



Small Scale Manufacturing for Rare Diseases

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EVP Gene Therapy
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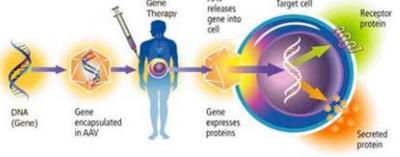
Agenda

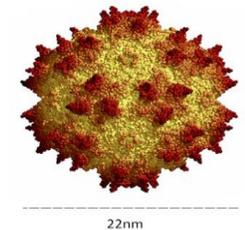
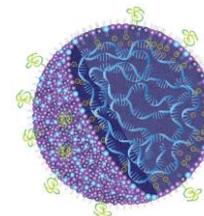
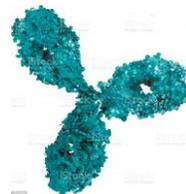
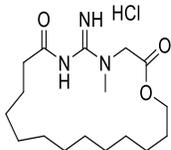
- Framing the Manufacturing Challenge
- How Ultragenyx Addresses These Challenges
- Manufacturing, QC and CMC Regulatory Risk Across Product Lifecycle
- CMO Management, GxP requirements
- Q&A

Framing the Manufacturing Challenge

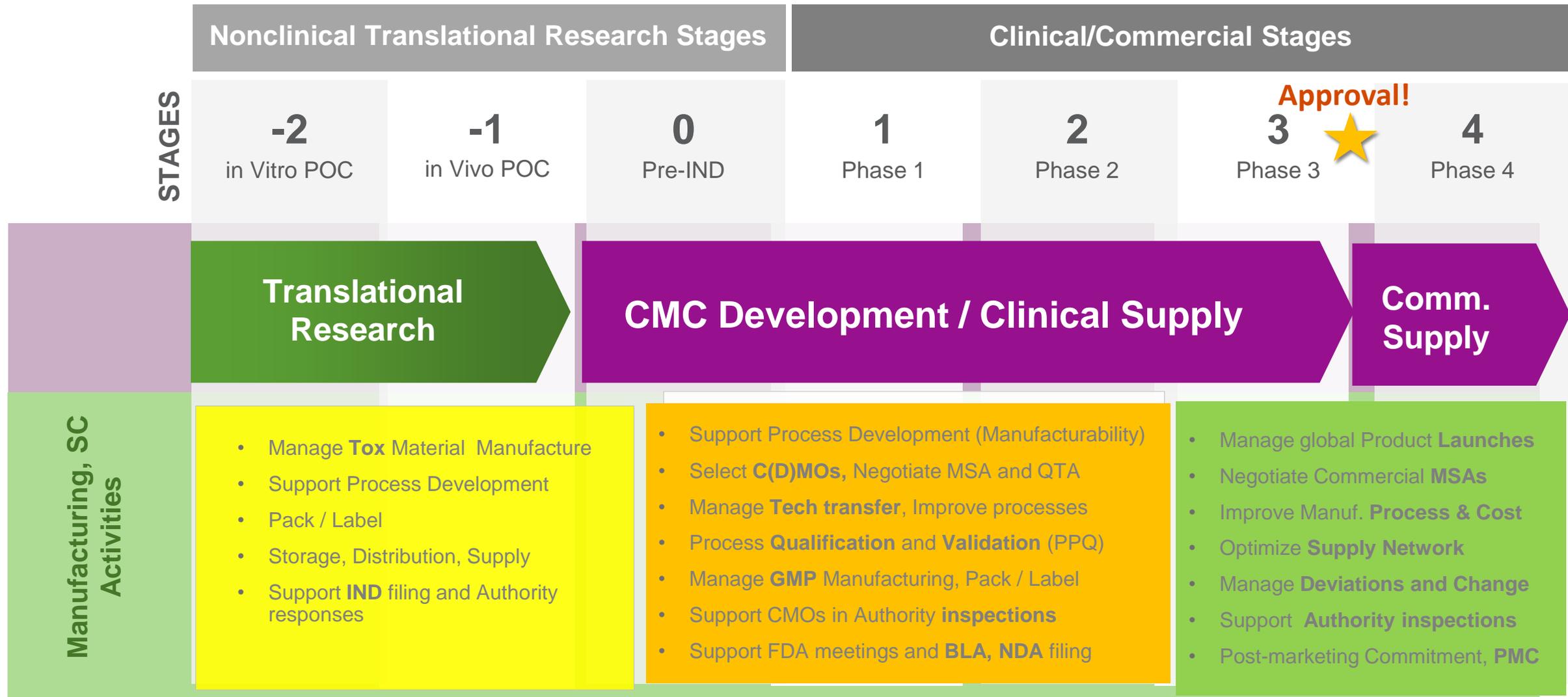
- Know the “race” you are running
 - eg; Fastest to IND, Fastest to Approval, Cost effective to IND, Cost efficient until value inflection point?
- What modality to use?
 - Biology is biology
 - Understand the tradeoffs with the different modalities
- Be as explicit about the risks as you can
 - What 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	 <p>Dojolvi</p>	<p>Burosumab Mepsevii Evkeeza</p> 		
Clinical	<p>ATX95 (mRNA) Prednisolone (GT) Na Acetate (GT)</p>	<p>UX143</p> <p>Plasmid in E.coli (GT and mRNA)</p>	<p>GTX102 (ASO)</p> <p>UX053 (mRNA)</p>	<p>DTX301 DTX401 UX701 UX111</p>
Pre-Clinical	<p>UX068 UX016</p>	<p>UX100 (E.coli)</p>		<p>UX055 UX810</p>



Key Manufacturing Activities Along Lifecycle



Testing also Has a Significant Lifecycle to Consider as Well

Analytical comparability may need to occur during the lifecycle

Analytical Development

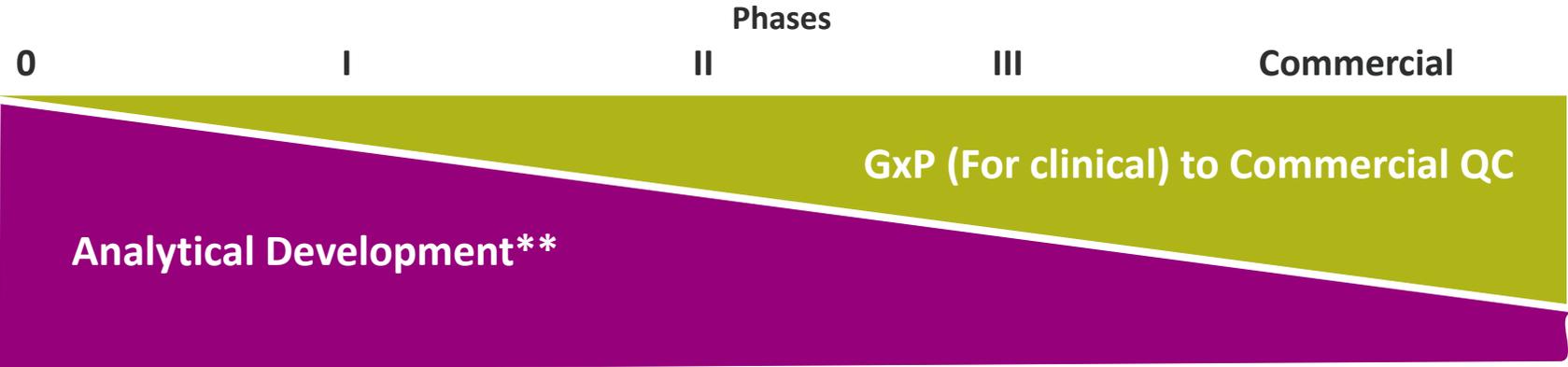
- :Develop scientifically sound methods
- :Methods transfer
- ::Methods characterization
- :Process Dev Support and R&D In-process testing
- :Product & process characterization
- : Determining Critical Quality Attributes
- :Development stability
- :Comparability studies
- ::Post approval improvements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

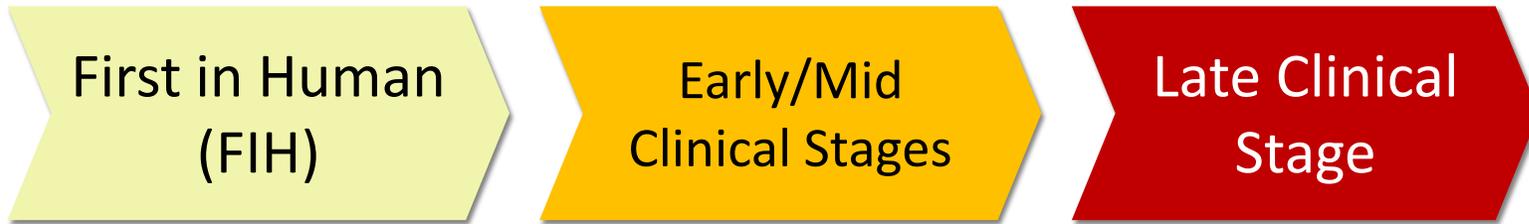
Close Collaboration is key:

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

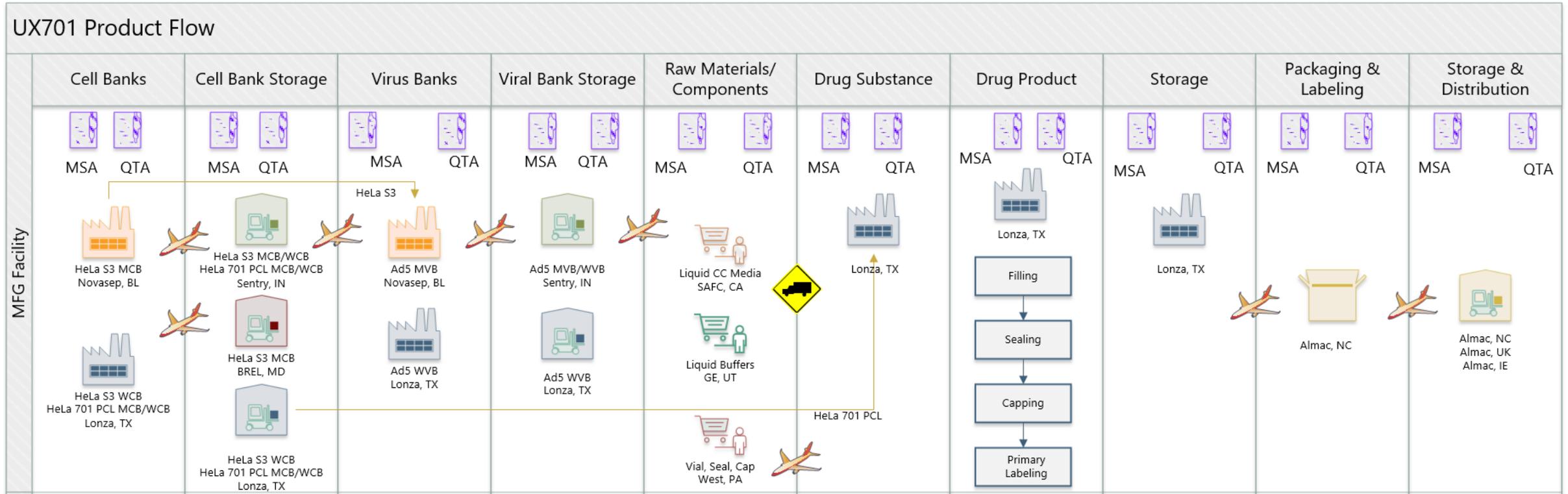
CMC Regulatory Risk Associated with Clinical Stage of Development



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



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