PDA
Parenteral Drug Association

Technical Report No. 83

Virus Contamination in Biomanufacturing: Risk Mitigation, Preparedness, and Response

PDA Virus Contamination in Biomanufacturing: Risk Mitigation, Preparedness, and Response Technical Report Team

Authors and Contributors

Houman Dehghani, Ph.D., Allogene Therapeutics (Co-Lead)

Robert Kiss, Ph.D., Sutro Biopharma (Co-Lead)

Marshall Dinowitz, Sc.D., Pacific BioDevelopment (Retired)

Jim Gilbert, Ph.D., Consultant

Linda Hendricks, Johnson & Johnson

Rajesh Krishnan, Ph.D., Oncternal Therapeutics

Yuling Li, Ph.D., Apollomics Inc.

Mark Lutgen, KBI Biopharma

Eric Mundhenke, KBI Biopharma

Anne Stokes, Ph.D., GlaxoSmithKline PLC

Dominick Vacante, Ph.D., Janssen R&D, LLC

Michael Wiebe, Ph.D., Quantum Consulting, LLC

Virus Contamination in Biomanufacturing: Risk Mitigation, Preparedness, and Response

Technical Report No. 83

ISBN: 978-1-945584-10-7

Table of Contents

FIGURES AND TABLES INDEX

1.0 Introduction

Several orthogonal measures ensure viral safety of biotechnology-derived therapeutics produced in mammalian cells, such as testing and characterization of the cell substrates, control and testing of raw materials, lot release and in-process testing for adventitious viral contaminants and characterization of the purification process for clearance of adventitious viruses. These control measures for biotechnology-derived therapeutics have proven effective, as there have been no reported cases of transmission of an adventitious agent to patients. However, the potential for contamination of mammalian cell culture processes used in the manufacture of such products by a range of adventitious agents, including viruses, still exists. Though rare, contamination of large-scale cell culture processes with adventitious agents has been reported in the literature and at scientific conferences. And animal-derived raw materials, such as fetal bovine serum, provide the most obvious point of entry. For this reason, most modern cell culture processes are adapted to growth in animal-serum-free media, significantly reducing the risk of such contaminations. Other nonanimal-derived raw materials can also harbor viruses, however, some of which are resistant to desiccation and can survive in powdered components. Other potential sources of virus entry into the manufacturing process, such as environment, materials, and personnel also present a threat.

1.1 Purpose

The purpose of this technical report is to describe the principles used and measures that can be taken to mitigate the risk of contamination by viruses and to provide guidance in preparing for and responding effectively should such an event occur.

Having an effective and active contamination response plan in place and a team ready to implement it will significantly reduce the time, effort, and expense that such an event can incur. For organizations that have not yet experienced a viral contamination event and may not have defined virus event planning and response systems, this technical report presents approaches to prevent an event from occurring and to prepare for and effectively deal with an event, should one occur.

The intent of this document is to provide guidance on appropriate mitigation and response strategies that have proven successful at reducing the risk of introducing adventitious viruses into the production process and to provide guidance in effectively planning for, and responding to, a contamination event should it occur. The intended approach is illustrated in **Figure 1.1-1.**

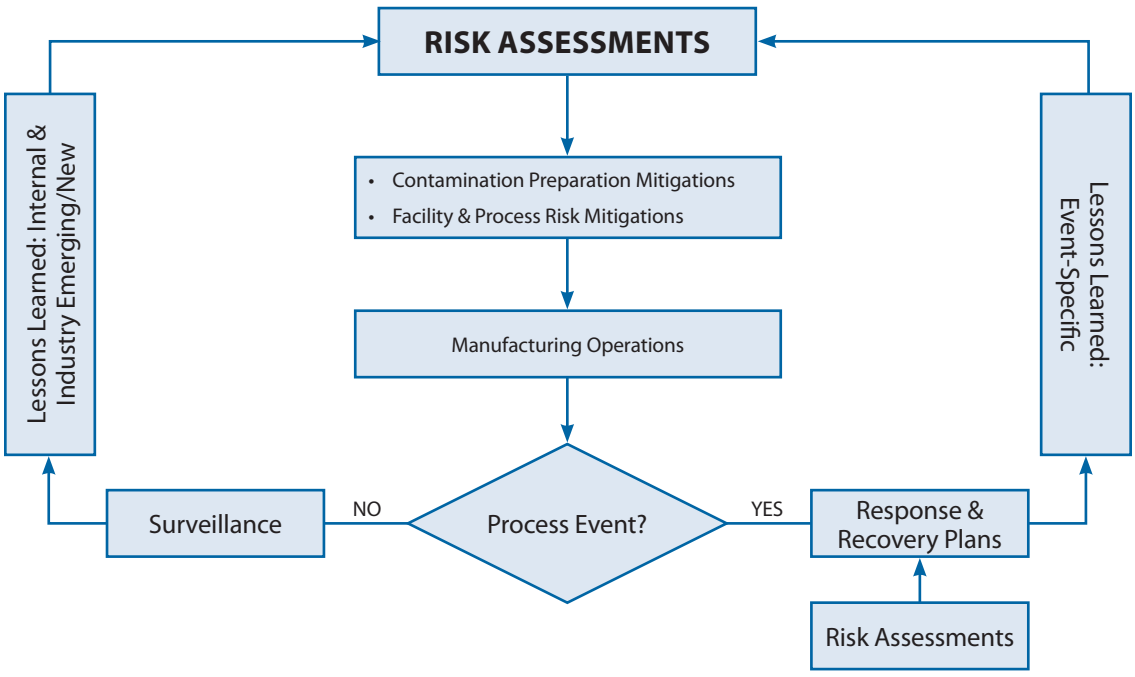

Figure 1.1-1 Virus Contamination Risk Management Approach

1.2 Scope

This document is designed to cover manufacturing processes using in vitro mammalian and other eukaryotic cell cultures to produce biopharmaceutical products. While many of the principles and practices discussed here may be applicable to the production of Advanced Therapy Medicinal Products (ATMPs), such as engineered human T-cells, such ATMPs present additional challenges outside the scope of this document due to the lack of downstream virus clearance operations as part of the overall virus risk control strategy. Likewise, although many of the principles and suggested guidance may be applicable to production by other organisms, bacteria and yeast, for example, those additional host systems are not within the scope of this document either because they are not subject to mammalian virus infection.

2.0 Glossary

Animal-Derived Raw Materials *(1)*

Primary

Contains in the final raw material or uses in the manufacturing process of the final raw material, any raw material derived directly from bovine or other animal tissues, for example, bovine serum, porcine-derived trypsin, and animal-tissue-derived hydrolysates.

Secondary

Non-animal in origin but may be derived from processes that include materials from animal components that come in direct contact with the raw material, for example, a recombinant protein produced in an *E. coli* fermentation that uses fermentation medium containing tryptone, or a recombinant protein expressed in plants that are exposed to bovine manure fertilizer.

Tertiary

Sourced from synthetic components but includes animal-derived components used during the manufacture of the raw material that do not come in direct contact with the raw material, for example, polymers or elastomers used in process equipment or plumbing that may contain or may have been exposed to animal-sourced materials such as stearates or slip agents.

Cells

Cell line

Type of cell population with defined characteristics that originates by serial subculture of a primary cell population that can be banked ***(2).***

Cell substrate

Cells used for the manufacture of a biological medicinal product ***(3).***

Host cells/Parental Cells

A non-transfected cell substrate that is generally well-characterized and banked. It can be manipulated to generate a cell substrate for production of a biological medicinal product.

Master cell bank (MCB)

The MCB represents a collection of cells of uniform composition derived from a single source prepared under defined culture conditions, aliquoted into multiple vials, cryopreserved and stored in the vapor phase of liquid nitrogen ***(4).***

Working cell bank (WCB)

The WCB is derived from one or more vials of cells from the MCB, which are expanded by serial subculture. The pooled cells are dispensed into individual vials and cryopreserved and stored in the vapor phase of liquid nitrogen ***(4).***

Contaminant

Any adventitiously introduced material (e.g., chemical, biochemical) or microorganisms including viruses not intended to be included in the manufacturing process of the drug substance or drug product ***(5,6).***

Raw Materials

Starting materials, reagents, and solvents used in the production of intermediates or APIs/drug substance ***(4).***

Viral Inactivation

Reduction of virus infectivity caused by chemical or physical modification ***(7).***

Viral Removal

Physical separation of virus particles from the intended product ***(8).***