2023 Patient Safety Conference

Overview of Materials and Practices in Cell and Gene Therapy

Raj Shah,
Avantor Global Supplier Quality

Avantor's leading bioproduction solutions

Designed to meet the unique challenges of the industry

Cell culture components characterized & specified for customer scale up
(e.g., J.T.Baker® Media Supplements, Avantor Seradigm Serum)

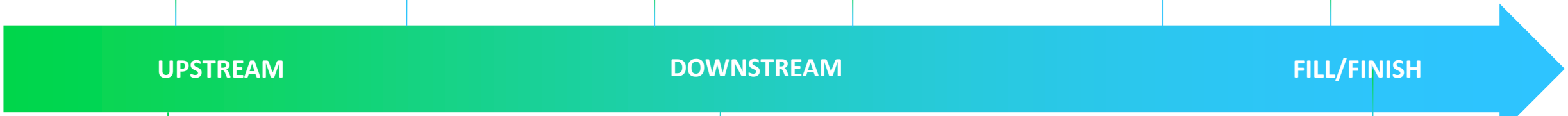
Customized products and solutions
(e.g., hydrated buffer solutions, Direct dispense packaging)

Fluid handling solutions
Single Use assemblies, Masterflex® Peristaltic pumps

cGMP Production chemicals, process ingredients, chromatography resins
specified for customers' processes

Tailored processes and services
(e.g., supply chain data analysis and process optimization services) that cater to complex needs

High-purity customized excipients
supporting drug stability & shelf life



Avantor's solutions specified in **>80% of the top 20** biologic drugs

10 of top 10 biotechs and pharma companies

Downstream buffer product line covers **100% of the traditional buffers packages** used in a biopharmaceutical process

A global network of **cGMP manufacturing and ISO-certified distribution** facilities present on **3 continents**

Formulation product line covers **95% of the excipients** used in commercial mAbs

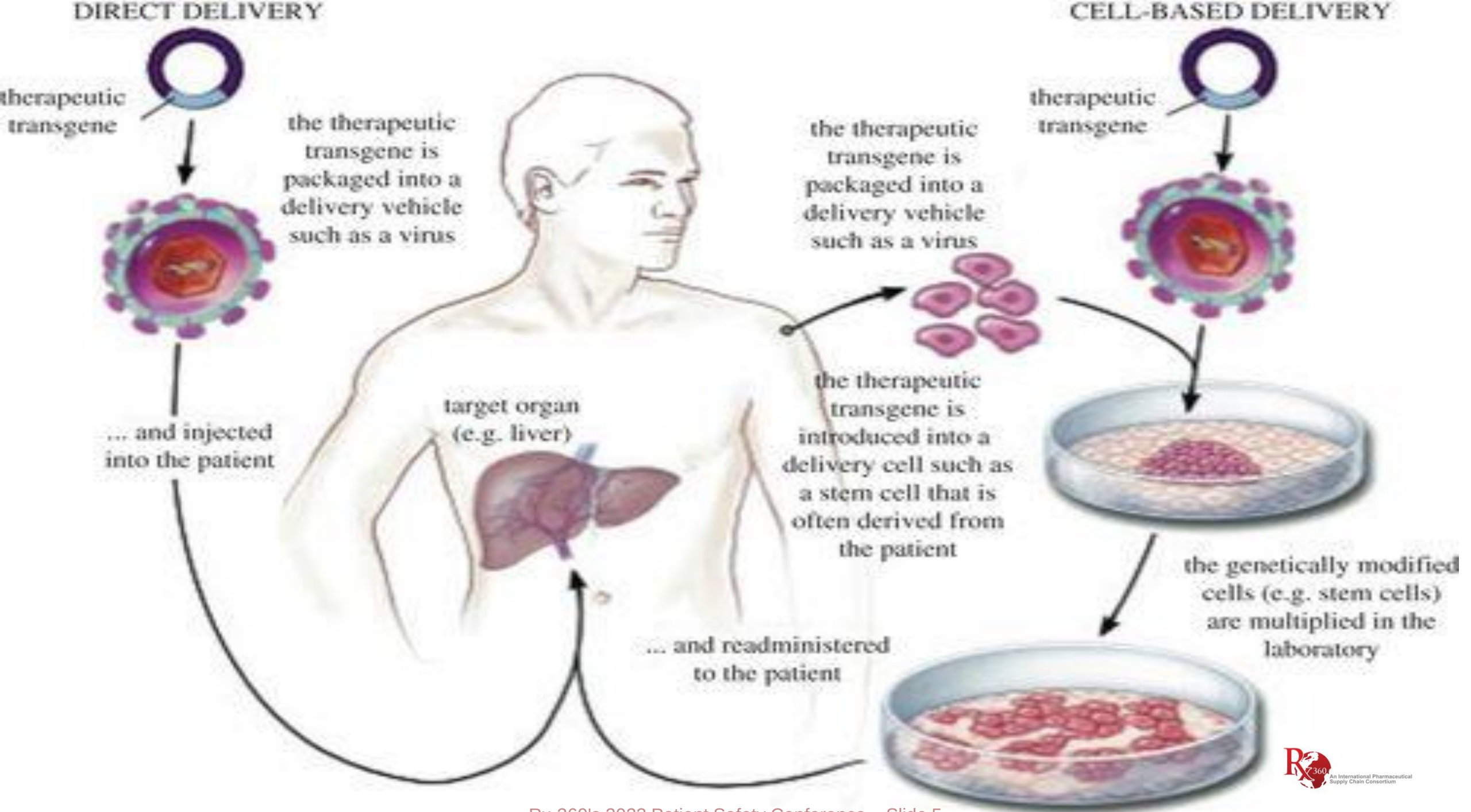
Cell & Gene Therapy Work Group

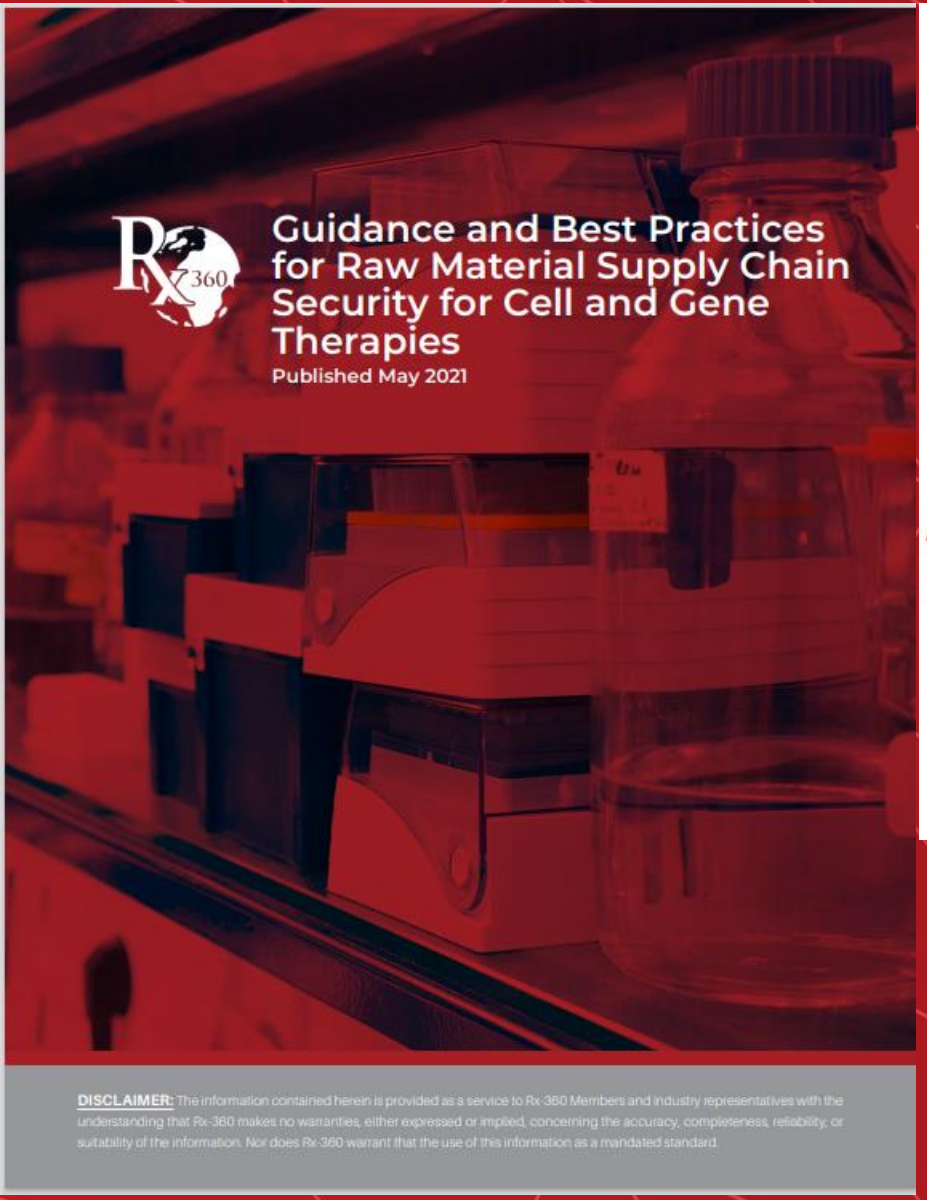
- Member Companies in the Group:

Rx-360 Guidance and Best Practices for Raw Material Supply Chain Security for Cell and Gene Therapies

- Cell and gene therapies (CGT) are novel therapeutic modalities with greater than one thousand clinical trials ongoing globally
- Consistent, safe and cost-efficient manufacturing of cell and gene therapies has been identified as a key challenge in many talks and publications by regulators.
- As the manufacturing processes have limited or no purification, there is a need to mitigate the risk from adventitious agents such as viruses and mycoplasma upstream
- There is a strong focus on the quality and supply of raw materials to mitigate risk to product quality and thereby patient health

The Cell and Gene Therapy Working Group developed a best practice guide to meet regulatory and industry expectations.


DIRECT DELIVERY
therapeutic transgene
the therapeutic transgene is packaged into a delivery vehicle such as a virus
... and injected into the patient
target organ (e.g. liver)
... and readministered to the patient
CELL-BASED DELIVERY
therapeutic transgene
the therapeutic transgene is packaged into a delivery vehicle such as a virus
the therapeutic transgene is introduced into a delivery cell such as a stem cell that is often derived from the patient
the genetically modified cells (e.g. stem cells) are multiplied in the laboratory



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"The new realm of cell and gene therapy drugs has created new challenges in the way raw materials are used in the manufacturing process. This guide outlines the regulatory, quality, safety and supply considerations for raw materials. By looking at raw materials through these attributes, the reader will have a better understanding of what is needed when selecting the raw materials that are used in the manufacturing process and the potential impact on final drug product and the regulatory acceptance."

Manjula Aysola
Sr. Regulatory Consultant PSS, LS Regulatory Management
MilliporeSigma

Summary of White Paper (May 2021)

SCOPE

"US FDA Guidance for Industry: CMC information for human gene therapy investigational new drug applications (January 2020) describes raw materials as: "… reagents (or ancillary materials) are those materials used for manufacturing (e.g. cell growth, differentiation, selection, purification, or other critical manufacturing steps) that are not intended to be part of the final product such as FBS, digestive enzymes (i.e. trypsin, collagenase, Dnase/Rnase, restriction endonucleases), growth factors, cytokines, mAb, antibody-coated beads, antibiotics, media, media components and detergents."

REGULATORY	SAFETY	QUALITY	SUPPLY CHAIN
Intrinsic Risk: chemically defined cell culture medium is lower risk than BSE (MAO). X Intended Use: (product contact is higher risk)	Viral Inactivation / Clearance - Gamma irradiation - Heat inactivation (HTST) - Purification methodologies - pH (5.5 or lower) - Filtration - Detergents	ID Testing Certificates of Analysis (CoAs) Acceptance Criteria (range) Material Qualification Program Stability of Materials & Shelf Life Quality Management System Quality & Change Agreement	Supplier Agreement Duration, Term, & Continuity Order, Shipping, & Delivery Product Inspection & Rejection Price, Payment, and Relationship Raw Material Traceability
PHA / FD&C Act FDA's Inspection Guide on BDP ICH Q5B, Q5D, Q7 chapter 16/18 ICH Q7 + GMP Guide on API Q&A 21 CFR 600 and 820 USFDA Guides for Industry, 2020 USP <85>, <788>, <1125> EMA / Annex I Directive 2001/83 PICS / EC Guidelines INDs: Guides for Industry	Lot Chain of Custody Leachables / Extractables Particulates		

Opportunities

To set up a paper for starting materials such as unmodified patient cells, viral/nonviral vectors, nucleic acid / protein used for gene modification, plasmids, and recombinant proteins (mRNA).

Regulatory

- CGT regulations emphasize on the need to ensure high quality of raw materials
- Key guidance from FDA and EMA is summarized in this section. Guidances globally require
  - Measures to avoid contamination
  - Minimize variability of the raw materials
  - Quality suitable for the intended use
  - Documentation to demonstrate the above

Safety

- Risks to patient safety due to raw material quality are often heightened with cell and gene therapy products due to
  - short shelf-lives
  - reduced or non-existent adventitious agent removal
  - limited ability to conduct extensive in-process and release testing
  - these products may be expanded in vivo after administration to the patient
- A risk-based approach is recommended to characterize raw materials and implement appropriate mitigation steps in accordance with the identified risk. Various criteria for risk assessment summarizing several guidance documents and standards are provided in Appendix A
- Risks due to adventitious agents, extractables and leachables, particulates and other impurities are discussed

Quality

- Quality management and GxP methods ensure that products manufactured are fit for their intended use during the product lifecycle and meet compliance requirements. This is accomplished through the methodical application of controls to ensure consumers are not harmed.
- In the context of raw material quality, these controls are summarized in the sections on
  - Material specifications
  - Certificates of analysis (COA)
  - Material qualification and quality agreements between the drug product manufacturers and their suppliers.
  - QMS

Supply

- Carefully authored supply agreements provide a vehicle to the realization of value across multiple dimensions in your supplier relationships
- Beyond stability in pricing and greater assurance of supply, supply agreements can contribute to compliance, quality, process efficiency, continuous improvement, alignment of expectations, risk reduction, value creation, and early access to innovation
- Appendix C discusses some of the points to consider when developing a supply agreement that can facilitate their negotiation and inspire greater engagement and benefit for both parties.
- A potential model for assisting in the development of a disciplined, documented, and well-structured management process for supplier notifications of change is also presented

Rx-360 Human Blood Origin Materials
Supplier Questionnaire for Advanced Therapy Products

- Human-derived raw materials, or blood-derived products, such as human serum albumin, transferrin, etc. of human or animal origin is not encouraged by regulators due to the inherent risk of transmitting adventitious agents such as viruses, mycoplasms, bacteria and TSE agents, potential for adverse immune reaction, and the potential variability in composition and quality due to their biological origin.

- Human blood origin materials used in cell and gene therapy manufacturing is one type of material where different requirements exist between supplier and therapy manufacturer.

- Each party required their own set of information, so a questionnaire was developed to collect the safety and quality requirements based on EU and US regulations and guidelines as the basis.

The Cell and Gene Therapy Working Group developed a best practice questionnaire to meet regulatory and industry expectations.

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Human Blood Origin Materials for Cell & Gene Therapy Manufacturing Supplier Questionnaire

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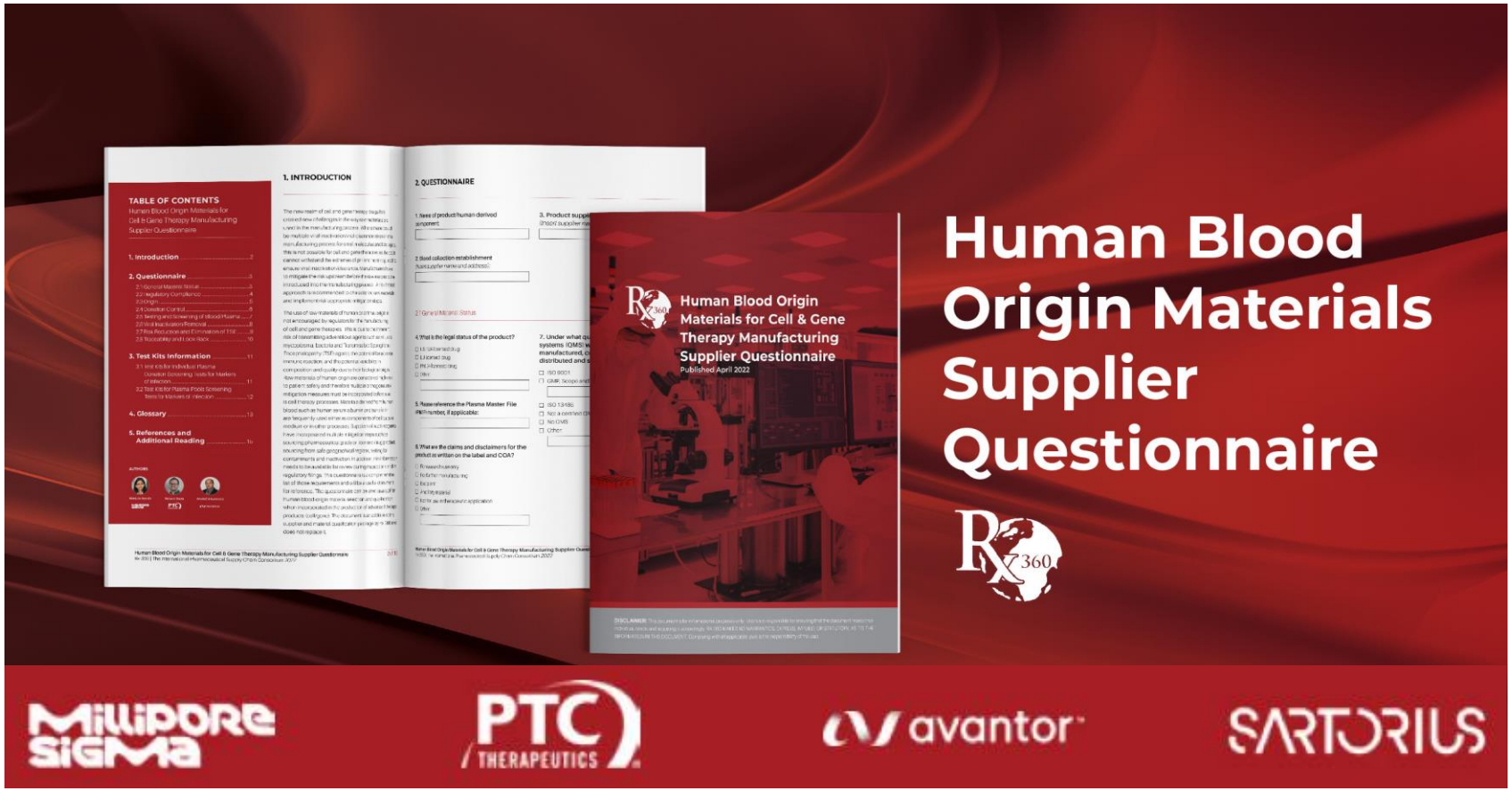

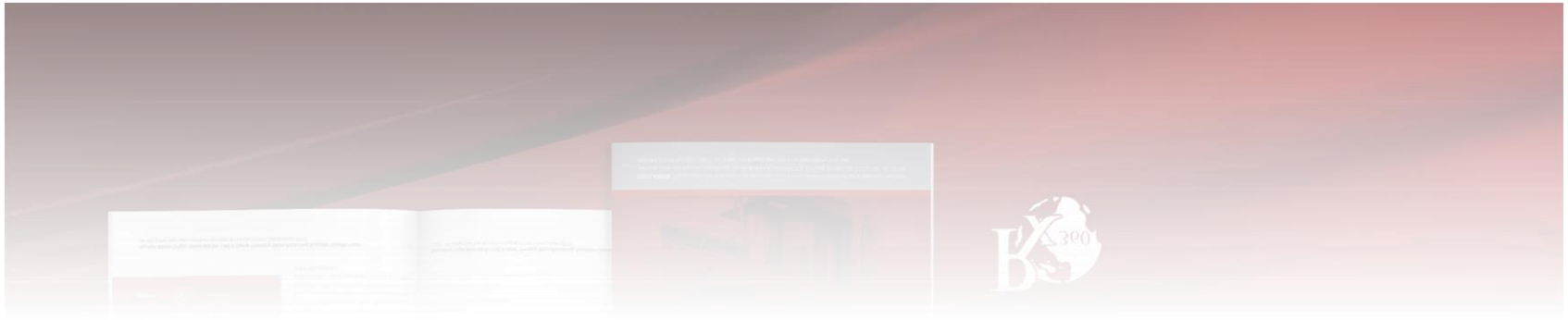

Donation and Plasma Pool Screening Test Kit Summary

LAB NAME AND ADDRESS	VIRUS	TEST METHOD	KIT'S MANUFACTURER	FDA APPROVED (YES/NO)	CE MARKED (YES/NO)	CLIA/OMCL/ PLASMA DONATION CENTER ID NUMBER	EFFECTIVE DATE	EXPIRY DATE	LAB RELEVANT CERTIFICATION CODE
	Anti-HIV 1/2								
	Anti-HCV								
	HBsAg								
	HCV genome								
	HBV genome								
	HIV-1 M genome								
	HIV-1-0/ HIV-2 genome								
	HAV genome								
	Parvo B119 genome								

Cell & Gene Therapy Work Group

New Project Survey

Sent to 60+ participants. Only nine (9) responded selecting all that applies.

- Q1 Have you attended any Rx-360 Cell & Gene Therapy Working Group meetings in 2022? **Five (5) stated they attended.**

- Q2 Why do you attend Rx-360 Cell & Gene Therapy Working Group meetings? **Four (4) find topics and/or projects helpful, two (2) considered part of their job, and three (3) skipped the question.**

- Q3 Why don't you attend Rx-360 Cell & Gene Therapy Working Group meetings? **Seven (7) shared current bandwidth does not allow them to participate, three (3) shared current discussions or projects are not interesting, and two (2) shared time/day not suitable.**

- Q4 What topics would you like the Rx-360 Cell & Gene Therapy Working Group to focus on in 2023? **Working Group Charter.**

Working Group 2023 Charter

Mission Statement:

Bring together subject matter experts from the Cell and Gene Therapy (C&GT) industries to ensure/promote patient health and safety by standardizing and setting best practices for product supply chains and material and supplier qualifications across both suppliers and end-users.

Goals:

Standardize practices related to supply chain and material and supplier qualification across end-users by bringing together the best minds in industry to facilitate discussion and develop guidance documents and tools (such as questionnaires, checklists, and Webinars).

Group Leadership:

Chair: Bobby Stein (PTC Therapeutics Inc.)
Co-Chair (Back-up/Project Lead): Arvind Srivastava (Avantor)
Other (Project Leads): Raj Shah (Avantor), Ravid Grimberg (Sartorius)

Enabling Projects:

Topics:

1. Expand on previous C&GT WG paper to focus on Plasmid and Cell Bank (Starting Materials) considerations
2. Create an Audit-Specific Questionnaire for Cell and Gene Therapy that Defines Critical Quality Attributes
3. Cell and Gene Therapy-Specific Quality Technical Agreement Template
4. Packaging, Shipping, Supply Chain, Handling Considerations for Cell and Gene Therapy Products
5. External/Guest Speaker on a C&GT Topic
6. Benchmarking

Measures of success:

1. One document/tool approved by end of year.
2. Next project identified with project lead by end of year.
3. Present at RX-360 (either project-specific or about the working group/progress)


QUESTIONS
Rx 360