Small Scale Manufacturing for Rare Diseases

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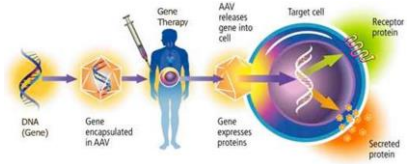
Agenda

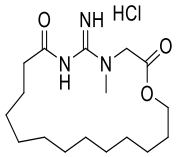
- Framing the Manufacturing Challenge
- How Ultragenyx Addresses These Challenges
- Manufacturing, QC and CMC Regulatory Risk Across Product Lifecycle
- CMO Management, GxP requirements
- Q&A

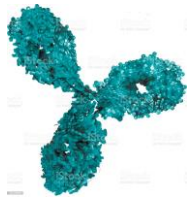
Framing the Manufacturing Challenge

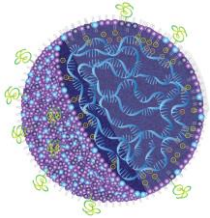
- Know the “race” you are running
  - eg; Fastest to IND, Fastest to Approval, Cost effective to IND, Cost efficient until value inflection point?
- What modality to use?
  - Biology is biology
  - Understand the tradeoffs with the different modalities
- Be as explicit about the risks as you can
  - What is sufficient?
  - What scale should I operate at?
  - Technical and scientific
  - Regulatory
  - Benefit / risk
- Recognize you are learning too

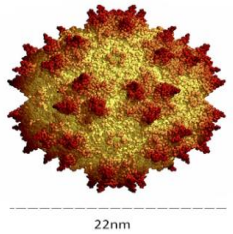
Ultragenyx Pipeline by Modality and Stage

	Small Molecule	Traditional Biologics	Nucleic Acid Therapy	AAV Gene Therapy
Commercial	 Dojolvi	Burosumab Mepsevii Evkeeza 		
Clinical	ATX95 (mRNA) Prednisolone (GT) Na Acetate (GT)	UX143 Plasmid in E.coli (GT and mRNA)	GTX102 (ASO) UX053 (mRNA)	DTX301 DTX401 UX701 UX111
Pre-Clinical	UX068 *UX016*	UX100 (E.coli)		UX055 UX810

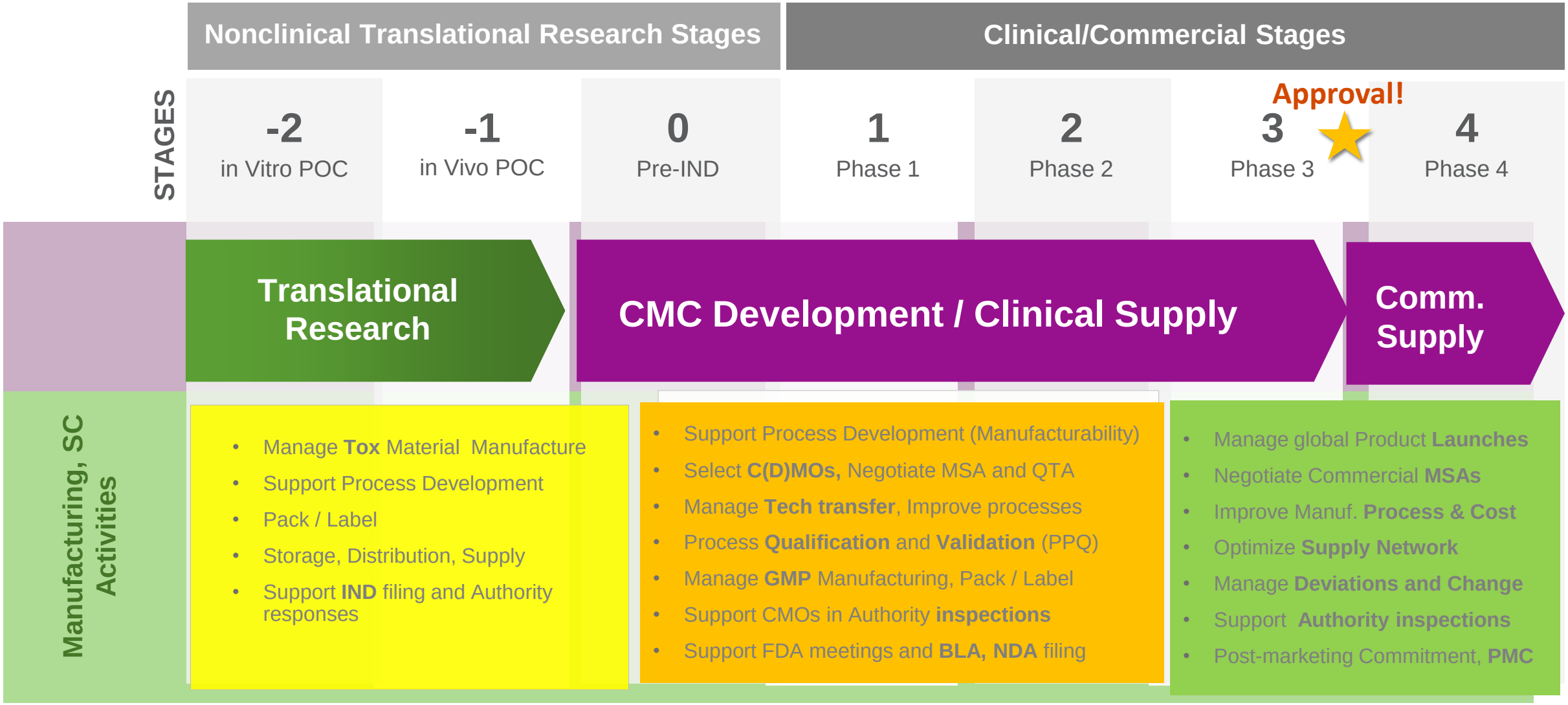








Key Manufacturing Activities Along Product Lifecycle

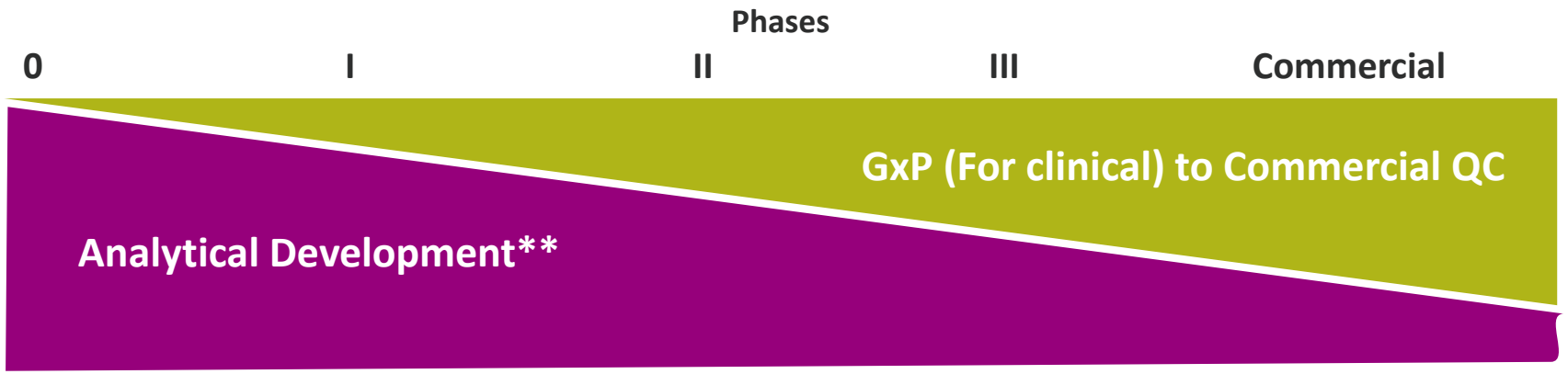


Testing also Has a Significant Lifecycle to Consider as Well

Analytical comparability may need to occur during the lifecycle

Analytical Development
:Develop scientifically sound methods
:Methods transfer
::Methods characterization
:Process Dev Support and R&D In-process testing
:Product & process characterization
: Determining Critical Quality Attributes
:Development stability
:Comparability studies
::Post approval improvements
:Support regulatory filing

Quality Control
:Good Mfg Practices (GMP) In-process testing
:Release testing
:Stability studies
:Methods validation
:Testing investigations
:Method Life Cycle
:Process Validation support
:GMP studies
: Support regulatory filing

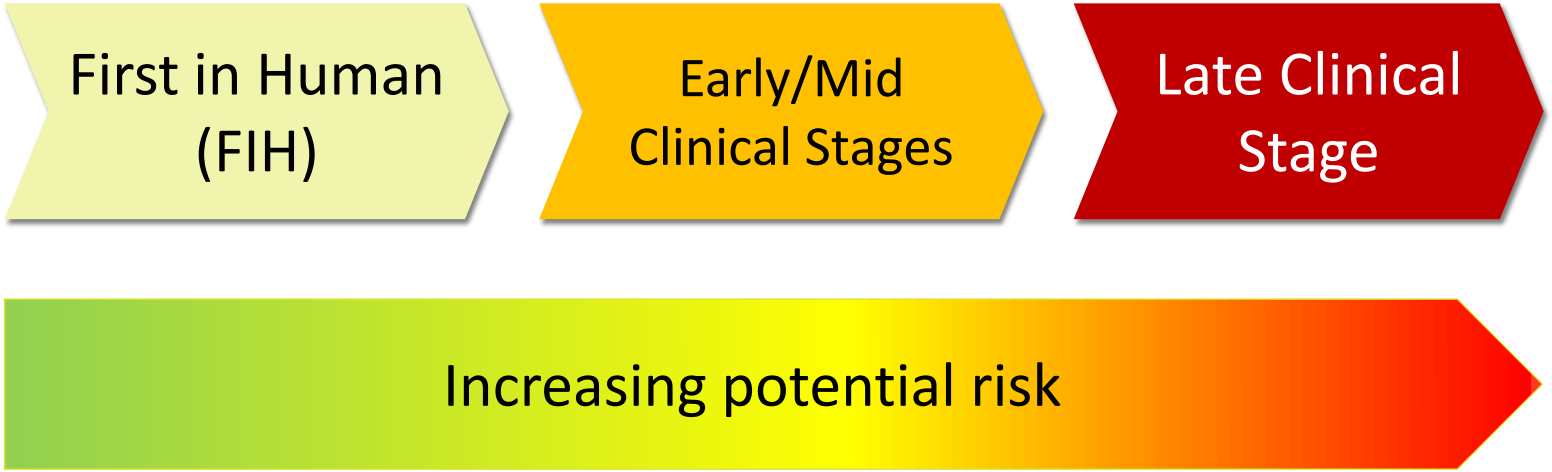


Close Collaboration is key:

Tech Dev
Analyt. Dev.
Manuf,
QC, QA
CMC Reg
CDMOs, CROs

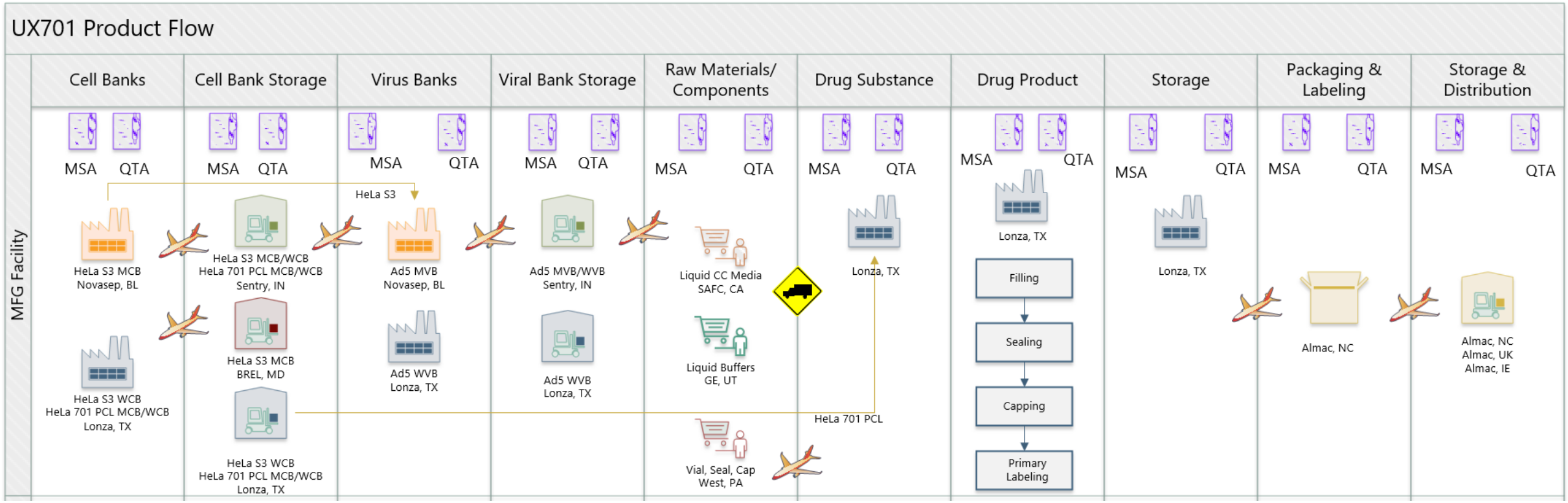
**AD work may be sustained post approval for PMC, Process improvements or trouble shooting purposes
PAV = Phase Appropriate Validation; PA = Phase Appropriate; with rapid CMC consideration

CMC Regulatory Risk Associated with Clinical Stage of Development



ICH Q5E: Product comparability by Clinical Stage	
Prior to Clinic	Not required
Early Clinical Stage	Not extensive
Mid Clinical Stage	More comprehensive
Late Clinical Stage	Comprehensive

Supply Chain Can Be a Critical Success Factor



External Manufacturing requires a lot of management attention and oversight

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Questions?

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Thank You