Identifying and Mitigating Risks of Advanced Therapy Manufacturing (Part A)

With rapid innovation to make life and healthcare better, our systems are becoming complex.

Cell and gene therapy manufacturing involves multiple biological materials and complex multi-step procedures which introduce major risks to the quality, safety and efficacy of advanced therapies

Hence, most regulatory authorities globally emphasize a risk-based approach to be part of advanced therapy manufacturing processes. A true risk-based approach is based on the identification of various risks associated with the clinical use of advanced therapies and risk factors inherent to the manufacturing process with respect to quality, safety and efficacy. This calls for a careful risk mitigation strategy from cell and gene companies.

This checklist will help advanced therapy manufacturers identify and mitigate their risks to a great extent. It can also be combined with Part B of this checklist for efficient usage.

A. SOURCING

SL. NO.	PROBABLE RISKS SOURCES	POSSIBLE MITIGATION STRATEGY	REMARKS
1	Unidentified route of agents from the source	Traceability of cell-line and associated materials, reagents and excipients from procurement to end-user is well established.	☐ Complies ☐ Non compliance ☐ Not Applicable
2	Unable or Inadequate cell retrieval	Use characterised cell banks (from certified) or reliable laboratories only.	☐ Complies ☐ Non compliance ☐ Not Applicable
		Ensure dedicated handling within isolators with qualified equipment is established.	☐ Complies ☐ Non compliance ☐ Not Applicable
		Supplier qualification program.	☐ Complies ☐ Non compliance ☐ Not Applicable
3	Material deterioration, cross contamination of cell bank, and infection	Evaluate collection centres and maintain adequate storage system, Cryopreserve Cell Bank (example −80 °C or store in liquid nitrogen, etc.), and ensure dedicated handling within isolator with qualified equipment is available	☐ Complies ☐ Non compliance ☐ Not Applicable
4	Microbial & viral contamination in origin along with associated materials, reagents and excipients	Supplier or Vendor qualification program	☐ Complies ☐ Non compliance ☐ Not Applicable
		Choice of raw material grade should be compatible	☐ Complies ☐ Non compliance ☐ Not Applicable
5	Donor cells	Evaluation of Master Cell Bank (MCB) and Screening for markers for infection are mandatory activity	☐ Complies ☐ Non compliance ☐ Not Applicable

6	Process-related impurities and product-related impurities	Identify potential CQAs (critical quality attributes) & CPPs (critical process parameters),	☐ Complies ☐ Non compliance ☐ Not Applicable
		Define QTPP (Quality target product profile)	☐ Complies ☐ Non compliance ☐ Not Applicable
		Sterilization of final product (if applicable)	☐ Complies ☐ Non compliance ☐ Not Applicable
7	Risks associated with processing steps such as washing, selection, formulation	Control elements should be in place such as - changes in pH, - oxygen, - temperature fluctuations and - other factors such as cell density, culture time, and number of passages	☐ Complies ☐ Non compliance ☐ Not Applicable
		Prevent product mix-ups, cryopreservation, buffer replacement, etc.	☐ Complies ☐ Non compliance ☐ Not Applicable
8	Risks associated with cell engineering and culturing	Evaluation of transcriptome, proteome and secretome should be understood	☐ Complies ☐ Non compliance ☐ Not Applicable

The key to successful risk-based efforts is to understand what drives the risk, what can actually be controlled and avoided, and what has to be "accepted." That is why relying on robust QMS practices specifically designed to mitigate risks associated with advanced therapies is key.

ComplianceQuest is a next-generation AI-powered Quality and Safety platform built on Salesforce. ComplianceQuest provides all the tools needed for fast-growing advanced therapy organizations to standardize processes, proactively mitigate risks, and achieve regulatory approval.

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REFERENCE:

A. CFR TITLE 21- FDA, Chapter I-Food and Drug administration, Sub-Chapter L – Regulations Under Certain Other Acts Administered By The Food And Drug Administration, PART 1271 – HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS; Subpart D - Current Good Tissue Practice – USFDA

B. Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use – Guidance for Industry and Food and Drug Administration Staff, July 2020 – USFDA

C.CFR TITLE 21- FDA, Chapter I-Food and Drug administration, Department of health and human services, Sub-Chapter F – BIOLOGICS, PART 606, Current Good Manufacturing Practice For Blood And Blood Components - USFDA

D. Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced therapy medicinal products (11 February 2013 EMA/CAT/CPWP/686637/2011 Committee for Advanced Therapies – EMEA

E. Committee for medicinal products for human use (CHMP) – Q&A on gene therapy (17th December 2009 Doc. EMA/CHMP/GTWP/212377/2008) – EMEA

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