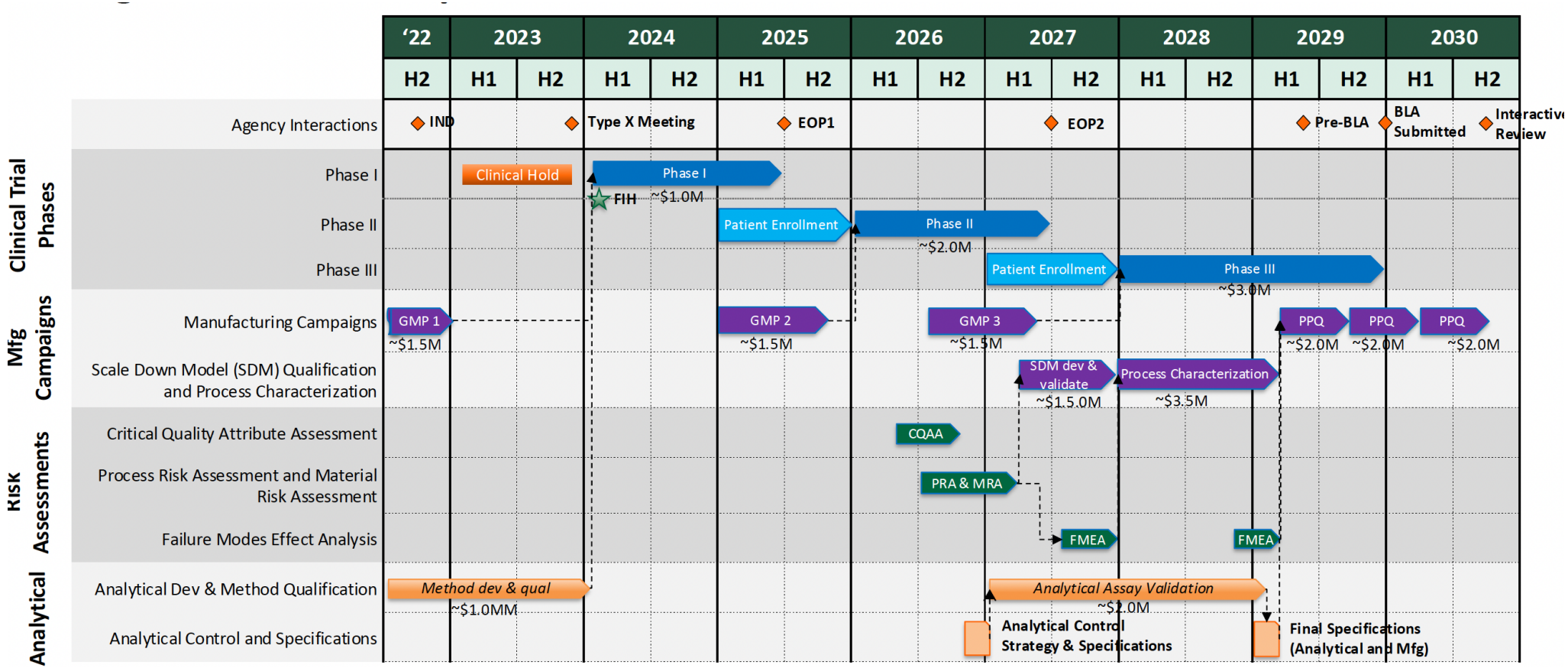
Roadmap Example

- Roadmaps help everyone see the overall plan and timing
- The tool is a nice way to visualize how to shorten timelines by taking risks or what the impact of a delay may be



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Manufacturing Considerations

Internal vs. external manufacturing

Internal manufacturing

Pros:

- Control your own destiny
  - Cues and manufacturing schedules are up to you
- Designed for your product(s)
- Can be stage gated (i.e., expansion space can be designed in)

Cons:

- Build, maintenance and staffing come at a high price
- Time to design, permit, build, commission and EMPQ can take 2+ years

External manufacturing

Pros:

- Less expensive start up costs
- Knowledge base and experience for manufacturing lies with CDMO
- Have many of the systems in place (e.g., facility, equipment, QMS, personnel)
- Steering committees can help to resolve conflicts quickly and keep manufacturing on track

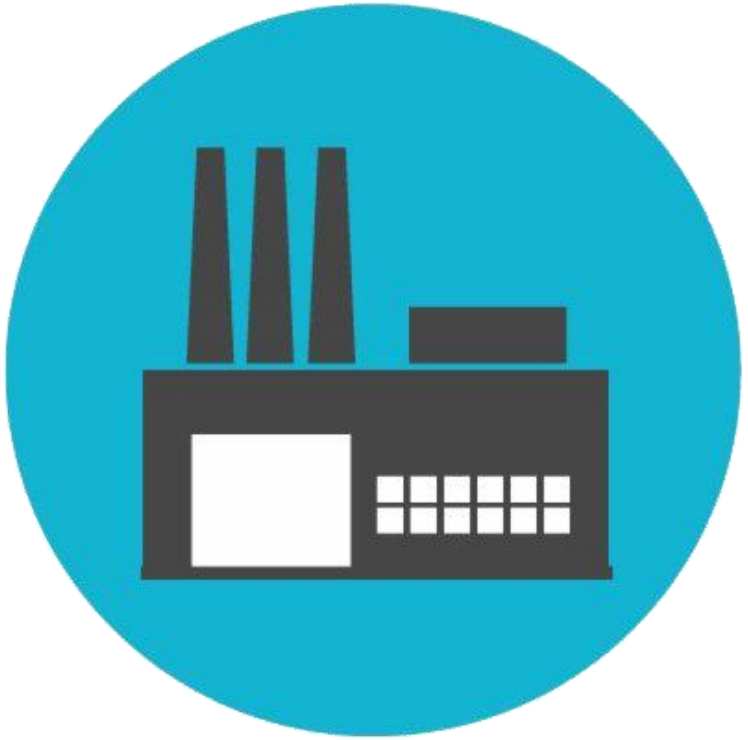
Cons:

- Cues
- Platform may not be best for your product
- CDMOs need to make a profit (high overhead)
- May not have late-stage experience (i.e., validation)

Manufacturing Considerations

Facility

- Considerations
  - Is the facility appropriately designed and run for GMP manufacturing?
    - Consider:
      - Flows: personnel, material, waste, and product
      - HVAC coverage
      - Contamination control strategy
      - Multiproduct facility
      - Quality management system in place
      - Personnel trained and qualified
  - Is/will the facility be commercial ready
    - Could the facility pass a PLI
    - Is there a plan in place to move the facility to become commercial ready
    - Is the plan to move at some point to a commercial ready facility
  - Validation
    - Have they been through the process validation process (e.g., FMEAs, Process characterization, PPQs



Manufacturing Considerations

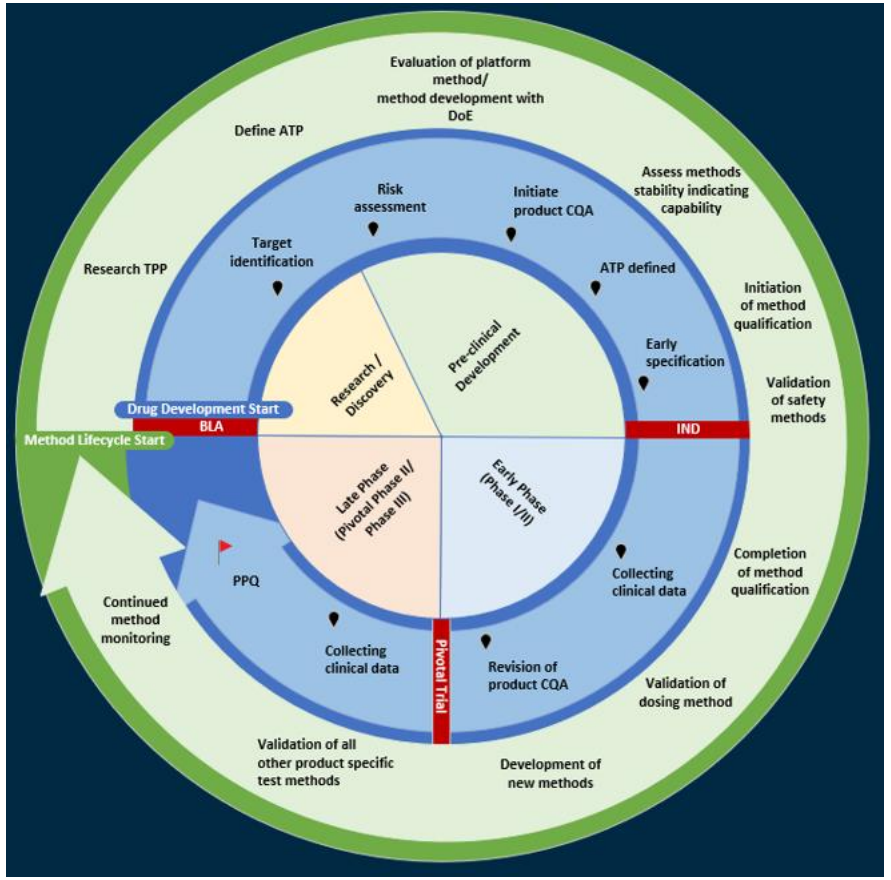
Process

- Raw materials
  - Recommend a phase appropriate approach to qualifying raw materials
- Batch records
  - Batch records should evolve as the process matures
  - Collection of data early on will help setting appropriate acceptance criteria and informing early validation planning
- Scale
  - Often necessary to scale up as the product moves into late-stage trials
  - Considerations should be given early on to comparability
- Comparability
  - Early discussions with health authorities regarding manufacturing changes and comparability will save time and money
- Validation
  - Validation is a lengthy and expensive process. Ensure staff has experience and the process is performed correctly

Recommendations for Phase Appropriate Product Decisions

Analytics

- Phase appropriate analytics
  - Development and pre-clinical stages:
    - Method development and qualification
    - Identify stability indicating methods
    - Initiate assay qualification
    - Validation of safety assays
  - Early phase clinical:
    - Complete assay qualifications
    - Develop new methods if needed
    - Begin validation of critical assay needed for late stage
  - Late phase clinical/pivotal:
    - Continue method validation
    - Full validation of critical assays (e.g., titer, potency)
  - BLA:
    - All assays are fully validated



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Regulatory Considerations

Points to consider

- Heath authorities
  - Want to see these products approved
  - Are willing to work with sponsors and manufactures
  - Concerned with the safety and efficacy of products
- Recommendations
  - Know your product
    - You are the expert of your product. Not the regulators!
  - Engage with the agencies early
  - Detail your path and proposals
    - Regulators want to understand your plans and how you intend to support it
    - Have a fallback plan
  - Get a written and clear agreement
  - General questions get general answers

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Bio

Scott Cross Sr. Principal / Head of Gene Therapy CMC. Dark Horse Consulting Group

- 25+ years in CGT space
  - Merck & Co.
  - Indiana University Vector Production Facility / NGVL
  - Cincinnati Children's Hospital Viral Vector Manufacturing Facility
  - University of Florida / Florida Biologix / Brammer Bio
  - Orchard Therapeutics
  - Dark Horse Consulting Group

- Fully invested in advancing the CGT field and moving products into the clinic and through to commercial approval

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