SINGLE USE SOLUTIONS FOR OVERCOMING CHALLENGES ASSOCIATED WITH MANUFACTURING AND COMMERCIALIZATION OF CELL AND GENE THERAPY PRODUCTS

Tim Korwan
Director, New Product Development

avantor™

Disclaimer

This presentation has been prepared by Avantor Funding, Inc. (“Avantor or the “Company”) for the exclusive use of the recipient hereof (the “Recipient”).

This information presented herein is intended as a general overview only. This information may not apply or be accurate or complete in all circumstances or to any specific purchaser’s or user’s applications or needs. All purchasers and users should conduct their own testing and regulatory review to satisfy themselves as to the adequacy and appropriateness of these materials for their specific needs and uses, as well as with respect to regulatory requirements and compliance requirements.

Although the Company believes the information doe not, when taken as a whole, contain any untrue statement of material fact or omit to state a material fact necessary in order to make the statements contained herein not materially misleading in light of the circumstances under which such statements are made, the Company does not make any representation, warranty or undertaking either expressed or implied, as to the accuracy, completeness or reliability of the information contained in this presentation. Any estimates or projections contained in this presentation as to events that may occur in the future (including projections of future financial performance and forward looking statements) were prepared in good faith and based upon assumptions that the Company believed to be reasonable at the time presented.

The presentation may include certain forward-looking statements and projections provided by the Company. Any such statements and projections reflect various estimates and assumptions by the Company concerning anticipated results, believed by the Company to be reasonable at the time made and not to be viewed as facts.

No representations or warranties are made by the Company as to the accuracy or reliability of any such statements or projections. Whether or not any such forward looking statements or projections are in fact achieved is subject to significant uncertainties and contingencies, many of which are beyond the control of the Company. Accordingly, no assurance can be given that any particular projection will be realized and actual results during the period or periods covered by any such projections may differ significantly from the projected results and such differences may be material. Statements contained herein describing documents and agreements are summaries only and such summaries are qualified in their entirety by reference to such documents and agreements.

Nothing contained herein is, or shall be relied upon as, a promise or representation as to the past or future. The Company expressly disclaims any and all liability relating to or resulting from the use of this presentation. In addition, the information contained in this presentation is as of the date hereof, and the Company has no obligation to update or supplement such information or otherwise provide additional information, including in the event that such information becomes accurate.

CAR-T: An exciting development to treat cancer

2 Approved drugs

500+ Companies in cell therapy pipeline globally

650+ Active clinical trials

$15B Expected revenue by 2024

The New York Times

In Girl's Last Hope, Altered Immune Cells Beat Leukemia

Emily Whitehead, with her mother, Kari. Emily was near death in 2011 from acute lymphoblastic leukemia but is now cancer free after undergoing treatment with CAR-T.

Global & regional expansion strategy; classic Pharma play to increase pipeline value

2018

Approvals

Spark (Roche)	LUXTURNA	Gene therapy for RPE65 inherited retinal disease
Novartis	KYMRIAH	Second indication (diffuse large B-cell lymphoma) European approval for DLBCL and pediatric ALL, Canadian approval for pediatric ALL & adult DLBCL, Australian approval for pediatric ALL and adult DLBCL
TiGenix (Takeda)	ALOFISEL	Allogenic stem cell therapy for Chron's fistulas (European MA)

2019

Approvals

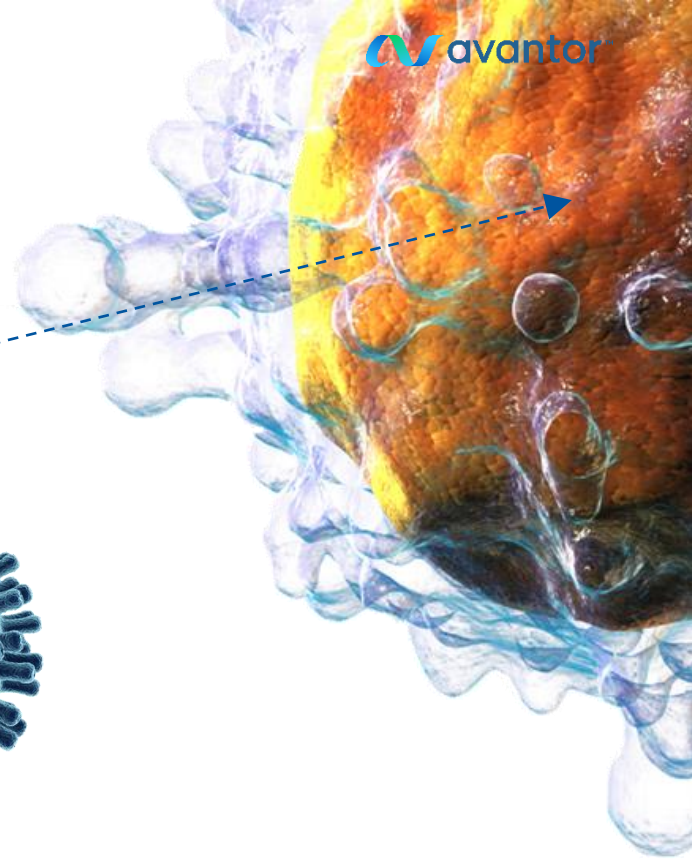
Novartis	KYMIRIAH	KYMRIAH Japan approval for pediatric ALL & adult DLBCL
Kite (Gilead)	YESCARTA	Canada approval for rrLBCL
Avexis Novartis	Zolgensma	Pediatric gene therapy for spinal muscular atrophy (SMA)

Q1-2019 Revenues

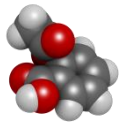
Kite (Gilead)	YESCARTA	> $96M > 1500 patients to date > 75 centers US > 25 centers EU
Novartis	KYMRIAH	> $45M > CMS recommend reimbursement coverage with evidence development

Drug development

As complexity increases, drugs are being defined by the process – not the product



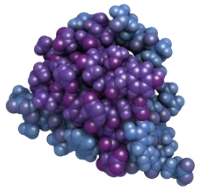
INCREASING SIZE & COMPLEXITY



ASPIRIN
180 daltons
21 atoms

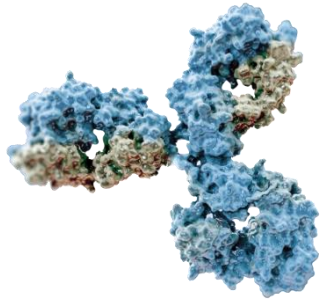
1800's…

Small Molecule



INSULIN
~5,700 daltons
777 atoms

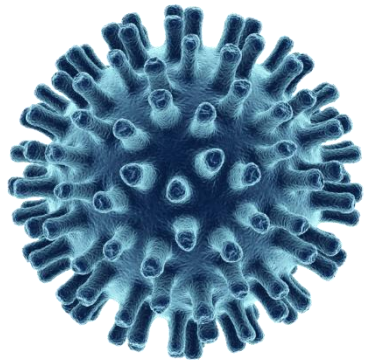
1920's…



MONOCLONAL ANTIBODIES
~150,000 daltons
~25,000 atoms

1990's …

Large Molecule



LENTIVIRUS

T-CELL

21st Century

Cell & Gene Therapy

Challenges

> …In contrast to traditional drug review, some of the more challenging questions when it comes to gene therapy relate to product manufacturing and quality, or questions about the durability of response, which often can't be fully answered in any reasonably sized pre-market trials…
>
> – Scott Gottlieb. M.D., Commissioner of FDA on Agency's efforts to advance development of gene therapies
>
> July 11, 2018

5 Key focus areas for cell & gene therapy manufacturing

Biological Risk Reduction
- > Raw material safety (Biohazard)
- > Virus replication competency

Cost Reduction
- > Process risk reduction
- > Move to allogeneic models
- > Virus out-sourcing & technology improvements

Regulatory Clarity
- > Harmonization of EU and FDA guidelines
- > Guidance on product safety & medical devices
- > Accelerated submissions (BLA & CMC)
- > GMP oversight for C&GTx production

System risks
- > Automated & closed systems
- > Raw material consistency

Workflow
- > Raw material efficiencies
  - – Smaller pack sizes
  - – Liquids (FBS) packed in bags (delivery system)
  - – Cleanroom considerations
- > COC / COI
- > Freeze / Transport / Thaw Systems & Logistics

Industry insights

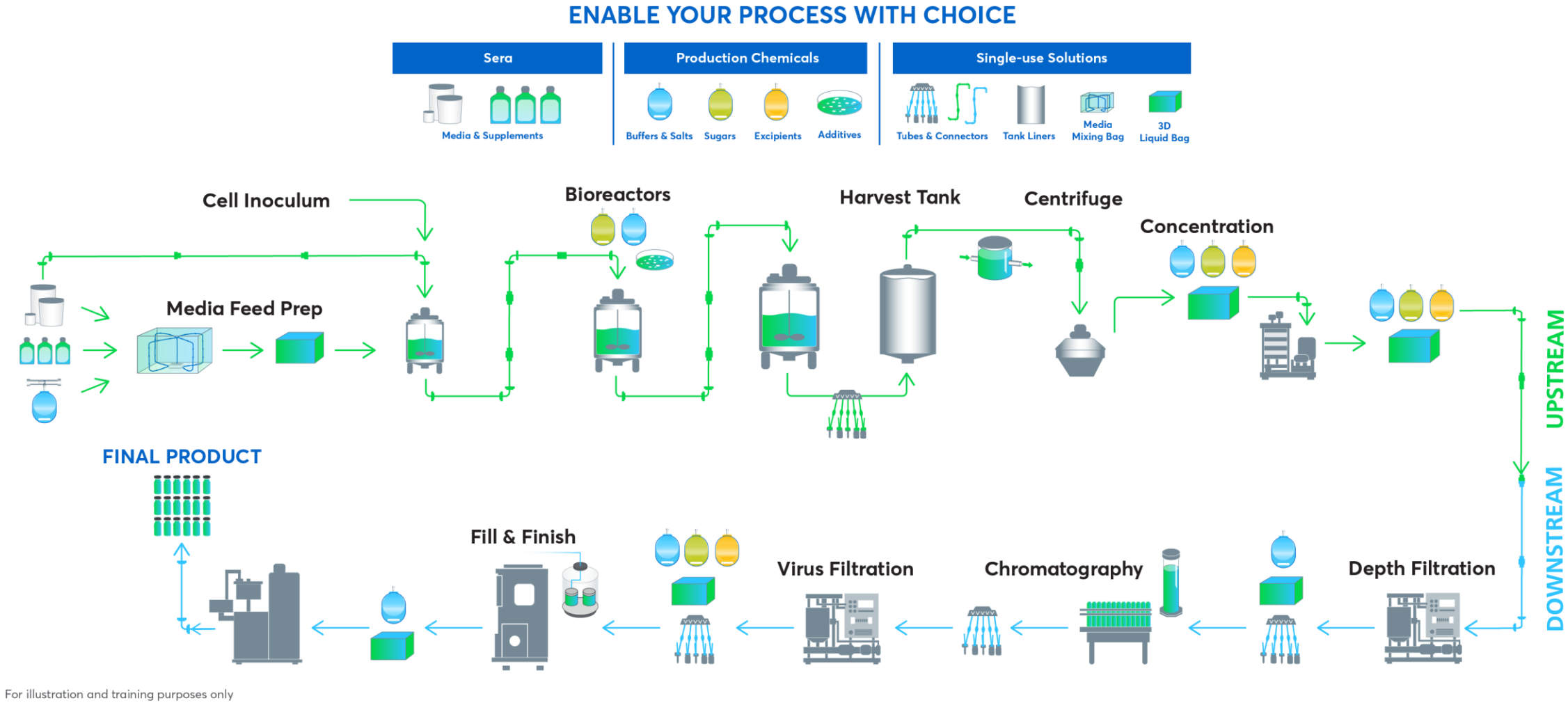
"Your process is your product, because there is no final filtration, reducing risk through closed system solutions and only using GMP grade raw materials will be critical to our success"

"One of our greatest concerns is security of supply of critical materials, we're having to over-order to have these critical supplies on hand"

"As a CDMO we're struggling with early phase developers that are using Non-GMP grade raw materials, resulting in time loss during tech transfer"

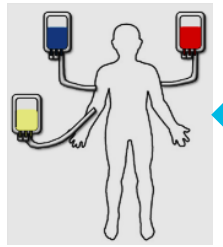
"We only have a limited volume to work with, minimizing sample volumes would increase our yields"

Typical process schematic – Biopharma manufacturing



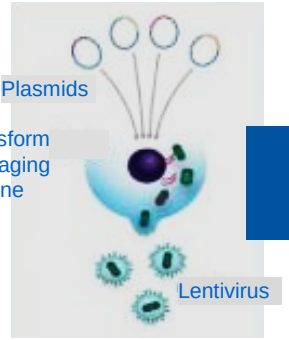
For illustration and training purposes only

CAR-T process overview and vector production



CAR-T Cell Process

- **Extract T-cells**
- **Send to manufacturing facility and activate**
  - **Flexible solutions** Single Use sterile fluid transfer … increased security
- **Cells expanded ex vivo**
  - **Cell culture components** Cell Therapy characterized & specified
- **CAR T-cells are transfused back into the patient**
  - **High-purity customized excipients** supporting stability & shelf life

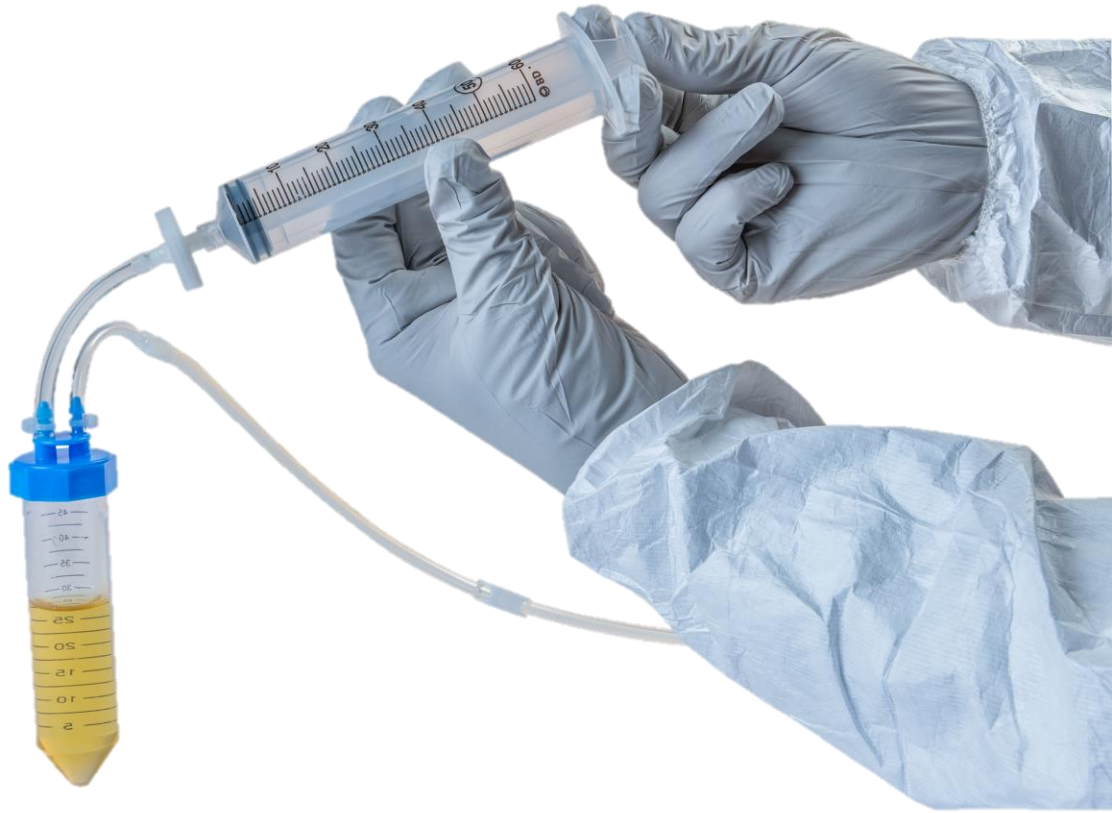


Viral Vector Manufacturing

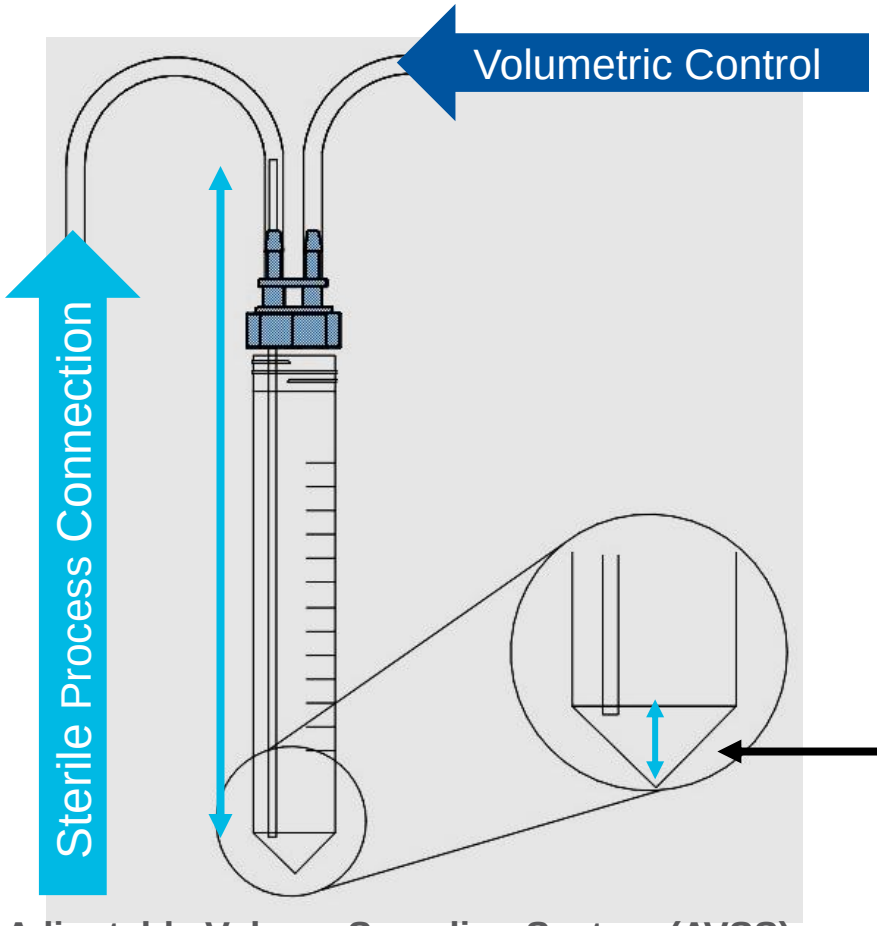
- **Vector Amplification**
  - **Cell culture components** characterized & specified
- **Vector Expansion**
- **Purification**
  - **Production chemicals** specified for customers' processes
- **Fill & Finish**
- **Virus w/ therapeutic payload**
  - **Flexible solutions** Single Use sterile fluid transfer… increased security

Closed system transfer solutions

Open Process = Contamination Risks



Exact volume sampling in a cell & gene therapy process Step 1



Adjustable Volume Sampling System (AVSS)
Patent Pending

Diptube is adjusted to the desired sample volume

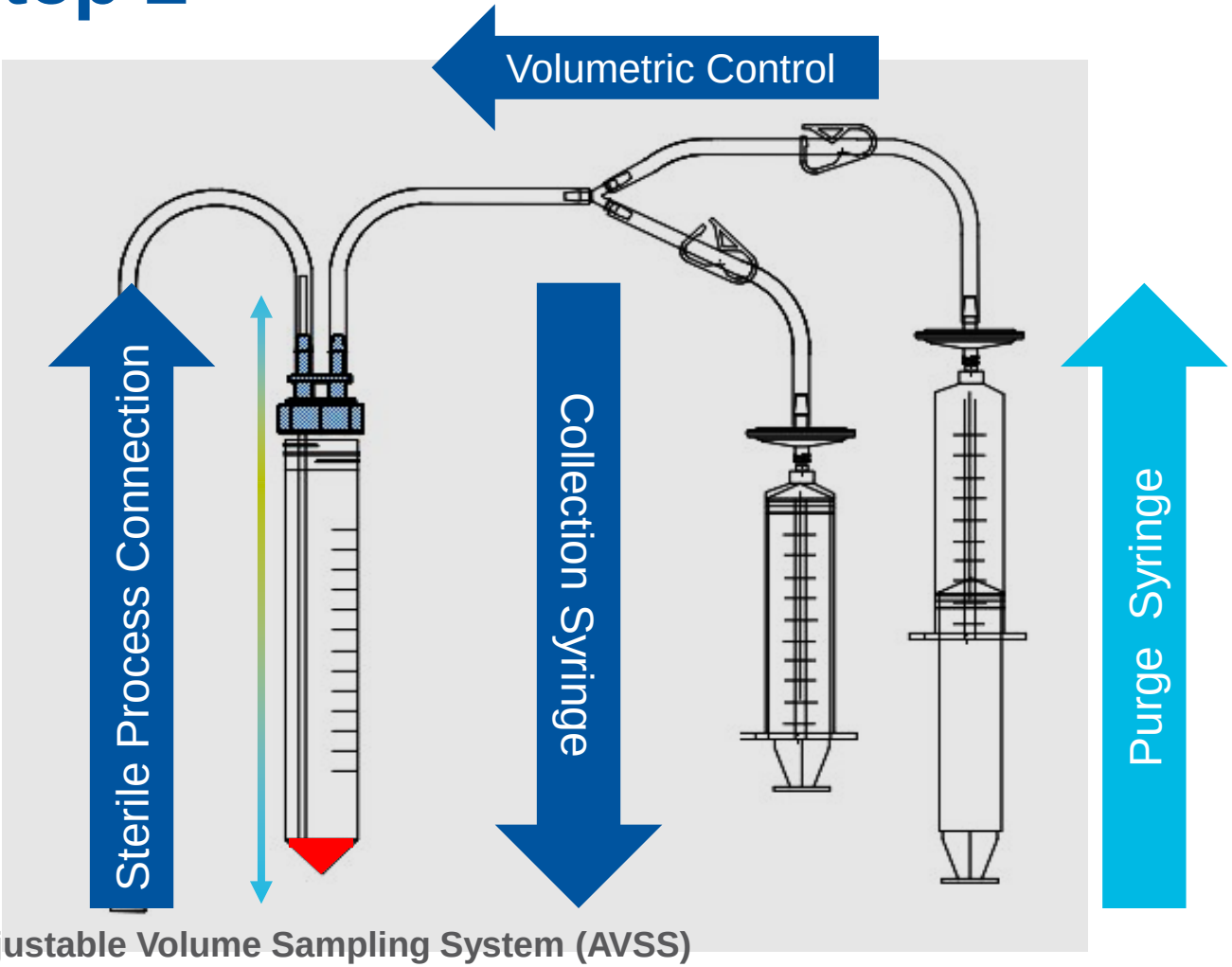
Challenge

- C&GT process volumes are small and finite.
- Reducing sample volumes and eliminating line losses between sample times can greatly increase product yields.

Exact volume sampling

- OmniTop Sample tubes 15mL
- Diptube can be adjusted in-situ to the exact sample volume 0.1mL to 15mL
- Remove the use of open processes and the biological safety cabinet.

Exact volume sampling in a cell & gene therapy process Step 2



Adjustable Volume Sampling System (AVSS)
Patent Pending

Collection – STEP 2A

> System has two pre-attached syringes that are sterilized with the sample collection vessel.
> Retracting the plunger on the collection syringe pulls the sample volume into the OmniTop vessel. Overfill is OK.

Purge – STEP 2B

> Using the purge syringe add sterile filtered air to the OmniTop.
> This will drive excess volume to the exact sample volume and clear the line back to the origin vessel.
> Sample can be removed for analytical analysis.

Personalized solutions – Pre-formulated buffers & sterile solutions in single-use assemblies

Customized solutions offer a efficient path from research to commercialization while reducing risk and enhancing quality

1 Streamline workflow at any scale

> Sterile single-use bags filled to exact volume
> Customer-defined performance characteristics
> Wide variety of formulation capabilities; apply to your process from cell culture to fill & finish

2 Reduce risk

> Convert critical-to-quality steps of process to a closed system, minimizing contamination risk

3 Stay compliant

> Fully validated, cGMP products

Solution Capabilities

Buffers spanning the production process:

> Cell culture
> Cell expansion
> Lysis
> Disaggregation
> Neutralization
> Sanitization
> Preservation

Avantor single use assemblies:

> Custom fittings to adapt to any process
> Inline testing using patent-pending sampling technology streamlines testing, minimizes losses

cGMP process

> Fully validated production process & testing
> Guaranteed transparency & consistency
> Robust management of change program

Personalized solutions: Pre-formulated buffers & sterile solutions in single-use assemblies

Value Proposition

Streamlined works flow at any scale

> Sterile single-use bags filled to exact volume for cell culture to fill & finish

> Customer-defined application specific performance characteristics

Reduce risk

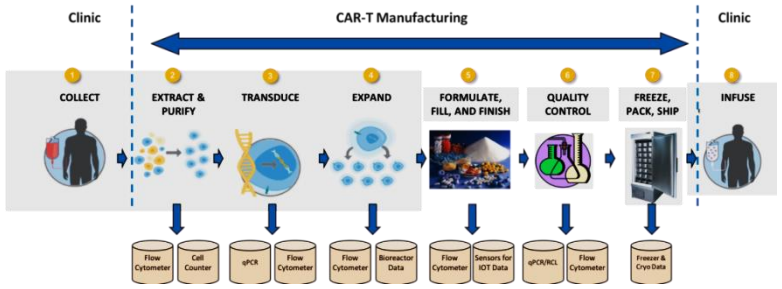
> Convert critical-to-quality steps of process to a closed system, minimizing contamination risk

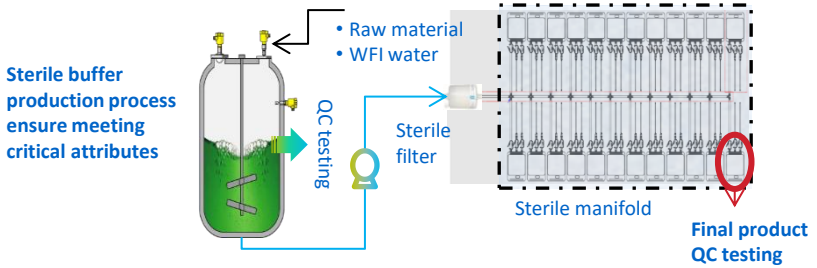
cGMP products

> Fully validated, cGMP products

Process Flow with Avantor Product

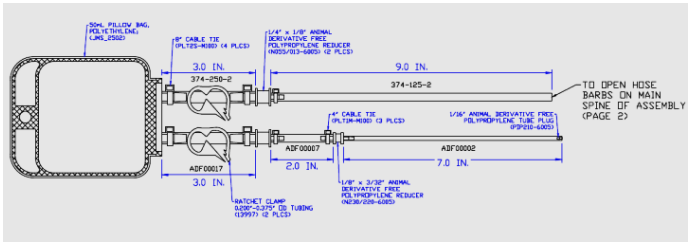
Buffers spanning the CAR-T production process





Final product in single-use

Single use bag (50ml) with cGMP sterile solution allow closing the system and reducing risks



Managing your risk: Quality & regulatory compliance

- Animal origin-free or EMA/410/01 compliant materials
- Sterility validation per ANSI/AAMI/ISO 11137 (VDmax25)
- Sterile barrier shelf-life validation per ANSI/AAMI/ISO 11607
- ISO 11137 sterility validation
- Endotoxin USP <85> and particulate USP <788> lot release testing available
- BPOG standardized extractables testing protocol in use

Summary

Industry at an inflection point … moving from lab scale processes to consistent regulated manufacturing

- Contamination: Significant concern with sample collection, bioprocessing, transport, transfer and storage
- Scalable, pre-formulated single use solutions for viral vector, CAR-T and gene therapy manufacturing to reduce contamination risk
- Personalized formats for media, sterile solutions, excipients, pre-formulated buffers and tailored sampling and transfer technologies

THANK YOU

Tim Korwan
Timothy.Korwan@avantorsciences.com
Director, New Product Development

avantor™