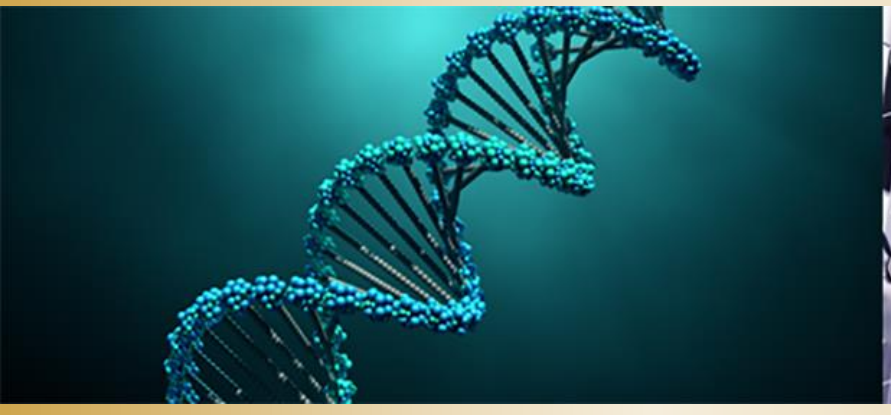
SAREPTA
THERAPEUTICS

SETTING THE STANDARD IN GENE THERAPY MANUFACTURING

PALANI PALANIAPPAN, PH.D., SR. VICE PRESIDENT, TECHNICAL OPERATIONS

APRIL 2019



FORWARD-LOOKING STATEMENTS

This presentation contains "forward-looking statements." Any statements that are not statements of historical fact may be deemed to be forward-looking statements. Words such as “believe,” “anticipate,” “plan,” “expect,” “will,” “may,” “intend,” “prepare,” “look,” “potential,” “possible” and similar expressions are intended to identify forward-looking statements. These forward-looking statements include statements relating to the creation of stable producer cell lines’ potential to simplify processing while increasing virus productivity; our plan to develop robust fixed-bed and “single-cell” suspension BRX production platforms; the expectation that sufficient process development will improve overall product recovery for AAV downstream processes; our plan to design and implement chromatography-based purification strategy; the anticipation that manufacturing will likely be the rate limiter for regulatory approval; our manufacturing, supply and control strategies and our plans regarding LPD/3PL readiness and inspection readiness; our product candidates and programs, including with strategic partners, and their potential benefits and market opportunity; and the estimated number of patients suffering from DMD, LGMD, MPS IIIA, CMT and Pompe disease.

These forward-looking statements involve risks and uncertainties, many of which are beyond our control. Actual results could materially differ from those stated or implied by these forward-looking statements as a result of such risks and uncertainties. Known risk factors include the following: the expected benefits and opportunities related to the agreements with Brammer, Paragon and Aldevron may not be realized or may take longer to realize than expected; Sarepta’s dependence on its manufacturers to produce vectors, plasmids and other materials to fulfill Sarepta’s needs for its gene therapy clinical trials and commercial supply, including any inability on Sarepta’s part to accurately anticipate product demand and timely secure manufacturing capacity to meet product demand, may impair the availability of products to successfully support various programs, including research and development and the potential commercialization of Sarepta’s gene therapy product candidates; if these manufacturers were to cease providing quality manufacturing and related services to Sarepta, and Sarepta is not able to engage appropriate replacements in a timely manner, Sarepta’s ability to manufacture its gene therapy product candidates in sufficient quality and quantity would adversely affect Sarepta’s various product research, development and commercialization efforts; if these manufacturers fail to adhere to applicable cGMP and other applicable government regulations, or experiences manufacturing problems, Sarepta will suffer significant consequences, which could significantly delay or negatively impact the success of Sarepta’s development efforts for its product candidates; Sarepta may not be able to successfully scale up manufacturing of its product candidates in sufficient quality and quantity or within sufficient timelines, or be able to secure ownership of intellectual property rights developed in this process, which could negatively impact the development of its product candidates; if the actual number of patients suffering from DMD, LGMD, pompe disease, CMT and/or MPS IIIA is smaller than estimated, our revenue and ability to achieve profitability may be adversely affected; Sarepta’s gene therapy programs may not result in any viable treatments suitable for clinical research or commercialization due to a variety of reasons, including the results of future research may not be consistent with past positive results or may fail to meet regulatory approval requirements for the safety and efficacy of product candidates; and even if Sarepta’s gene therapy programs result in new commercialized products, Sarepta may not achieve any significant revenues from the sale of such products; and those risks identified under the heading “Risk Factors” in Sarepta’s most recent Annual Report on Form 10-K for the year ended December 31, 2018 and most recent Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) as well as other SEC filings made by the Company which you are encouraged to review.

Any of the foregoing risks could materially and adversely affect the Company’s business, results of operations and the trading price of our common stock. You should not place undue reliance on forward-looking statements. Sarepta does not undertake any obligation to publicly update its forward-looking statements based on events or circumstances after the date hereof, except to the extent required by applicable law or SEC rules.

CORPORATE MISSION STATEMENT

Armed with the most advanced science in genetic medicine,
we are in a daily race to rescue lives otherwise stolen by rare disease.

At Sarepta, every day is another 24 hours to stand up
for patients, advance technology, challenge convention and
drag tomorrow into today.

SAREPTA BY THE NUMBERS

572

Employees*
(and growing!)

13

Global
Locations

25

Pipeline
Programs

3

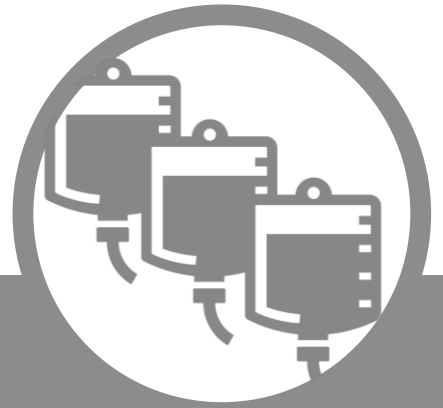
Therapeutic
Modalities

**Full-time employees as of March 22, 2019*

LANDSCAPE: OVERARCHING GENE THERAPY MANUFACTURING CHALLENGES AND CONSIDERATIONS

CRITICAL COMPONENTS: GENE THERAPY MANUFACTURING

QUALITY

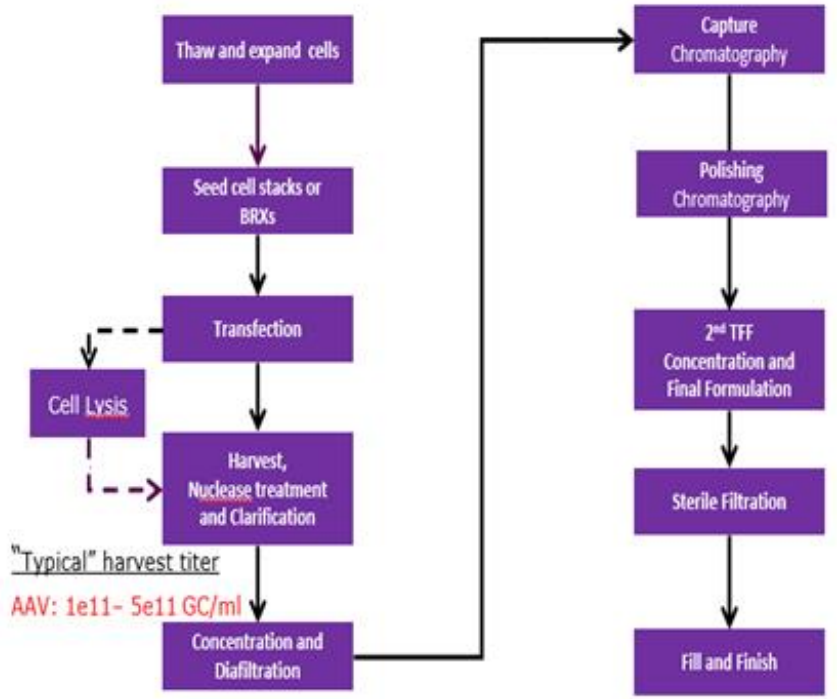


COMPATABILITY

CAPACITY

CHALLENGES EXIST FOR PRODUCERS OF AAV-BASED GT'S*

- Lot of focus still on early POC supported by academic/laboratory processes
- Use of plasmids rather than "producer" cell lines for virus production
- Lack of scalability for industrializaion
- Presence of animal-derived components
- Significant downstream yield losses
- Non-"optimized" analytics
- External MFG capability & capacity
- Recent FDA Guidance provides greater clarity
  - Additional guidance expected from health authorities



The current & future demand for many AAV gene therapy products is generally outpacing the capabilities and resources required to make them.

SAREPTA THERAPEUTICS

* Partial list, not all-inclusive

OPTIONS TO INDUSTRIALIZE PH 1>> PH 3 >>COMMERCIAL

- **Scale-out** strategy to support **low demand**
  - Adherent to Adherent
  - Hyperstacks to hyperstacks
- **Scale–up/Scale-out** strategy to support **high demand**
  - Adherent to adherent
  - Hyperstack to iCellis 500
- **Scale-up/higher tankage** to support **high demand**
  - Adherent to Suspension mammalian
  - Adherent to Suspension insect cells

EXPRESSION/PROCESS

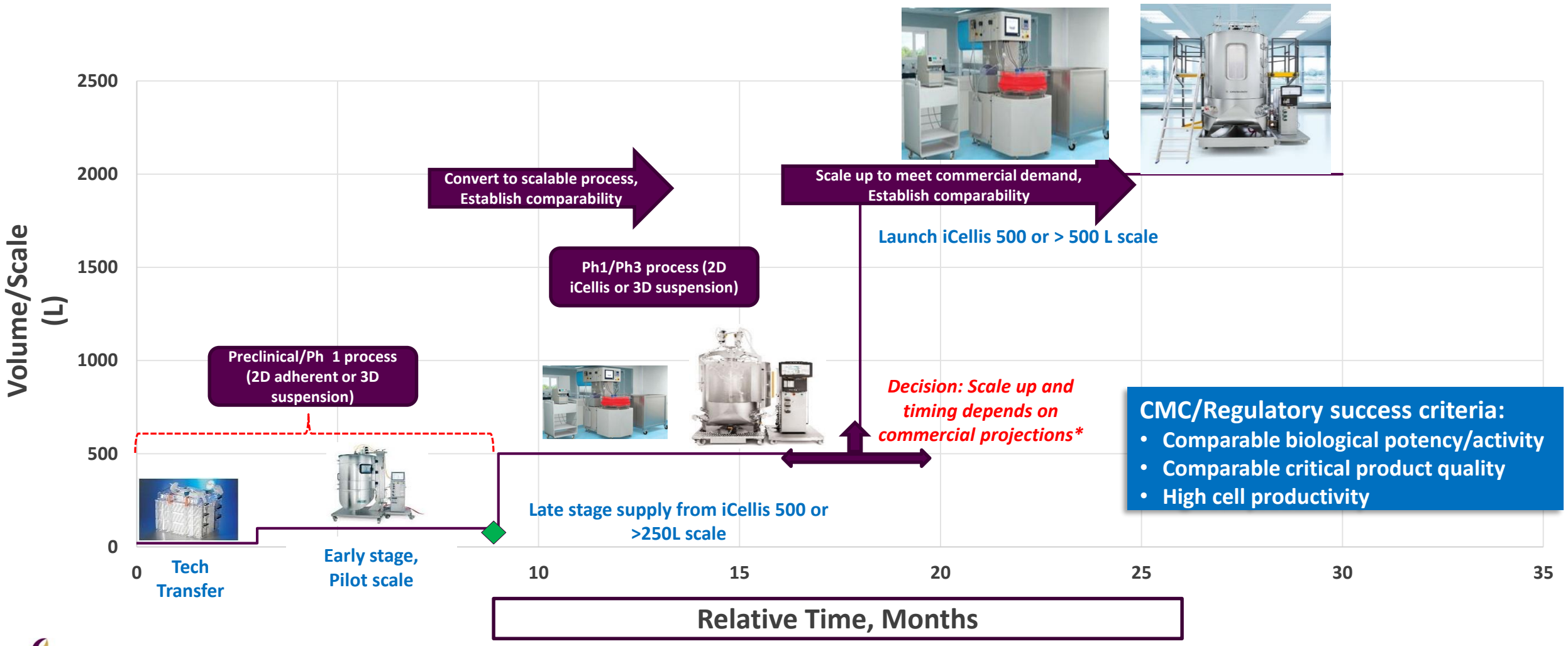
- Mammalian HEK vs. Insect Sf9/BV
- Adherent (Cell stacks or iCellis up to 500 m2)
- Suspension (500-2000 L)

Platform/Step	USPD	DSPD
HEK	Adherent, iCellis, Suspension	Gradient, Column
Sf9 BV	iCellis, Suspension	Column
Producer cells	Suspension	Column

Late Stage: HEK/Sf9, Suspension/iCellis, 500L-1000L
Commercial: HEK/Sf9, Suspension/Icellis, 2000L

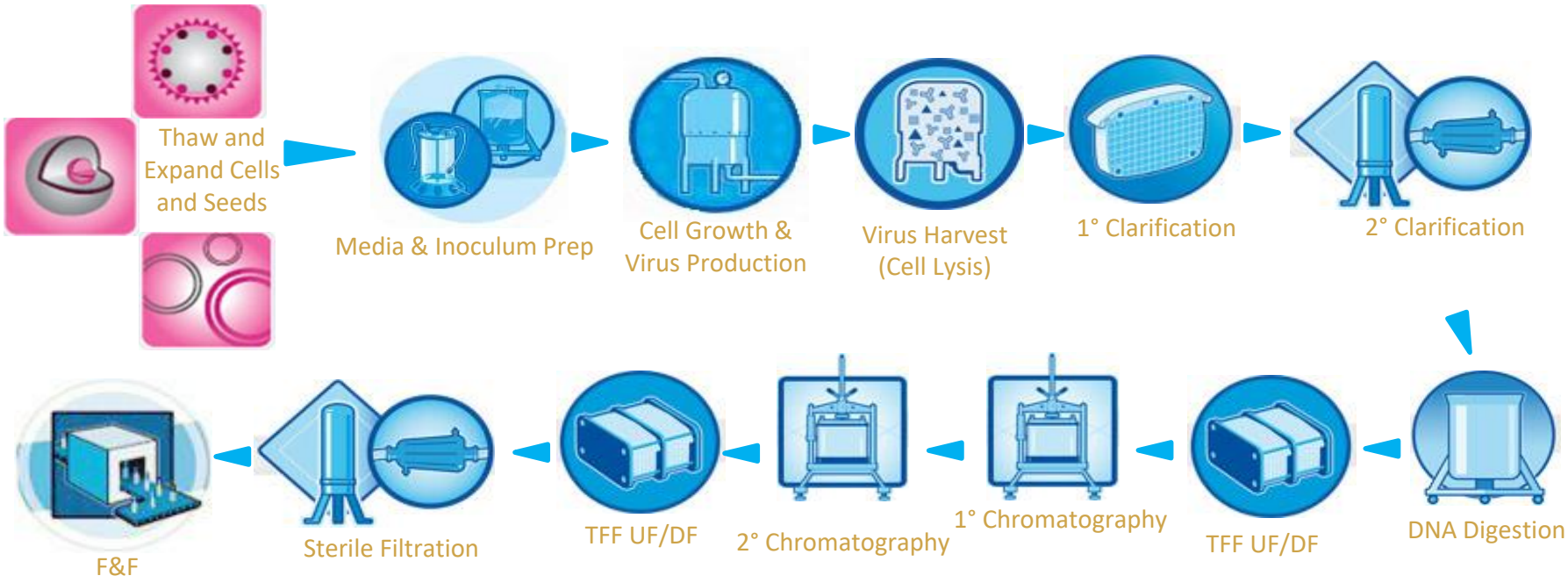
DELIBERATE APPROACH FROM PH1 TO LATE STAGE & COMMERCIAL

SAREPTA'S CASE-BY-CASE APPROACH FOR FINAL PROCESS BASED ON YIELD, CTQ AND COMPARABILITY BURDEN

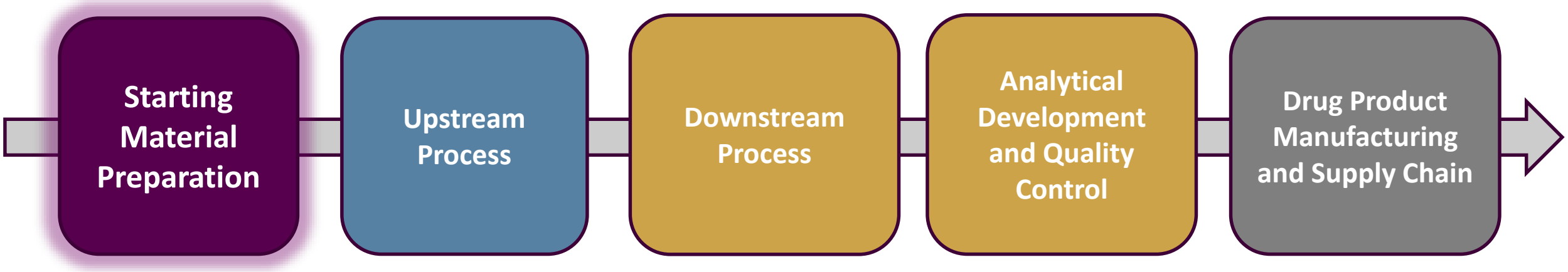


AAV-BASED GENE THERAPY PRODUCTION

- Production of any viral (biologic) product is a challenging process
- Safety and efficacy of product depends on each step in the manufacturing process to remove impurities



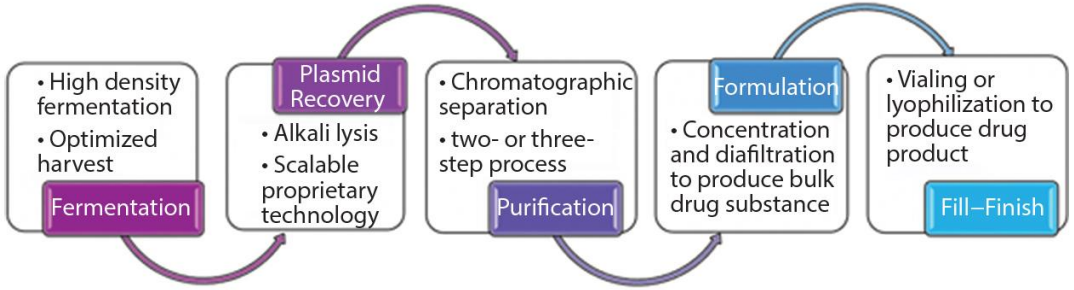
FOR THE PURPOSES OF THIS PRESENTATION WE'LL CONSIDER AAV PRODUCTION IN THE FOLLOWING "SECTIONS"



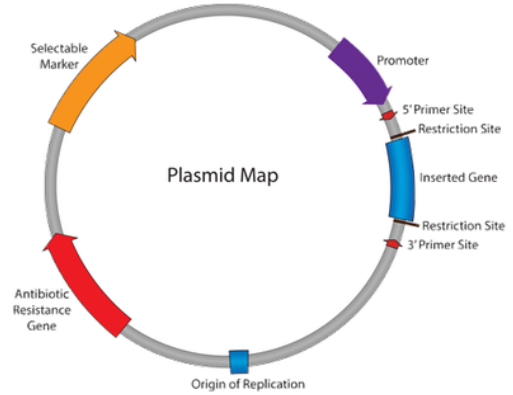
(DNA) PLASMIDS & HOST CELL LINES ARE TYPICALLY CLASSIFIED AS “CRITICAL STARTING MATERIALS” FOR VIRUS PRODUCTION

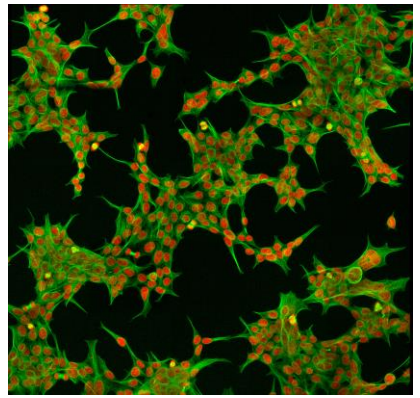
Starting Material Preparation

- **Plasmids**
  - Supercoiled DNA-based structures (most are < 15 Kb)
  - Typically produced in e coli, low expression, expensive, variable
    - Generally each e coli cell bank is encoded w/ one plasmid sequence
    - Microbial resistance selection markers typically used to confirm effective prep
      - Increasing regulatory scrutiny
  - Sarepta uses several external organizations to provide our stocks
    - Aldevron, among others

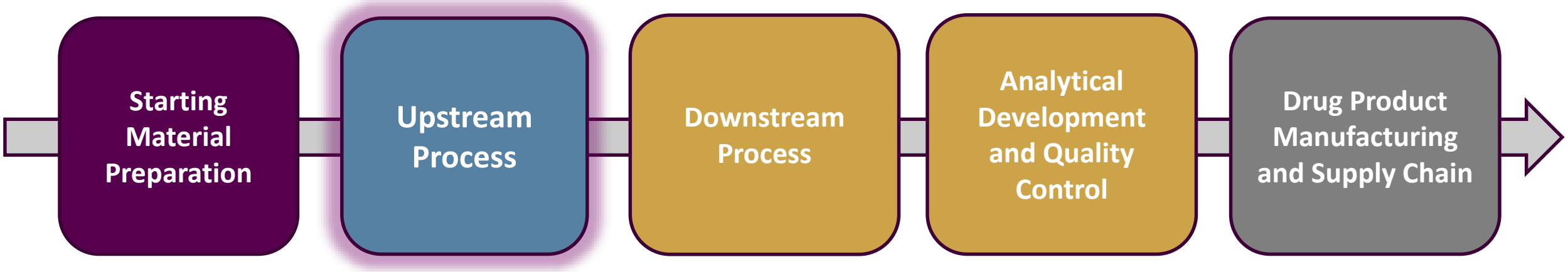


- **Cell line**
  - AAVs produced via “transient transfection” are most often made in HEK293 cells
    - Human Embryonic Kidney cells
      - Clone is encoded w/ critical Ad “helper gene” required for AAV assemblage
      - Not the only way to make AAV
    - Critical step is to produce the master & working cell banks (MCBs & WCBs) and characterize them before production starts



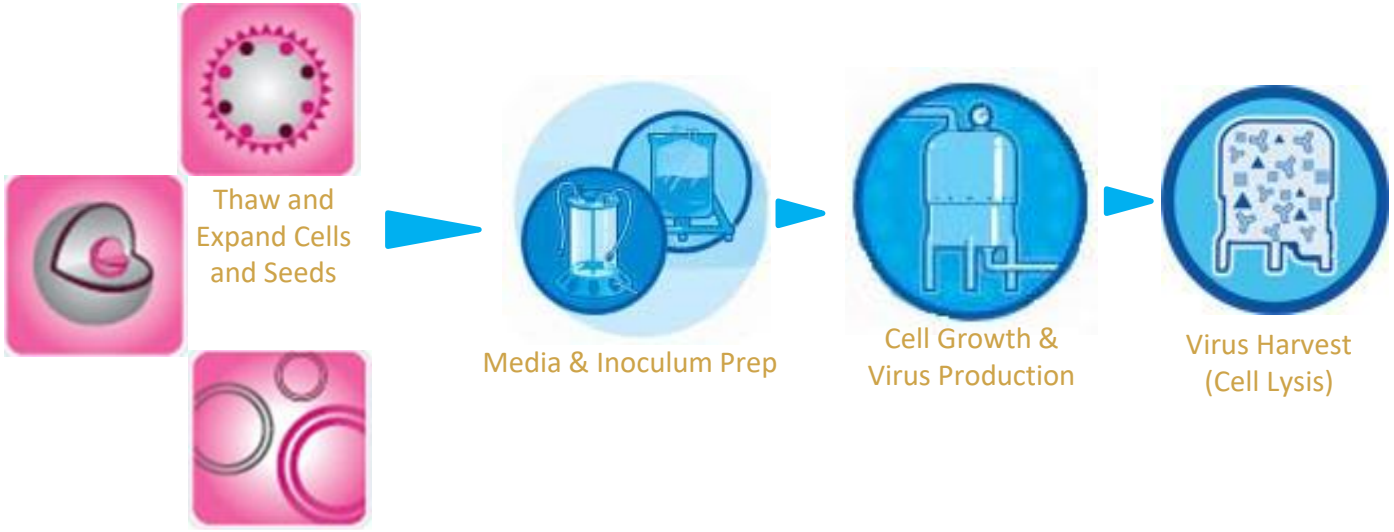


KEY CONSIDERATIONS BY PHASE



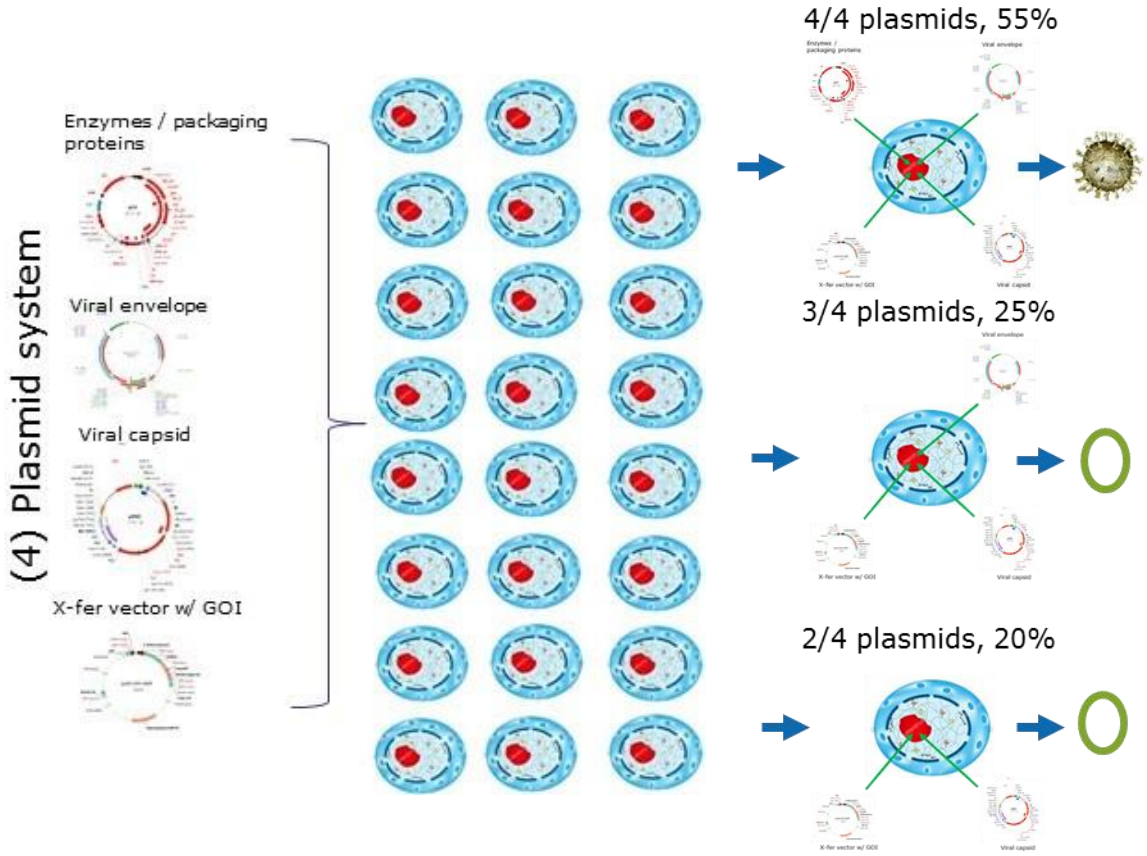
“UPSTREAM” AAV MANUFACTURING PROCESS

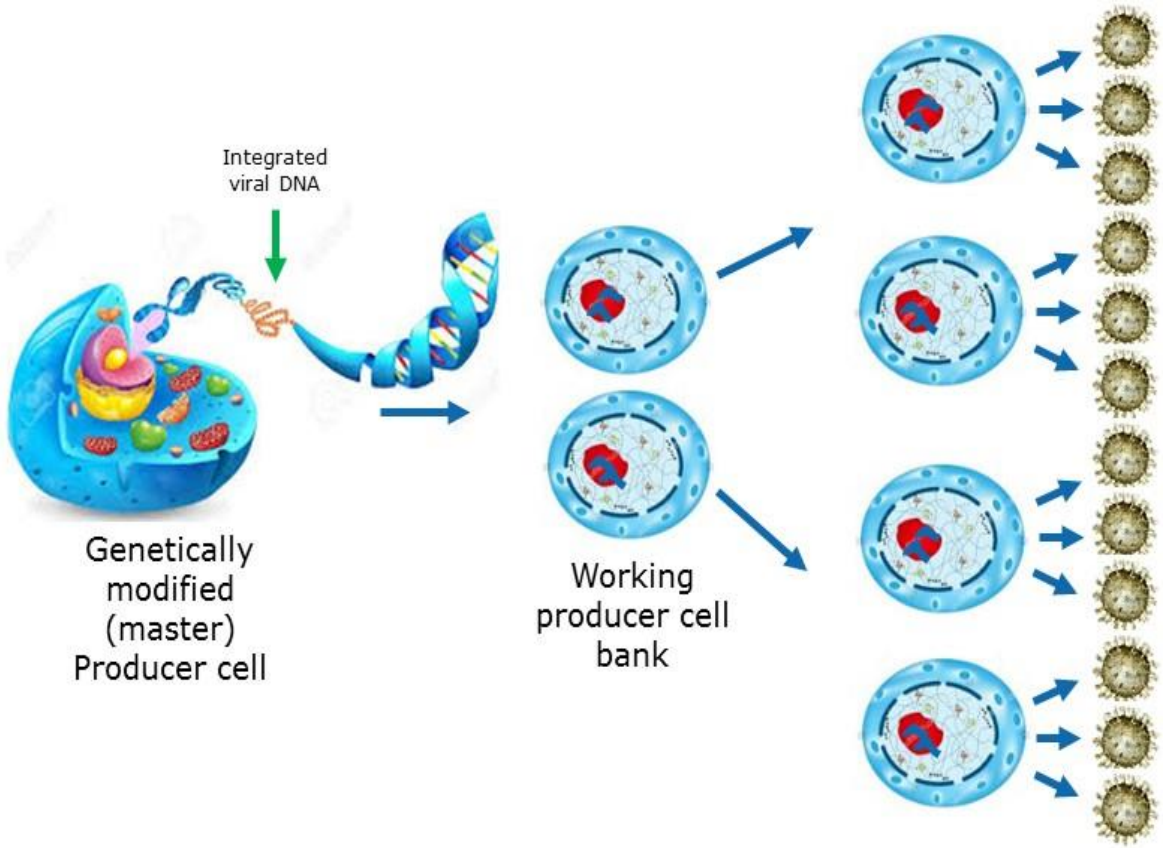
Upstream Process



“TRANSIENT” TRANSFECTION IS INHERENTLY VARIABLE

Upstream Process





The creation of stable producer cell lines has the potential to simplify processing while increasing virus productivity!

"2D" CELL CULTURE PROCESSES ARE MANUAL, NON-AUTOMATED, & SCALE *OUT*, NOT UP

Upstream Process

Current state

Vial thaw

Desired state

Vial thaw

* Seed training may not involve cell stacks, included here for illustrative purposes only

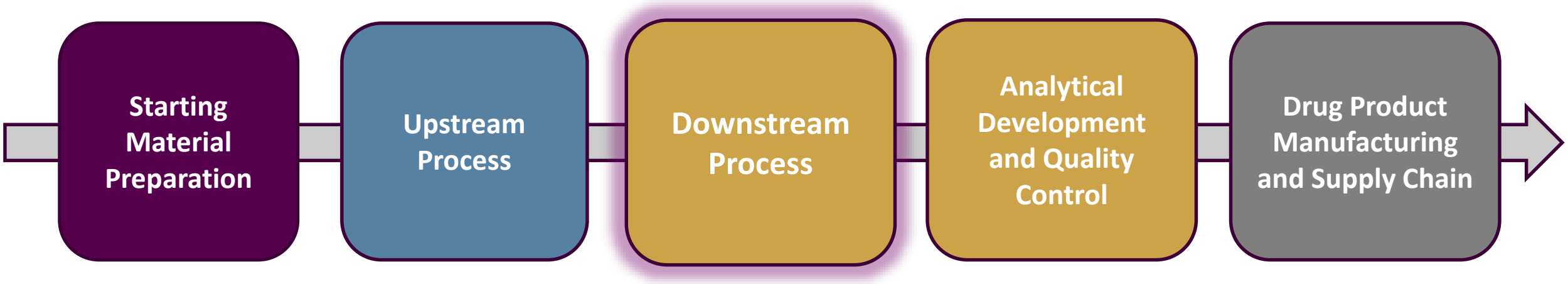
PD is working internally & with our partners to develop robust fixed-bed & "single-cell" suspension BRX production platforms!

SUMMARY OF UPSTREAM CHALLENGES/CONSIDERATIONS

Upstream Process

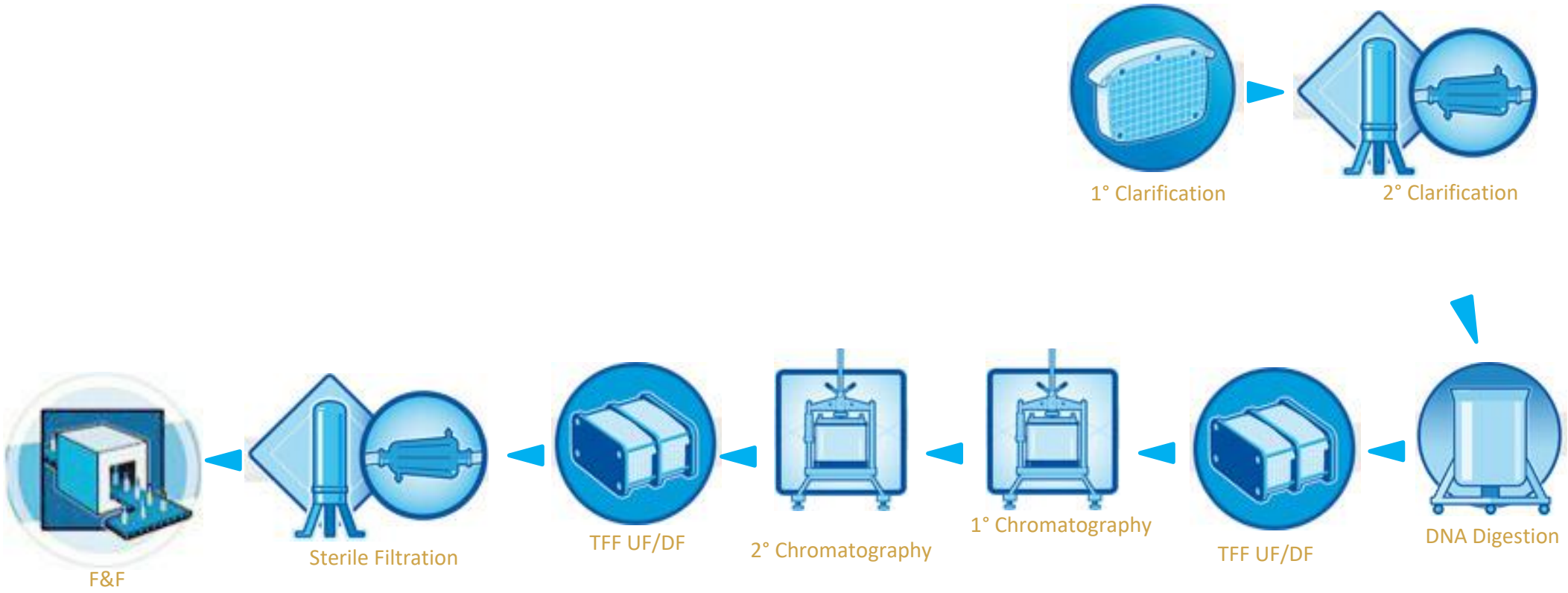
Step	Consideration
Plasmid transfection	2X or 3X system, Producers cell lines
X-fection optimization	Plasmid to plasmid ratio, total DNA to cell ratio, choice of reagent, etc.
Cell culture / virus production	2D adherent vs. “3D” vs. (Single cell) Suspension
Media	Animal-derived components (ADC) vs. animal free (AFC) vs. chemically defined (CD)
Lysis method	Chemical (detergent) vs. Physical

KEY CONSIDERATIONS BY PHASE



“DOWNSTREAM” AAV MANUFACTURING PROCESS

Downstream Process



ESTABLISHING & OPTIMIZING A ROBUST DOWNSTREAM PROCESS IS CRITICAL TO ENSURING PRODUCT QUALITY

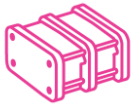
Downstream Process

Capture Step

- Separates product from "crude" harvest broth
- Reduces process-related impurities (e.g. host cell proteins)

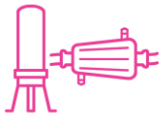
Polishing Step

- Reduces product-related impurities (e.g. "empty AAV capsids")
- Further reduces process-related impurities



TFF for Concentration & Final Formulation

- Concentrates DS to final dose level
- Buffer exchanges DS pool into proper formulation solution



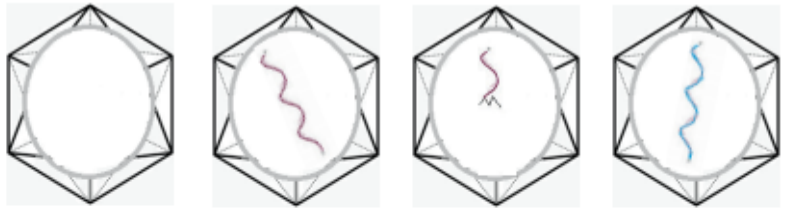
Sterile Filtration

- Patient safety step to eliminate any potential microbial contamination

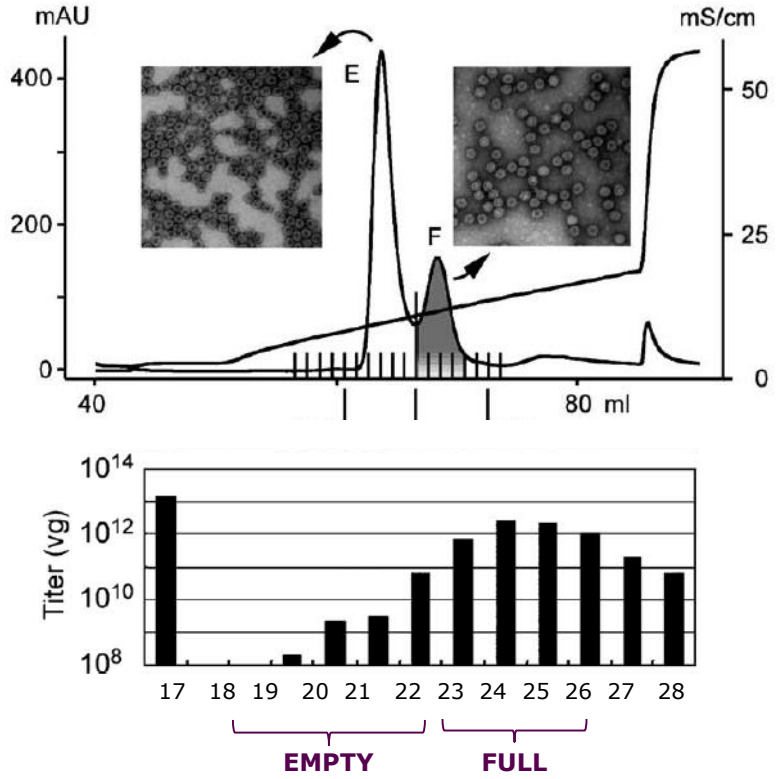
Overall product recovery for many AAV downstream processes can be low and sufficient process development will improve the situation

SEPARATING "INCOMPLETE" VIRAL PARTICLES REMAINS A SIGNIFICANT DOWNSTREAM CHALLENGE FOR AAV PRODUCERS

Downstream Process



A high percentage of capsids may contain no genetic material at all, and would be termed "empty" capsids. Additionally, capsids have been shown to contain incomplete portions or fragments of the transgene-coding DNA, or even non-target, extraneous nucleic acid contaminants[2,3].



Removal of Empty Capsids from Type 1 Adeno-Associated Virus Vector Stocks by Anion-Exchange Chromatography Potentiates Transgene Expression

Masashi Urabe,[1,*] Ke-Qin Xin,[2] Yoko Obara,[1] Takayo Nakakura,[1] Hiroaki Mizukami,[1] Akihiro Kume,[1] Kenji Okuda,[2] and Keiya Ozawa[1]

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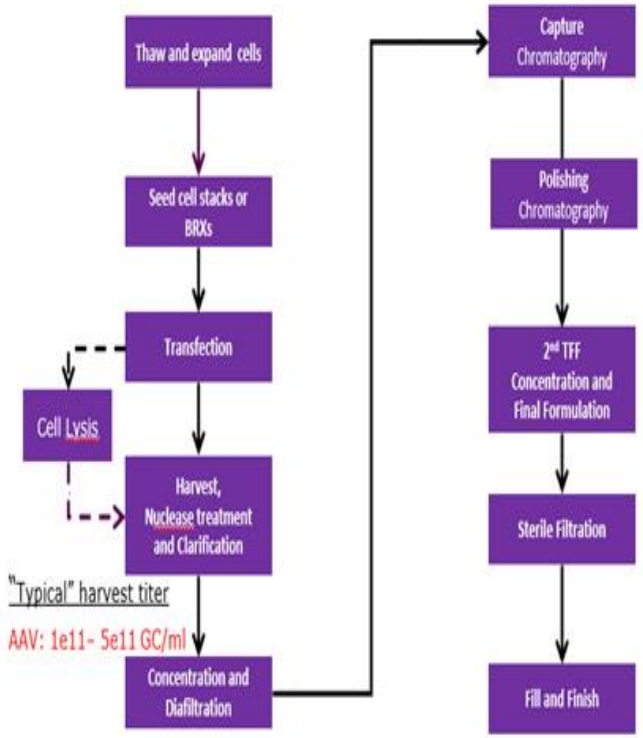
1525-0016/$30.00

SUMMARY OF DOWNSTREAM CHALLENGES/CONSIDERATIONS

Downstream Process

Step	Consideration
Chromatography configuration	One, two, or three-column process(es)
Overall configuration	Impurity removal capabilities vs. maximized step recoveries

SUMMARY OF THE MOST SIGNIFICANT CONSIDERATIONS FOR AAV PRODUCTION

Processing challenge	Sarepta's approach	Key takeaways for this section of the module	Overall DS Process summary
Upstream: Yield (overall process capability) **Downstream: Purity (enhanced impurity clearance)**	Evaluate and implement the iCELLis fixed-bed BRX platform to increase virus production Design and implement a chromatography-based purification strategy	Improved productivites will help meet long-term demand more robustly Robustly clearing process & product–related impurities while maximizing product recovery represents the "holy grail" of AAV purification.	

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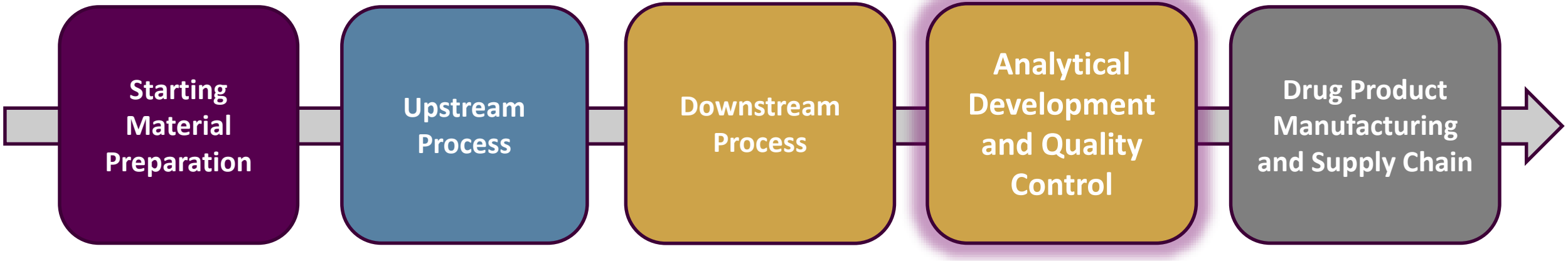


LIKE ALL OTHER ASPECTS OF PRODUCTION, ASSESSING QUALITY OF GT PRODUCTS IS ALSO CHALLENGING

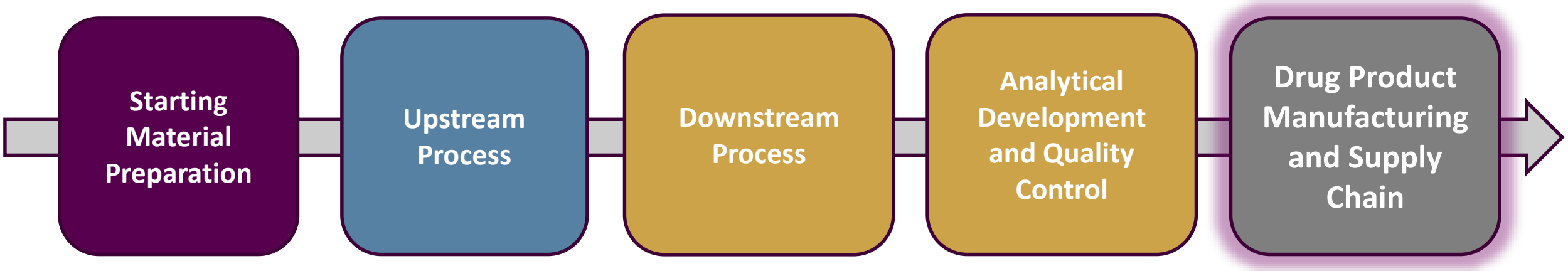
Analytical Development and Quality Control

Quality	Attribute	Technique
Identity	Confirm presence and identity of viral vector	SDS-PAGE, Mass spectrometry (MS), Western blot (immunoblot), Genome sequencing (NGS), PCR
Potency	Physical viral titer	DNA hybridization, Real-time PCR (qPCR, ddPCR), Optical density ($A_{260/280}$), NanoSight, HPLC
	Functional viral titer	Plaque-forming assay, Fluorescence foci assay, $TCID_{50}$ (end point dilution assay)
Purity	Process-related impurities	MS, Chromatography, TEM
	Host cell-related Impurities	Host cell DNA/RNA: Picogreen, DNA Threshold assay, qPCR, Host cell proteins: ELISA,TEM
	Capsid content (empty: full capsids)	TEM, AUC
Safety	Sterility	Standard sterility tests (EP 2.6.1, USP71)
	Endotoxin	LAL method (EP 2.6.14, USP85), Rabbit pyrogen assay
	Mycoplasma	PCR, Cell cultured based-assays
	Replication Competent Virus (presence of *rep* or *cap* sequences)	Southern blotting, qPCR
	Adventitious Agents	*In vivo* and *in vitro* assays
Stability	pH	Potentiometry
	Osmolality	Osmometry
	Aggregate formation	Light microscopy, DLS, SEC-MALS, TEM, AUC, FFF-MALS

Challenges:

- Lack of established standards
- Lack of well-established fail/pass criteria from regulators
- Some assays are low-throughput
- Some assays depend on project-specific cells or animals

KEY CONSIDERATIONS BY PHASE



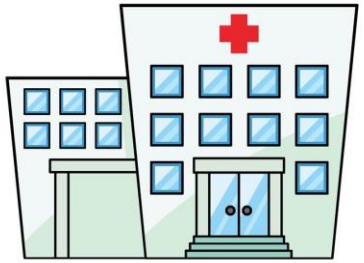
GENE THERAPY DRUG PRODUCT RESPONSIBILITIES

Drug Product Manufacturing and Supply Chain

- Manage the tech transfer and production of the gene therapy Drug Product
- Oversee drug product formulation development
- In collaboration with QC/Analytical, provide support for stability testing and compatibility studies
- In collaboration with other key stakeholders (Clinical, Commercial, Regulatory, etc.) select the final clinical/commercial container closure components to support each individual gene therapy drug product
  - Considerations:
    - Material (Glass vs. Plastic)
    - Vial size and fill volume
    - Ability to handle low temperatures for storage and transport
    - Vial types supported at CMOs or other Fill/Finish Facilities
- Characterize final container closure components through
  - Dimensional Analysis
  - Container Closure Integrity
  - Extractables and Leachables testing
- Assess CMO capabilities to support gene therapy drug product fill/finish

MOVEMENT & STORAGE OF GT DRUG PRODUCT IS MANAGED CAREFULLY THROUGHOUT THE COMPLEX SUPPLY CHAIN

Drug Product Manufacturing and Supply Chain



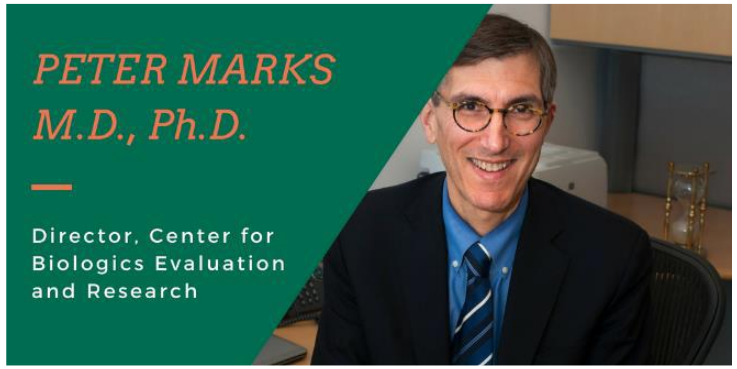
Raw Materials (Plasmids and Cell Banks) → Manufacture and Release of Drug Product → Packaging and Labeling → Transport and Storage of Frozen Drug Product → Distribution of Drug Product → Delivery to Clinic/Patient

GENE THERAPY – A PARADIGM SHIFT

In contrast to traditional drug review, where 80% of the review is focused on the clinical portion and 20% is focused on the product issues, this ***principal is almost completely inverted when it comes to cell and gene therapy****.*

Pharmaceutical manufacturing paradigm of supporting early-stage development with drug produced through a pilot process before graduating to a commercial process for late-stage development and marketing does not fit the realities of gene therapies.

Manufacturing is likely to be the rate limiter for regulatory approval - The 'Process' is the 'Product'



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ICH
harmonisation for better health

pmda

SAREPTA THERAPEUTICS

SAREPTA'S STRATEGY

TO MEET THESE CHALLENGES HEAD-ON, SAREPTA IS ASSEMBLING THE RIGHT TEAM AT THE RIGHT TIME

Discovery

Quality Assurance

Process Development

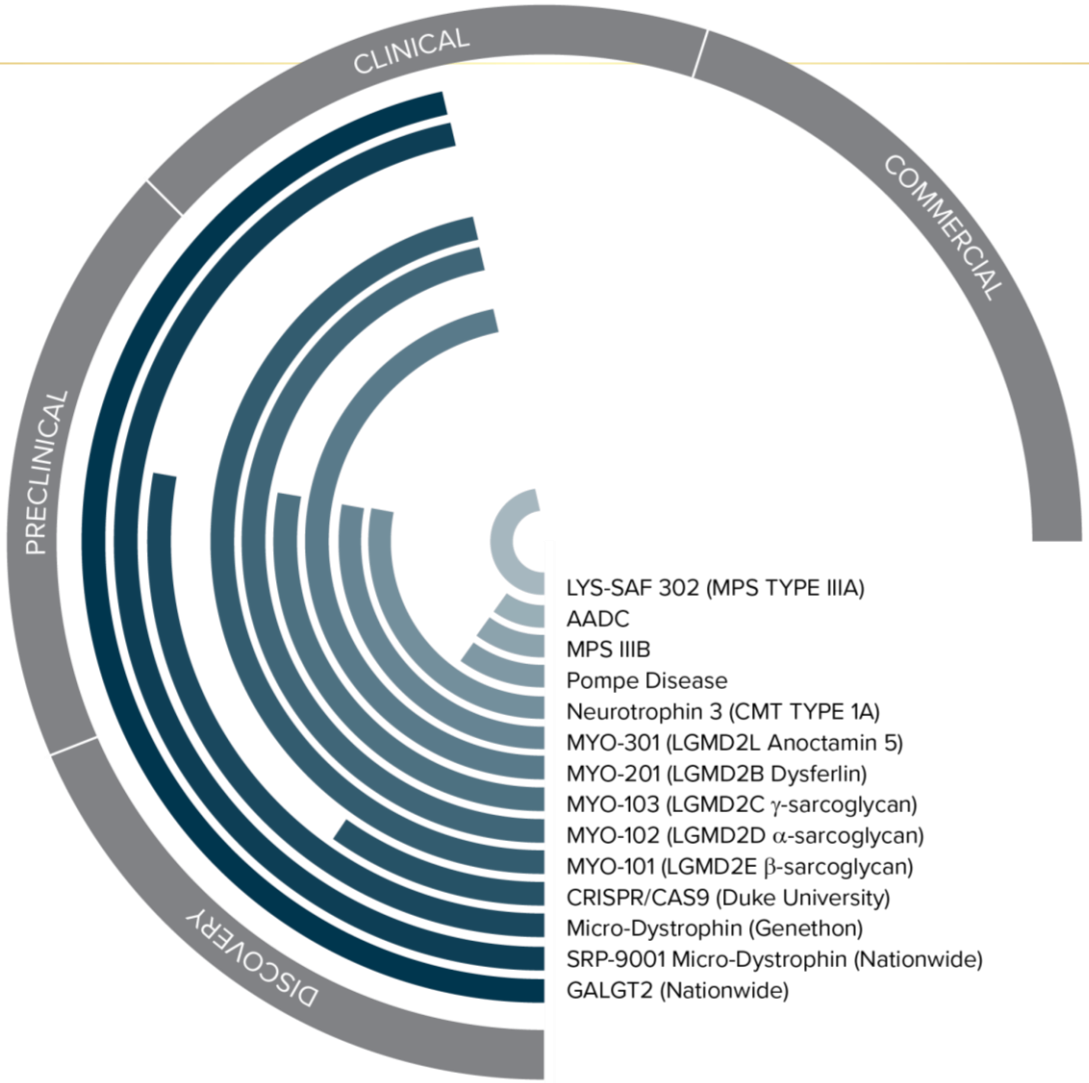
Drug Product

Analytical Development/
Quality Control

Supply Chain

Manufacturing expertise has been gathered relative to all aspects of AAV-based gene therapy manufacturing, leveraging its extensive disease biology expertise in DMD and broad portfolio

DEEP GENE THERAPY PIPELINE

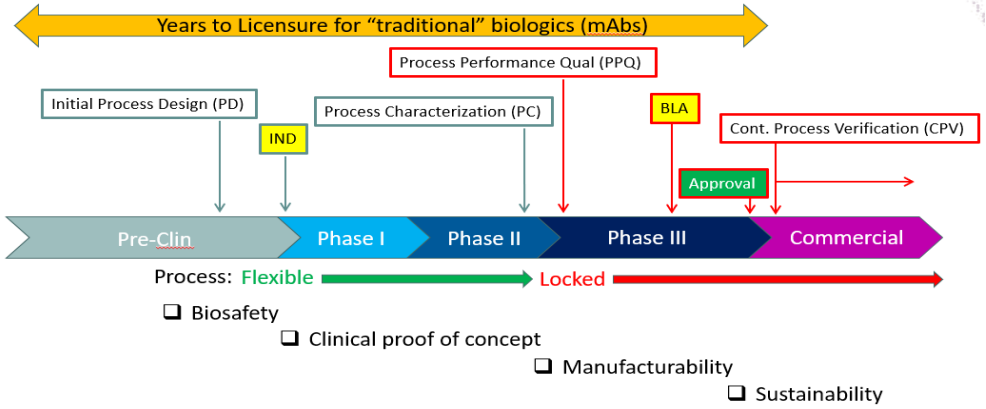


SAREPTA THERAPEUTICS

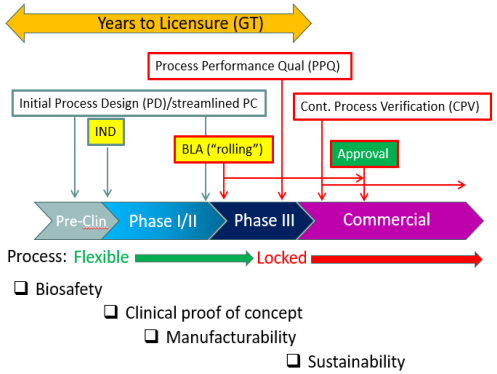
HYBRID STRATEGY AND CASE-BY-CASE APPROACH

Historical Biologics Lifecycle Models No Longer Apply for GT Innovators

- ✓ What once took 10+ years from conception to approval is now being done in less than half that
  - Sarepta is building the internal expertise to ensure our place as thought leaders in this evolving space
  - In parallel, partnering with external thought leaders to strengthen expertise in areas of development and manufacturing capacity
  - Because of pipeline, adopt case by case approach for process



- ✓ Our focus on innovation includes upstream, downstream, & analytical examples
  - Upstream approaches include evaluations of several different configurations
  - Likewise innovative purification methods are also being studied



Sarepta continues to build an impressive gene therapy portfolio so speed & precision are essential to achieving our ambitious goals

HYBRID STRATEGY- EXTERNAL THOUGHT LEADERS COMPLEMENT OUR INTERNAL EXPERTISE

GENERAL FOUNDATIONS OF CMC READINESS FOR SUBMISSION

- **Supply Strategy-** Develop Options based on CMO performance, yield and demand

- **Control Strategy-** Develop defendable positions to meet regulatory requirements
  - Plasmid, DS, DP and FGs
  - Data expectations for various health authority interactions and alignment on submission strategy
  - Process and analytical validation plan is in place, and can support commercial supply needs and launch readiness
  - Specification strategy is in place and plan for commercial spec
  - Release testing plan is in place for late stage and commercial
  - Acceptable expiry of material via suitable stability plan (primary and supporting data) to enable access (may vary for regions)

- **LPD/3PL Readiness**
  - LPD strategy for late stage is in place
  - Cold chain shipping validation is in place
  - Team is ready to support blinding/placebo strategy

- **Inspection Readiness**
  - Regulatory inspection from various zones are considered
  - Identify and establish quality documentation needs internally and at CMOs/CTOs
  - Perform risk analysis and mock audits across supply chain

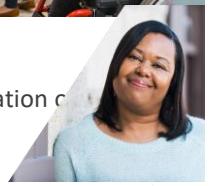
EXAMPLES OF CRITICAL ISSUES AND READINESS FOR LATE STAGE AND COMMERCIAL

Step	Considerations
Stability	What is an optimum expiry? When process is locked, can one use late stage clinical stability as primary stability?
PPQ	In a scale out model, how is PPQ designed to cover for upstream/downstream?
Commercial Specifications	How does the clinical batches help in setting up proposed commercial spec?
Change Control	What changes trigger comparability considerations?
Drug Product	What is the strategy for DP validation?
Potency Assay	In vitro mechanism based models?
Critical Quality Parameters	Case-by-case analysis

MANUFACTURING FOR TODAY AND THE FUTURE….

DUCHENNE MUSCULAR DYSTROPHY (DMD)[1,2]	▪ Affects 1 in 3,500-5,000 males born worldwide ▪ Rare, progressive neuromuscular genetic disease; 100% fatal; ~400 deaths per year in the U.S. ▪ Average lifespan of mid- to late-20s; typical diagnosis occurs between ages 4-5 ▪ Caused by genetic mutation that encodes dystrophin, a protein that exists in infinitesimally small amounts in the body (0.002 percent of muscle), but plays a key structural role in muscle fiber production ▪ Even small amounts of dystrophin production have shown significant benefits (Example: exon 44 amenable individuals)
LIMB-GIRDLE MUSCULAR DYSTROPHY (LGMD)[3,4]	▪ Autosomal recessive, monogenic, rare neuromuscular diseases that affect thousands globally ▪ LGMDs are progressive, debilitating muscle-wasting diseases with no therapies, caused by missense and deletion mutations ▪ Affect males and females equally; death can result by age 30 ▪ Affect skeletal muscle and cardiac muscle in some types ▪ Symptoms often develop before age 10; loss of ambulation often in early teens ▪ More severe forms mimic DMD ▪ Consistent disease progression within each LGMD subtype
POMPE DISEASE (CNS DISORDERS)[5]	▪ Caused by mutation in the gene that codes for the enzyme acid alpha-glucosidase (GAA), responsible for metabolizing glycogen in lysosomes ▪ Mutation causes buildup of glycogen in the body's cells, which in certain organs and tissues, especially muscles, impairs ability to function normally ▪ Progressive and often debilitating, disables the heart and skeletal muscles with muscle weakness worsening over time ▪ Affects both sexes equally and often fatal ▪ Early onset (or infantile form); late onset (or juvenile/adult)
CHARCOT-MARIE-TOOTH DISEASE (CMT)	▪ Inherited, heterogeneous group of peripheral nerve disorders affecting 1 in 2,500 persons ▪ Caused by mutations in genes that produce proteins involved in the structure and function of either the peripheral nerve axon or the myelin sheath ▪ Degeneration of motor nerves results in muscle weakness and atrophy in the extremities (arms, legs, hands, or feet), and in some cases the degeneration o sensory nerves results in a reduced ability to feel heat, cold, and pain ▪ Most patients are diagnosed at infancy, while other patients develop symptoms at adolescence
MUCOPOLYSACCHARIDOSIS TYPE IIIA (MPS IIIA)	▪ MPS IIIA is a rare inherited neurodegenerative lysosomal storage disorder characterized by intractable behavioral problems and developmental regression resulti in early death ▪ MPS IIIA affects about 1 in 100,000 newborns and is inherited in an autosomal recessive pattern; and there are currently no treatment options for patients ▪ Caused by mutations in the SGSH gene, which encodes an enzyme called Heparan-N-sulfamidase necessary for heparan sulfate (HS) recycling in cells ▪ The disrupted lysosomal degradation and resulting storage of HS and glycolipids such as gangliosides leads to severe neurodegeneration




1. Emery AE, Population frequencies of inherited neuromuscular diseases—a world survey. Neuromuscul Disord.; 2. 1991;1(1):19–29pmid Emery AE. The muscular dystrophies. BMJ. 1998;317(7164):991-995; 3. www.nih.gov; 4. www.mda.org/disease/limb-girdle-muscular-dystrophy/causes-inheritance; 5. www.nih.gov

SAREPTA THERAPEUTICS

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SETTING THE STANDARD IN GENE THERAPY MANUFACTURING

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