GUIDE:

Advanced Therapy Medicinal Products (ATMPs)

Autologous Cell Therapy



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Preface

In March of 2018, the Steering Committee of the ISPE Biotechnology Community of Practice (CoP) submitted a Guidance Document proposal for this first of its kind Guide for ATMPs. The vision of the mission was to expand the growing body of knowledge of this life-changing platform for what was referred to as “personalized medicine” in the industry. We had no idea of the events that would unfold in the months ahead and how the journey would end.

The goal of the Guide is to provide current best practices addressing the key design and operational challenges for the commercial manufacture of ATMPs under cGMP. The rapid pace of change within the ATMP space is unprecedented in the industry. Science and regulatory guidance is being expanded and challenged on what seems like a monthly basis. As it is today, the rapid growth of the product pipeline creates opportunities for life-changing therapies along with significant challenges that must be addressed.

Developing a new guidance document for industry in “normal” times takes a lot of effort from very talented and dedicated professionals. Building on the current ISPE body-of-knowledge, creating new content, and delivering that content during a global pandemic required even more from this special group of people. This Guide, the first of a set of ATMP-focused guidance documents, introduces the ATMP platform and focuses on Autologous Cell Therapies.

On behalf of ISPE, the Biotechnology and ATMP CoPs, and the Members of this Guide Team, we hope this document becomes both a reference for those entering the ATMP space and the first of a growing number of guides expanding the industry’s knowledge of this life changing therapeutic platform.

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Core Team

The following individuals took lead roles in the preparation of this Guide:

Tom Bannon	PM Group	Ireland
Vince Cebular	IPS – Integrated Project Services	USA
Pinar Cicalese	Immatics	USA
Bruce Davis	BD Global Consulting	United Kingdom
Lesley Davis	Project Farma	USA
Norman Goldschmidt	Genesis AEC	USA
Christoph Herwig	Vienna University of Technology	Austria
Niranjan Kulkarni, PhD	CRB	USA
Brian Pochini	Sanofi	USA

Chapter Writers and Reviewers

The Lead and Core Team wish to thank the following individuals for their valuable contribution during the preparation of this document.

Phil Baratta	Project Farma	USA
Erich Bozenhardt	United Therapeutics	USA
Jose A. Caraballo	Kite Pharma, a Gilead Company	USA
Andrew Doppstadt	Project Farma	USA
Paul Fleming, PMP	Roche Genentech	USA
Emilie Pelletier	Iovance Biotherapeutics	USA
Prof. Dr. Christa Schröder	Fakultät Life Sciences	Germany
Aaron Weinstein	IPS – Integrated Project Services	USA

Other Contributors

The Team wish to thank the following individuals for their significant contribution to the document.

Arantxa Lera Anton	PM Group	Ireland

Regulatory/Subject Matter Expert Input and Review

Particular thanks go to the following for their review and comments on this Guide:

Martine Powell Senior GMDP Inspector	MHRA	United Kingdom

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600 N. Westshore Blvd., Suite 900, Tampa, Florida 33609 USA
Tel: +1-813-960-2105, Fax: +1-813-264-2816

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1 Introduction

1.1 Background

Advanced Therapy Medicinal Products (ATMPs) are based on genes, cells, or tissues delivered to patients to provide a therapeutic benefit based on a specific target of interest. For ATMPs, the therapy is cells, engineered tissues, or the manipulation of the patient's genome. This is in contrast with traditional manufacturing processes for compounds that are synthetically derived (i.e., small molecule) or proteins or peptides expressed by cellular systems (i.e., large molecule biopharmaceuticals).

There are two general primary focus areas for ATMPs:

- **Cell therapy** products are manipulated whole living cells, sometimes using gene therapy methods that are introduced into the patient and act at the cellular level to treat disease or injury. There are two categories of cell therapy products:
  - Autologous: Cells are derived from a patient and returned to the same patient after *in vitro* manipulation.
  - Allogeneic: Samples are derived from donors and the final cell therapy can be used to treat many different patients.
- **Gene therapy** refers to a rapidly growing field of medicine in which genes are introduced into the body to treat or prevent diseases. Gene therapy active substance contains recombinant nucleic acid that will regulate, repair, replace, add, or delete a genetic sequence in the patient. Although a variety of methods can be used to deliver the genetic materials into the target cells and tissues, modified viral vectors represent one of the more common delivery routes because of their transduction efficiency for therapeutic genes.

These general definitions encompass a wide spectrum of products and treatment methods with unique manufacturing challenges that must be supported by appropriate facility designs. ATMPs often treat rare diseases with unmet needs, or dramatically improve upon existing therapies, so there are strong social and financial drivers for rapid commercialization. Once approved however, future process, equipment, or scale-out changes require regulatory re-approval, so designing scalable and preferably automated manufacturing processes with robust control strategies is necessary to mitigate the commercial supply risk.

This Guide acknowledges that the term ATMP is quite broad (e.g., allogeneic and autologous cell therapy, gene therapy, and tissue engineering) and that these are emerging therapies utilizing rapidly evolving technology and equipment. In recognition of this, this Guide covers autologous cell therapies for parenteral use while providing content that may be applicable to other types of ATMPs.

1.2 Scope and Purpose

This Guide focuses primarily on manufacturing facility development and design for autologous cell therapies for parenteral use.

The following areas are not in the scope of this Guide:

- Manufacture of autologous cell therapies for non-parenteral use
- Tissue-based autologous products
- Implanted autologous products

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- Processing or manufacture of ATMPs in a clinic/hospital setting
- Manufacture of medical devices or components used in combination devices that involve ATMPs

The development, regulatory path, facility design, qualification, and manufacture of ATMPs present significant challenges to manufacturers, engineers, and suppliers. The GMP regulations are evolving as novel processes are presented and manufacturing paradigms are being tested. This Guide intends to address facility engineering issues that are most applicable at the time of publication, as based on the experience of the authors. Where non-engineering issues are discussed (e.g., microbiological topics and operational issues unrelated to the facility), the information is included to show readers the importance of such topics and the impact they have on facility design.

This Guide primarily takes into account the following regulatory requirements:

- EU EMA [1]
  - EudraLex Volume 4, Part IV – GMP requirements for Advanced Therapy Medicinal Products [2]
  - EudraLex Volume 4, Annex 1 – Manufacture of Sterile Medicinal Products (2020 draft revision, version 12) [3]
- Pharmaceutical Inspection Co-operation Scheme (PIC/S) [4]
  - GMP Guide Annex 2A –Manufacture of Advanced Therapy Medicinal Products for Human Use [5]
- US FDA [6]
  - 21 CFR Parts 210/211, 1271, 600/600 [7]
  - Guidance for Industry: Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) [8]
  - Applicable sections from Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice [9]

The authors of this Guide have harmonized these requirements as much as possible, noting differences in requirements as applicable.

1.3 Structure of the Guide

While this Guide focuses on autologous cell therapies to the greatest extent possible, the authors recognize a significant amount of content is applicable to other types of ATMPs. Additionally, the ATMP body of knowledge is supported by existing guidance and body of knowledge covered in ISPE Guidance Documents [10], including:

- *ISPE Baseline® Guide: Volume 3 – Sterile Product Manufacturing Facilities (Third Edition)* [11]
- *ISPE Baseline® Guide: Volume 6 – Biopharmaceutical Manufacturing Facilities (Second Edition)* [12]

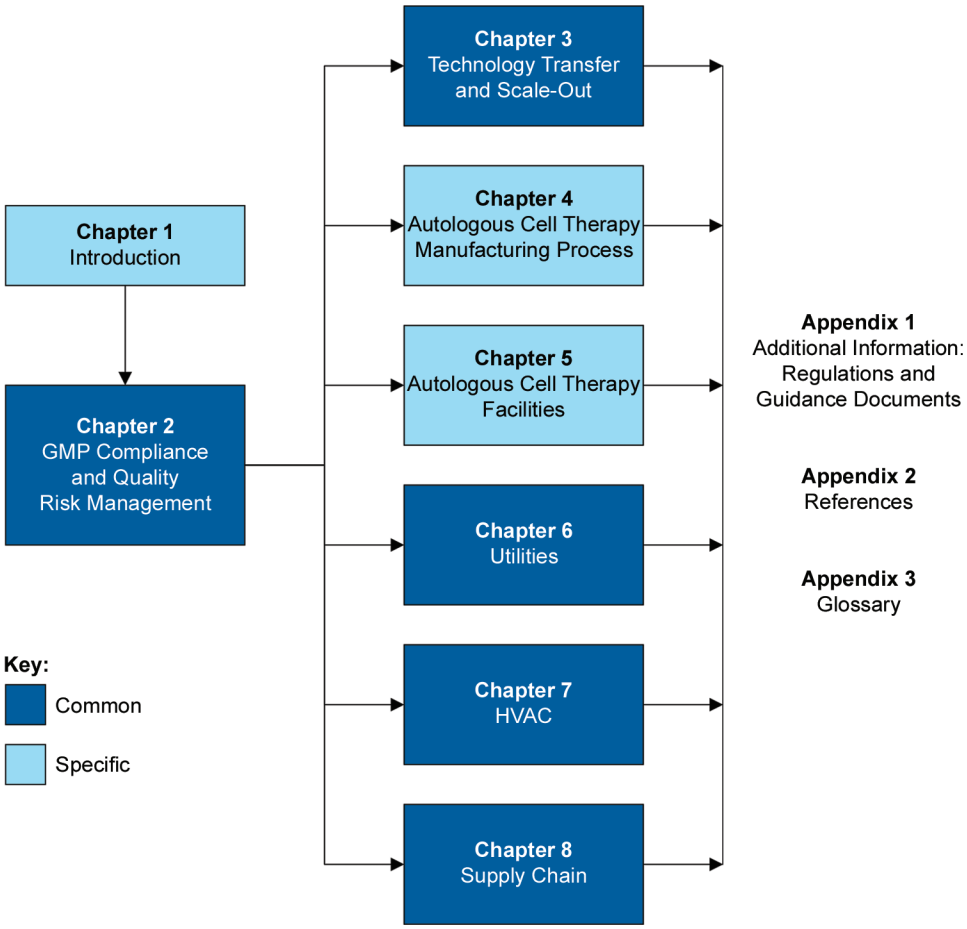
The structure of this Guide is shown in Figure 1.1. The chapters designated as “common” represent topics where there is expected to be a commonality between the various types of ATMPs, e.g., regulatory compliance, critical utility support, and supply chain logistics. The chapters designated as “specific” represent the core topics focused on autologous cell therapy. Appendix 1 contains additional information on regulations and guidance documents.

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Chapter 2 introduces the GMP compliance and Quality Risk Management (QRM) aspects of autologous cell therapy products. Many of these topics are further addressed in other chapters as applicable.

Figure 1.1: Overview of Chapter Structure



1.4 Manufacturing Process Overview

Figure 1.2 provides a high-level overview of a typical autologous cell therapy manufacturing process, which consists of the following steps:

1. Collection of patient material (e.g., apheresis) at the clinic/hospital
2. Transportation of patient material to manufacturing site
3. Receipt and verification of patient material
4. Cell processing: expansion, transduction (viral vector) or transfection (non-viral vector), selection (for apheresis/leukapheresis), washing/formulation, etc.
5. Filling
6. Inspection and labeling

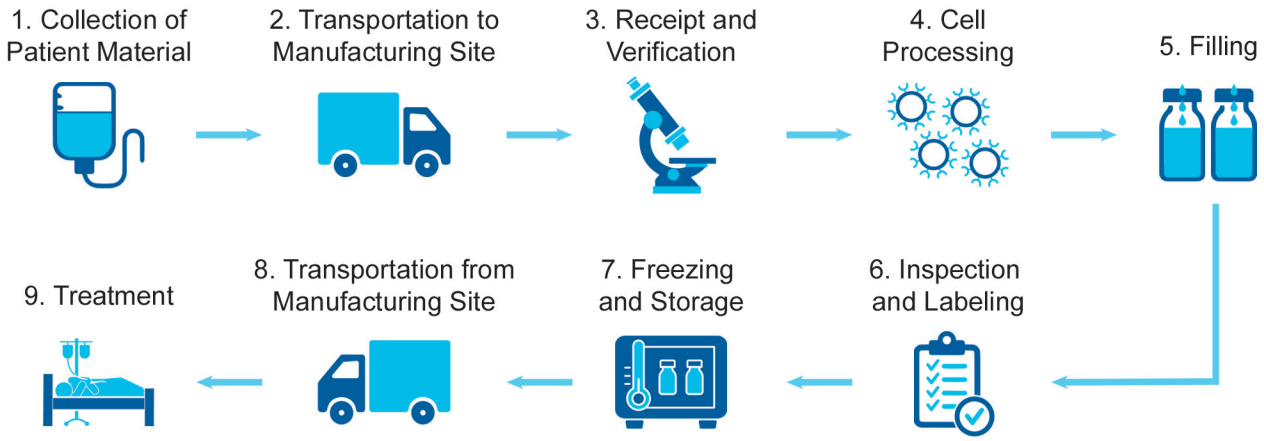
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7. Freezing and storage

8. Transportation of drug product to the clinic/hospital

9. Treatment of patient with the autologous cell therapy

Figure 1.2: High-level Overview of a Typical Autologous Cell Therapy Manufacturing Process



The advantages for the use of autologous cell therapies reside in the low risk to elicit adverse immune responses in patients that receive their own cell-based therapy. Because autologous cells must be handled and used to treat a single patient, these types of therapies cannot be considered “off-the-shelf” products and the ability to manufacture in advance to build inventory is limited. Due to the fact that autologous cells derive from one patient, and they can be used to treat only one patient, the production size is limited to a few lots and the manufacturing process is developed as a scale-out rather than a scale-up approach for production increases. During the processing of autologous cells, it is required to keep cells that are derived from different patients rigorously separated to avoid cross-contamination, therefore autologous therapies may require a significant amount of manual aseptic-controlled work due to the repetition of multiple *in vitro* operations.

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2 GMP Compliance and Quality Risk Management

2.1 Introduction

Specific regulations and guidance for ATMPs have been published. In particular, EU GMP Part IV [2] and PIC/S Annex 2A [5] provide industry guidance specific to the manufacturing of ATMPs to a greater level of detail than what was available in years past. These two primary documents, in coordination with other national guidance documents and regulations, set the foundation for GMP used in the manufacturing of ATMPs in a global market. Refer to Appendix 1 for a list of regulatory and guidance documents that set the stage and help define the GMP requirements for the manufacturing of ATMPs, and represent the basis for the content of this chapter.

This chapter focuses on GMP that is specific to ATMPs and does not go into further detail on general GMP requirements that are common to the production, packaging, and storage of all pharmaceutical and medicinal products. The scope primarily captures GMP and QRM principles as directly related to ATMP facilities, equipment, systems, manufacturing processes, and associated operations. This chapter also does not go into detail on the overall Quality Management System (e.g., FDA [6] Quality Systems Regulations, EMA [1] Pharmaceutical Quality System) that is necessary for the manufacturing of all medicinal products.

This chapter covers the following topics:

- Application of QRM
- Contamination Control Strategy (CCS)
- Identification of critical aspects, including Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs)
- GMP design requirements
- Multi-product/multi-patient processing
- Aseptic processing requirements
- Cleaning, sanitization, and Environmental Monitoring (EM)
- Qualification and validation
- Quality Assurance (QA) and Quality Control (QC)

2.2 Application of Quality Risk Management to ATMP Facilities

As with any biopharmaceutical manufacturing process, the application of QRM plays a critical role in the manufacturing of ATMPs. Whether an autologous or allogeneic cell therapy, gene therapy, or other ATMP, most processes require aseptic or bioburden-controlled manufacturing processes and environments. In particular, contamination, cross-contamination, or mix-up of an autologous cell therapy could have life or death consequences for the patient. Therefore, a robust QRM process is a necessity.

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As conveyed in the different global regulatory documents, there is consensus amongst agencies that aseptic processing and the manufacturing of sterile products is a complex process that requires special attention to detail and represents one of the greatest potential health risks to patients if contamination does occur. The manufacturing of ATMPs requires the application of QRM principles to ensure that contamination (microbiological, particulate, and pyrogen), cross-contamination, and mix-ups are prevented in the final product.

2.2.1 Quality Risk Management Principles

Processes, equipment, facilities, and manufacturing activities should be managed in accordance with QRM principles to provide a proactive means of identifying, scientifically evaluating, and controlling potential risks to quality throughout the entire product lifecycle – from investigation, through technology transfer, to commercial manufacturing, and ultimately ending with product discontinuation.

The principles of QRM are well defined in the ICH Q9 Quality Risk Management [13]. The ICH Q9 guideline provides valuable principles and example tools for the application of QRM and should be used as a reference in establishing a QRM program.

ICH Q9 states:

> *"Two primary principles of quality risk management are:*
>
> - *The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and*
> - *The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk."* [13]

With respect to the second principle, the risk level for ATMPs is considered high based on the fact that most are typically aseptically processed; the risk is compounded with the fact that ATMPs are complex biological products with differing levels of risks related to the nature and characteristics of the starting materials and the level of complexity of the manufacturing process. In addition, keeping the chain-of-identity is critical for autologous products to maintain patient traceability and to avoid mix-ups of different patient materials.

ATMPs, and autologous products in particular, have several specific consequences for the patient that should be included as part of the QRM process. There are many elements of risk that are unique to autologous products. For example, the decision to discard a batch can increase the risk to a patient by requiring another donation or collection and substantially delaying the delivery of a life-saving product. As the batches are patient specific, the risk profile must account for the fact that the patient cannot obtain the product from another source. The delay in treatment that results from having to create another batch may be in and of itself an unacceptable risk. In some instances, it may be necessary to involve the company's medical affairs and/or the patient's medical team in these decisions.

In addition, the unique risk profile for autologous products may drive process designs that limit the potential for single patient batch contamination. It may be prudent to design processes with multiple lots or batches per patient, so that in the event that one lot/batch becomes contaminated, the remaining lots/batches can proceed, resulting in the patient still being able to receive their life-saving treatment.

2.2.2 Risk-Based Approach

The Risk-Based Approach (RBA) is not new to the pharmaceutical industry. Risk-based approach guidances have been in place for nearly two decades, dating back to 2004 [14] and 2005 [13]). In the 2004 FDA Final Report titled Pharmaceutical CGMPs For The 21st Century - A Risk-Based Approach [14], the following objectives were described:

- Encourage the application of risk management techniques and quality systems approaches

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- Encourage industry to use good science and new technological advances
- Encourage innovation leading to improved benefit to the patient
- Focus both industry and agency attention on critical areas

The foundation and general principles set forth in EU Part IV [2] are based on the risk-based approach. The Part IV guideline elaborates on the application of the risk-based approach to the overall Pharmaceutical Quality System, the raw materials, the manufacturing and testing of ATMPs, as well as the principles that should be applied to the following (covered in the scope of this Guide):

- Personnel, including training and hygiene (clothing/gowning)
- Premises/facility
  - Multi-product facilities
  - Production areas (including environmental classifications and monitoring)
  - Storage areas
  - QC and ancillary areas
- Equipment
- Production, including utilities, prevention of cross-contamination, and aseptic processing
- Qualification and validation

QRM and associated risk-based approach require a thorough product and process understanding and should follow a Quality by Design (QbD) methodology for the design of the premises/facility, equipment, systems, and processes as part of the overall CCS. The utilization of QbD principles, risk assessment, and risk mitigation must begin in process development (with the goal of a closed process to the greatest extent possible), technology transfer, determination of site location based on proximity requirements for patients, and the early design phase for the manufacturing facility.

See also the EMA Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced therapy medicinal products [15].

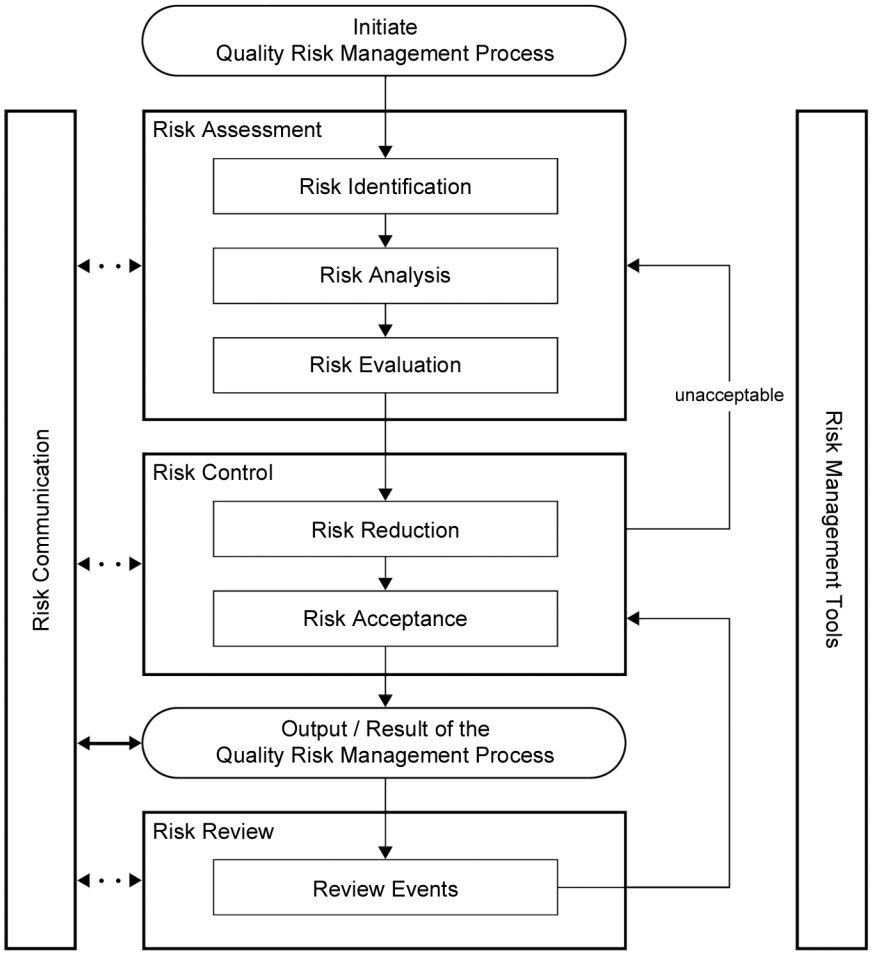
2.2.3 Risk Assessment and Risk Control

The application of QRM comprises *"systematic processes designed to coordinate, facilitate and improve science-based decision making with respect to risk."* [13] While QRM can be applied across a wide spectrum of activities, the scope of this section covers the risk as directly related to product contamination, cross-contamination, and mix-ups during the ATMP manufacturing process.

The ICH Q9 QRM process is shown in Figure 2.1.

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Figure 2.1: Overview of a Typical Quality Risk Management Process (ICH Q9 [13])



Risk assessment is based on three basic steps: risk identification, risk analysis, and risk evaluation. Three very fundamental questions that can be used during risk assessment, as stated in ICH Q9 [13], are as follows:

"1. What might go wrong?

2. What is the likelihood (probability) it will go wrong?

3. What are the consequences (severity)?"

In general terms, the facilities, equipment, systems, and processes should be designed to minimize or eliminate the potential for contamination (particulate, foreign substance/material, microbiological, and/or pyrogen) and/or cross-contamination (different product, batch, donor/patient material, or foreign viral vector) in the final product. Although not specifically captured in ICH Q9 [13], detectability is another factor that should also be considered in the risk assessment.

Rephrasing the fundamental questions to align with these objectives and to include detectability is represented as follows:

1. How could contamination or cross-contamination (including mix-up and carryover) occur with respect to the specific item, step, or activity?

2. What is the likelihood (probability) that the contamination or cross-contamination will occur?

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3. What are the consequences (severity) for the contamination or cross-contamination?

4. Would a contamination or cross-contamination event be detected?

The progression of the risk-based approach and risk assessments in industry and in the global regulatory guidelines continues to progress from the thought of being a beneficial process to one of a regulatory expectation and mandatory requirement (similar to qualification/validation). The risk assessment process should be formally documented, where an approved risk assessment and/or report is available for audit. In addition, risk assessments should be evaluated as part of a company's change control process, in order to assess if equipment, system, or process changes impact the associated risk profile. Risk assessments should also be subject to periodic review as part of a continual improvement process to further reduce risks or eliminate risk with the adoption of new technology or processes.

To effectively facilitate the second aspect of QRM risk control, the timing of risk assessments can be extremely important. In particular for the design of new facilities and selection of equipment/systems, risk assessments should be performed as early as possible in the development or design/engineering phase. This allows for risk to be truly mitigated or completely eliminated through the design processes and prior to potentially large capital expenditures. A failure that often occurs is when risk assessments are performed after the design is complete, the purchase is made, or even the construction is complete. In these scenarios, risk assessments are often used to justify what is in place or to implement procedural controls (as opposed to properly mitigating the risk at the beginning of the process/project). The risk is then mitigated by procedural controls rather than in a more robust process or design element.

In addition to facility/process design aspects, risk assessments should be applied to numerous other requirements such as validation requirements, EM program and locations, and extractable/leachable studies.

There are many tools for performing risk assessments, and the scope and complexity are captured in other reference documents. In particular, the following ISPE Guidance Documents can be referenced for specific details as related to risk assessments:

- *ISPE Baseline® Guide: Volume 5 – Commissioning and Qualification (Second Edition)* [16]
- *ISPE Baseline® Guide: Volume 7 – Risk-Based Manufacturing of Pharmaceutical Products (Second Edition)* [17]

Another critical aspect of the QRM and risk-based approach is the development of a CCS as detailed in the next section.

2.3 Contamination Control Strategy (CCS)

EU GMP Annex 1 (draft revision) [3] defines CCS for the manufacture of sterile products, and its QRM principles and controls are applicable in principle to the manufacture of autologous cell therapies. CCS is defined as:

> *"A planned set of controls for microorganisms, pyrogens and particulates, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to active substance, excipient and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control."* [3]

Autologous cell manufacturing has challenges in that it does not follow conventional manufacturing practices. For example, cells cannot be sterilized using typical biotechnology practices, the process can start at a clinic/hospital instead of a manufacturing setting, some GMP controls can start earlier (e.g., at the clinic/hospital), the process requires extensive operator manipulation, the drug substance can be considered the drug product, final product viral inactivation treatments are not applied, and a single batch is reserved for a single patient [18].

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As discussed in Section 2.3, processes should be managed using QRM principles, where phase appropriate GMP controls are applied commensurate with the impact to product quality and the ability to treat patients in a timely manner. A CCS is defined to address the most relevant contamination risks to product quality. The strategy considers the product lifecycle and incorporates periodic reviews to stay relevant and useful. Areas for improvement or correction are identified during the monitoring phase, ensuring a consistent quality output.

The most common contamination risks to mitigate are related to bacteria, prions, mycoplasma, fungi, and other adventitious agents (e.g., viruses). Autologous cell processes are developed initially in clinical settings before they are modified or scaled-out for commercial GMP production. The process parameters most related to the control of contamination are:

- Time (duration of manufacturing steps)
- Number of manipulations
- Aseptic techniques
- Type of process interventions (e.g., sampling, connections, transfers)
- Environments where the manipulations occur (e.g., closed processing, open processes)

Furthermore, there are testing challenges in that the cell viability determination has variability that is dependent on operator execution. Sampling could be a source for contamination or could consume too much of a batch intended for use. Additionally, the drug delivery to patients is very fast, thus making assays that take too long impractical [18].

As an overarching strategy, it is preferable to focus on contamination prevention measures and monitoring controls of contamination, rather than testing for sterility or microbial contamination. Suggested measures for microbiological contamination control are listed in Table 2.1. The CCS applies measures such as these to mitigate different risks. These risks are identified, analyzed, mitigated, and controlled using QRM tools.

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Table 2.1: Measures for Microbiological Contamination Control

Type of Measure	Process	Equipment and Facilities	Materials	Procedural
Prevention	• Qualification and validation • Identification and control of critical microbiological contamination parameters • Process risk assessments regarding microbiological contamination risks • Sampling quantity and methods • Process simulations • Process step durations • Process manipulations	• Physical segregation • Containment • Airlocks and Pass-throughs • Pressure differentials between rooms • Cleaning and disinfection • Qualification • Maintenance • Product, materials, waste, personnel flows • Clean Room classification and controls • Detection of trends in EM program • Level of process closure (closed processing)	• Raw material characterization • Utilities quality • Qualified consumables and single-use components • Components and materials free of microbiological contamination, sterile • Appropriate sampling methods • Donor qualification • Sterile gowns specification and inspection • Extractable and leachable controls	• Supplier Quality Management System • Approved Supplier List • General training • Gowning • Quality Management System • Production System • Manufacturing Execution Systems • Supervision • Employee health and safety • Procedures for spills and leaks • Waste management protocols • Aseptic processing training
Detection (testing for specific attribute)	• Out of trend parameters increasing microbiological contamination risks • Unexpected process manipulations	• Room pressure differential • Facility alarms • Utility Alarms	• Material traceability	• Aseptic personnel testing • Change control system • Supplier notification of changes
Monitoring (reviewing data for specific triggers, signals, trends, changes, etc.)	• Cell culture parameters	• Environmental monitoring	• Material variability and quality trends	• Quality Assurance • Employee health check • Aseptic Personnel Testing
Testing	• Out of specification parameters • In-process testing	• Preventive Maintenance • Calibration	• Raw Material incoming testing • Microbiological contamination testing (mycoplasma, endotoxin, bacteria, fungi, etc.)	• Rapid batch release process • Aseptic Personnel Testing
Other	• Analytical Comparability • Donor cell screening • Avoid process delays	• Use of active barriers, isolators, and Biological Safety Cabinet/ clean air hoods	• Vein-to-vein chain-of-custody • Product traceability • Product storage	• Authorized personnel access control • Pest controls • Product distribution • Donor cell collection controls

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2.4 Identification of Critical Aspects (including Critical Quality Attributes and Critical Process Parameters)

Autologous cell therapies are typically produced at a small scale in centralized facilities with controlled rooms and associated equipment. These facilities have the capability to deliver directly to a patient or may be co-located in the patient's point-of-care clinic/hospital. Manufacturers should consider the identification of quality attributes, quality parameters, and process controls critical to the development and manufacturing of safe and effective therapies. Each step must be identified along with the corresponding parameters needed to execute a successful process.

Automation is a desired feature for autologous cell therapy manufacturing. The process complexity and the execution of similar steps for each batch can benefit greatly from the use of automated process steps, though there are steps where automation may not be practical to implement. For example, automation of cell substrate seeding and control of mixing rates can significantly minimize variability in the process. Conversely, the process complexity and cell variability can make automation challenging. The recipes and system algorithms should be flexible enough to manage sources of variability and achieve better control and performance.

A QbD framework can be applied to the development of cell therapies, increasing understanding of the critical parameters and attributes for ensuring product quality and safety. The QbD framework focuses on process design (e.g., product mode of action, quality target product profile), process description (e.g., parameters, CQAs), and characterization (e.g., impurities). When the process design stage reaches the phase to produce late clinical stage material, the process is locked down to minimize major post clinical registration issues. Introducing changes at later stages of process registration becomes challenging and critical for autologous cell therapies given the need to ensure fidelity that sourced patient cells correspond to the correct and unique patient batch. A process control strategy for sustainability and improvement are also applied once the process is implemented. These therapies are often considered for breakthrough designations and as a result, the process is formalized early in the design process, limiting the introduction of improvements after the first regulatory submission.

The successful manufacturing and supply of autologous cell therapies depends on the time duration of the full supply chain, including transportation, storage time, and total time for manufacturing. The time sensitive nature for some cell therapy products may prevent the completion of all testing prior to treatment. If this is the case, a validated and characterized manufacturing process will ensure that appropriate safety and potency specifications are met. Additional challenges are the inherent sources of variability such as raw materials, equipment, execution of manual steps, analytical methods, sampling, and single-use components. The largest source of variability has proven to be the donor-to-donor variability of the patient's starting cells [12].

ICH Q8 [19] defines a Critical Quality Attribute (CQA) as:

> *"A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality."*

Identification of these attributes is achieved during the product development phase using existing product knowledge from scientific publications, clinical studies, specific design of experiments, risks assessments, and Quality Target Product Profiles (QTPP)[1]. During process development, the CQAs are identified as those that correlate to features representing product safety and quality.

For autologous cell therapies, the final product is patient specific, and lengthy data correlation studies may not be possible. For this reason, the identification of CQAs needs to incorporate formal risk assessments. Examples of CQAs include:

- Appearance (e.g., color, visible foreign particles)
- Potency (response)

[1] ICH Q8 [19] defines QTPPs as *"A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product."*

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- Safety (e.g., sterility, mycoplasma)
- Purity (e.g., microbiological contamination, cell viability)
- Identity (e.g., gene expression, markers)
- Dose (e.g., cell concentration)

CQAs are normally used as product specifications after justification is provided by the manufacturer and approved by regulatory agencies. Development of specifications is accomplished through non-clinical and clinical phases of the development program (lot history) and maturity of process characterization. Product specifications are established to confirm the quality of the cell therapies with the main focus on product characteristics that are useful to ensure product safety and efficacy.

A Critical Process Parameter (CPP) is:

> *"A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality."* [19]

CPPs must be controlled within an established and justified process range to ensure that the final product meets the attributes for safety and quality. Once the CQAs are defined, each process step is evaluated for potential parameters to be controlled. Through a formal risk assessment, the criticality of each parameter is evaluated to identify those that impact CQAs. Other non-critical parameters (e.g., key, well-controlled) relevant for process consistency are also considered for control and/or monitoring.

Refer to Chapters 4 and 5 for more information on control strategy considerations related to autologous cell therapies. Refer to PDA Technical Report 81 [20] for a comprehensive description of cell therapy control strategies.

2.5 GMP Design Requirements

The design of the process, type of equipment technology, and associated facility requirements are all key elements in the application of a risk-based approach. Technology in the ATMP sector is rapidly developing to accommodate and facilitate more robust and closed processes. During process development, risk assessments and risk mitigation strategies play a pivotal role in the risk profile of the clinical and future commercial manufacturing facility.

The ability to move from an open process with traditional manual interventions in a Biological Safety Cabinet (BSC)/ clean air hood to a fully closed process or within an isolator (when feasible), may be the single most critical factor in the reduction or elimination of contamination and cross-contamination risk. The facility design requirements for an open process versus a fully closed process can be significantly different, and closed (or isolated) processes may be crucial for concurrent autologous product manufacturing activities. Refer to Chapters 4 and 5 for more detailed information.

2.6 Multi-Product/Multi-Patient Processing

One of the most significant departures from traditional pharmaceutical product GMP is related to multi-product facilities and/or concurrent batch processing that may occur simultaneously within the same area or even the same room. With many traditional finished pharmaceutical manufacturing operations, GMP generally requires one product or batch per area/room at any given time to prevent cross-contamination and mix-ups. Recently, there have been more instances where multiple lots may be in the same area, but that is limited by process step, same viral vector, etc.

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To be commercially or even economically viable, ATMP manufacturing (especially for autologous products) may require concurrent multi-product, multi-batch, and/or multi-patient processing within the same room. Adequate segregation of flows is critical to prevent mix-ups and cross-contamination from waste, people and product. Avoiding mix-ups is vital to patient safety, and the inherent risks with concurrent multi-product/batch processing must be addressed through the QRM/risk assessment process.

Manufacturing of ATMPs in a concurrent, multi-product facility may be acceptable when appropriate risk mitigation measures commensurate with the risks are implemented to prevent mix-ups and cross-contamination. While Chapters 4 and 5 capture ATMP process and facility considerations in greater detail, the following items must be risk assessed and addressed for concurrent batch processing and/or multi-product facilities to ensure GMP compliance:

- **Facility/Process Design**
  - Elimination of the potential for cross-contamination from airborne aerosols or physical transfer by operators and/or shared equipment (incubators, centrifuges, cell processors/counters, etc.).
  - Adoption of closed processing, single-use components/technology, isolators, or other closed systems to prevent contamination.
  - Validation of cleaning and decontamination procedures between different patient batches and subsequent manufacturing steps within common rooms/areas, including BSCs/clean air hoods and isolators as applicable.
  - Segregation of production areas for viruses, viral vectors, and segregated areas or closed system boundaries for identified high risk drug product production activities.
  - Segregation and/or unidirectional flows for personnel and material when risks are identified.
  - Use of dedicated rooms, suites, or facilities when risks cannot be adequately controlled through all other identified measures.
- **Procedural/Organizational Controls**
  - Segregation by time and/or separation of activities (campaigning of products or batches, time separated activities, robust personnel and material flows to prevent cross-flow or simultaneous flows, demarcation lines within rooms to establish boundaries, physical segregation of workstations, color coding of surrounding work areas, labeling/barcoding of equipment and workstations, changing of sterile sleeves/gloves or complete degowning/regowning, etc.).
  - Implementation of procedures and organizational measures for shared process, incubation, and storage equipment to prevent cross-contamination and mix-ups.
- **Batch and Donor/Patient Material Controls**
  - Prevention of mix-ups through robust distinct labeling (using color coding/symbols) or electronic systems such a bar coding, electronic track-and-trace, and automated batch record platforms. These systems, whether paper-based or electronic, should track all starting materials including patient/donor material through to finished product. Each processing step should have a verification activity to avoid mix-ups.
  - When possible, backup cells should be banked as a protection for lot loss, but the backup cells (which may be in very long-term storage) require the same certainty of labeling, batch record enforced checks, etc.

See Section 5.2.2 for more information on multi-product operations.

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2.7 Aseptic Processing Requirements

2.7.1 General Considerations

As stated in the EU GMP Part IV [2]:

> *"The majority of ATMPs cannot be terminally sterilised."*

This indicates that most ATMPs will require aseptic processing when there is risk of contamination in the process. The definition and general approaches to aseptic processing are included in the EU [1] and FDA [6] guidances and ISPE Guidance Documents [10] and will not need to be repeated here. Instead, this section focuses on aseptic processing requirements that apply to ATMPs.

2.7.2 Environment Considerations

Open Systems – When the ATMP is exposed to the environment, it is a regulatory expectation that the processing take place in an ISO 5/Grade A unidirectional flow environment with an ISO 7/Grade B background. [2]

Closed Systems – When a closed system is used or manufacturing takes place in an isolator, an ISO 8/Grade C background is appropriate [2]. Note that EU and PIC/s guidance [2, 5] may allow for a Grade D background, but ISO 8/Grade C is still a common practice for global compliance. The integrity of closed systems can potentially become compromised when product contact surfaces are exposed during setup, samples are taken without the use of sterile connections, materials are added without a sterile connection or filtration (when appropriate), or other breaches of the closed state. Proper controls must be implemented to protect and maintain the closed functionality of the system.

For products that can be sterile filtered, process and expansion steps prior to sterile filtration can generally take place in an ISO 5/Grade A environment with an ISO 8/Grade C background. For aseptic processes with any open process steps or open connections, the final filtration and fill must take place in an ISO 5/Grade A environment with an ISO 7/Grade B background. If the final filtration step is a fully closed process with sterile connectors and filling is carried out within an isolator, an ISO 8/Grade C background may be appropriate. [2]

There are also rare instances (not typical for commercial manufacturing) where manufacturing of an ATMP may take place in controlled, non-classified areas, as described in EU GMP Part IV, paragraph 9.45 [2]. In this scenario patient material collection, manufacturing, and then administration of the therapy must all take place quickly and in the same room (e.g., an operating room in a hospital). For this to be acceptable, the manufacturer must:

- Demonstrate that the benefit to the patient outweighs the risk
- The environment is well defined and demonstrated to meet those requirements
- It is proven that the process is entirely closed or, if temporarily opened to the environment, all required controls are in place to eliminate risk
- When the materials present an increased risk of cross-contamination or to the operators (such as replication competent vectors or material from an infected donor), there should be additional precautions to prevent product release to the environment
- Provide visibility to the appropriate regulatory authorities, either through the regulatory filing (e.g., Clinical Trial Authorization or Marketing Authorization) or other regulatory notification.

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2.7.3 Aseptic Process Simulation

Setting boundaries for the media simulation program, as well as defining other programs such as individual aseptic qualification, needs to be done holistically for the entire process rather than for just a single discrete process (e.g., filling). Considerations related to Aseptic Process Simulation (APS) are as follows:

- Validation of the overall process should include an APS that uses media that can sustain microbiological growth. The simulation must capture the entire process and all activities, but particular attention is often focused on the open processing steps to demonstrate that the facility, equipment, and aseptic techniques combine to prevent contamination of the ATMP. If a system is entirely closed, the APS should concentrate on the manufacturing phases including the assembly and all connections made during the process.

- Number of Simulations and Timing: The APS should be initially conducted with at least three consecutive simulations. Subsequently, a single process simulation should be repeated periodically to provide ongoing assurance. The frequency should be determined based on a risk assessment. When there is a significant change to the facility or process, the APS should be re-initiated and include three consecutive runs.

- When performing the APS, it is important to make sure that media touches all surfaces within a given process material, such as a single-use bioreactor bag or the vial used to hold the final product. The goal is to have no microbiological growth. All growth should be investigated with an assessment of impact to previous batches, when appropriate.

- The APS for ATMPs must also address multiple processing steps in a single day, representative maximum batches/activities per day, process duration, maximum occupancy levels, training and qualification of individual personnel/operators (all applicable staff) as well as other customary APS activities.

- The potential for matrix or bracketing approaches for APS exists and, when applied, the rationale must be formally documented and approved.

2.8 Cleaning, Sanitization, and Environmental Monitoring (EM)

2.8.1 General Considerations

In many respects, the approach to cleaning, sanitization, and EM for ATMPs mirrors the approach to other aseptic facilities. In all cases, cleaning and sanitization should be executed per qualified procedures, and monitored by qualified EM processes.

The design of ATMP facilities should be such that the classified areas are easily cleaned and sanitized. This includes construction using smooth hard surfaces and floor to wall connections that are seamless and coved. Ceilings should be constructed in the same fashion. Suspended ceilings should be sealed. Horizontal surfaces and hard-to-clean recesses should be avoided to the greatest extent possible.

Cleaning and sanitizing agents should include a broad-spectrum disinfectant and sporicidal agent, and should be part of a rotational use program.

An EM program should be based on the activities taking place in a given area and should be implemented using a risk-based approach. Sampling location, frequency, sample type (active air, settling plate, surface, etc.), alert/alarm limits, and other factors determined critical should be based on the results of the risk assessment, appropriately documented, and formally approved. Monitoring and trending of temperature, Relative Humidity (RH), and Differential Pressure (DP) are typical. Total particulates and viable particulates should be measured and trended. The types of the microbial species and molds should be determined. When a parameter is critical and trended, alert and action limits should be established. All sampling should be based on the risk assessment, but some common practices are summarized in Table 2.2.

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Table 2.2: Common Approaches for EM Sampling Frequency

Area Classification (In Operation)	EM Sample Frequency
ISO 5/Grade A	During all operations, unless appropriately justified
ISO 7/Grade B	During critical operations
ISO 8/Grade C	Based on risk assessment (at least weekly)
Grade D	Based on risk assessment (at least monthly)

When the facility or area is idle, the EM frequency should also be based on a risk assessment which includes how the facility will be returned to service.

2.8.2 Specific Considerations

In many instances, the quantity of equipment needed for ATMP processing is much greater than would be encountered in a traditional aseptic facility. This presents a challenge to the cleaning, sanitization, and EM of the facility. In addition, ATMP manufacturing is often labor intensive, and the number of people expected within a given area per the design may seem overstated. This can make it a challenge to put the required number of people in the room (maximum occupancy) when the initial EM Performance Qualification is planned and executed. When establishing cleaning procedures and an EM program for an ATMP facility, the following items can be considered:

- In addition to being used for cleaning the walls, ceilings, floors, and tables (that are manufactured to withstand the chemicals), the cleaning and sanitization agents may also be used to disinfect the surfaces of storage, medical, and testing equipment. This equipment may not have been designed to be cleaned and sanitized by traditional cleanroom cleaning strategies or compatible with traditional cleaning and sanitizing chemicals.

- The frequency of wipe downs by operators and other personnel increases considerably, so the availability of the cleaning and sanitizing agents needs to be addressed.

- When deciding on sampling points and frequency, there are many more pieces of equipment in a given area. With many more portable pieces of equipment, there is also a great deal of movement within a given space. This movement presents the opportunity for increased particulates and bioburden and cross-contamination. Fully understanding the detailed operations and airflow patterns within a given space (including the movement of portable equipment) is critical to setting up a robust EM qualification and ongoing cleaning and EM operations.

- For rooms/suites that process numerous batches/lots throughout a given day, the worst-case conditions will occur at the end of the shift or the last lots of the day. The EM program must take these worst-case conditions into consideration.

2.9 Qualification and Validation

2.9.1 Qualification

Overall, the qualification of ATMP facilities, utilities, equipment, and systems are similar to other pharmaceutical facilities and can follow the principles and methodologies as detailed in the *ISPE Baseline® Guide: Volume 5 – Commissioning and Qualification (Second Edition)* [16]. The C&Q Guide details a compliant, integrated commissioning and qualification process that is based on a science and risk-based approach. The approach aligns well with the QRM and risk-based approach principles highlighted in this Guide and that are required in the manufacturing of ATMPs.

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Since many ATMP facilities and processes are “scaled-out” versus “scaled-up” for commercial manufacturing, this often creates a condition where facilities may have dozens or even more pieces of identical equipment (BSCs, incubators, refrigerators, freezers, centrifuges, cell counters, etc.). This creates a scenario for the possibility of grouped or representative testing of identical units. A science and risk-based approach could allow and facilitate some level of representative testing of identical units. In this scenario, an assessment needs to be performed to determine what qualification activities are identical for each unit (documentation verification, procedure identification, training verification, etc.), what verification activities test a design feature or control function for a specific model or version of software/program, and what activities test the actual performance of an individual unit. All decisions made with respect to qualification of identical equipment should be documented in a formal risk assessment.

Examples of qualification methodologies for numerous identical units (particularly for off-the-shelf equipment) may include, but are not limited to, the following:

- Prepare and approve one (Installation and Operational Qualification (IOQ) or Installation, Operational and Performance Qualification (IOPQ)) protocol for all identical units. Create controlled copies of the protocol and execute independently for each individual unit.

- Prepare and approve one protocol (IOQ or IOPQ) with two parts (or two separate documents) that are executed independently. Part 1 includes all qualification activities that are identical for each unit, and Part 2 includes activities that need to be executed for each individual unit. Execute Part 1 one time to cover all units and prepare a report after Part 1 completion. Execute Part 2 for each unit and prepare a report for each unit as applicable.

- In addition to the protocol(s) that test the individual units (only activities specific to a unit), prepare and approve a protocol for representative tests of identical units. Some examples of representative tests include the following:

    - Software/PLC program testing: Test the functionality, security, data integrity, etc. of the software and/or PLC program one time for all units. For each subsequent unit, verify that the software/program version(s) is the same as the version tested and that the system is configured per specifications. In some cases, a single image of the software is qualified and must be copied and installed on each subsequent unit. GAMP® [21] principals should be followed in determining the appropriate level of verification testing.

    Note: Due to the nature of ATMP manufacturing, there are many different manufacturers of equipment and associated software used in the process. In many cases, these systems were designed with a laboratory or hospital setting in mind and are more recently being used for ATMP manufacturing. It is important to understand the limitations of the software for both manufacturing and QC equipment and to be prepared to address the data integrity issues that may arise from these equipment manufacturers progressing to catch up to the biopharmaceutical industry.

    - Mapping of Controlled Temperature Units (CTUs): Open door recovery testing, power loss testing, and loaded chamber mapping may be subject to representative testing of the specific model. Based on the results of the risk assessment, it may be possible to perform one or more (but not all units) verification tests. For example, if each individual CTU has an empty chamber mapping, the mapping will demonstrate the proper operation and functionality of the individual unit. Then following the successful empty chamber of each unit, the representative testing can be performed on the representative/reduced quantity of units. These representative tests are not expected to change from unit to unit.

    - Airflow visualization (smoke profiling) of identical BSCs and clean air hoods: Smoke profiling during static conditions and dynamic conditions (assuming identical operations will be performed in each unit) may be performed for one or more, but not all units.

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2.9.2 Process Validation

There can be a great deal of inconsistency in the starting materials for ATMPs, as many of the processes utilize the cells of patients who are already immunocompromised. The variability inherent in many of these materials poses challenges to the process and, by extension, process validation. It is still expected that process validation will demonstrate that the ATMP meets predetermined criteria as detailed in regulatory filings.

General considerations for process validation of ATMPs are as follows:

- Process validation is the verification of the control strategy based on CQAs and CPPs. The process validation protocol should include the CQAs and CPPs and the associated acceptance criteria, equipment/facilities used, analytical methods, in-process testing and rational for selection, sampling, documentation procedure and methods, specifications for the final product, and the process for release.

- Process validation should generally be based on multiple consecutive batches (as determined through risk assessment). However, since this may be a challenge based on the availability of patient material, the approach to a reduced number of batches required for validation should include a rationale. Every attempt should be made to gain as much process data from each batch. In this way, a manufacturer can use the information to reinforce the robustness of the process.

- When starting material is scarce, there may be a rationale for using substitute materials for process validation. When this is implemented, the approach should include an evaluation of materials and their suitability to represent the actual starting materials.

- Concurrent process validation may be acceptable (regulatory authority may be required) but requires a rationale with a more intense focus on the data from subsequent batches.

- Closely related products that use the same manufacturing platform may be an opportunity to reduce the extent of process validation for subsequent products, after the initial process validation, by focusing on manufacturing steps with more variability or that are new to the process.

- Consider donor demographics in process qualification studies (as much as is practical) as incoming cell lines are the biggest source of variability.

- Consider Process Performance Qualification (PPQ) studies using the same donor cell line repeatedly, as this will allow the underlying process repeatability to be evaluated independent of cell line variability.

2.10 Quality Assurance and Quality Control

Autologous cells modified for use as therapeutics are considered drug products that require phase appropriate GMP. GMP for early clinical phases include phase appropriate requirements compared to commercial stage products. A Quality Management System is required to oversee the product lifecycle; from manufacturing to patient use of cell treatments. Some products are regulated as combination products, and therefore, medical device regulations would be relevant (e.g., use of Device History Files, Device Master Records, etc.). Manufacturing and distribution of autologous cell therapies often adopt distributed models for commercialization (e.g., multiple clinics/hospitals associated with manufacturing sites) and point-of-care models (patient-centric). This is driven by the product limited stability properties, and the equipment and support systems needed for administration of treatments. QA and QC require additional considerations to support product release and the commercial models. The remainder of this section covers special QA and QC considerations applicable to autologous cells. Several of these topics are also further discussed in Chapter 4 from a manufacturing process perspective, Chapter 5 from a facility perspective, and Chapter 8 from a supply chain perspective.

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2.10.1 Donor Cells

Cells are collected from the patient and intended for the same patient. There are safety screening requirements for the collected cells to ensure safe handling, processing, and use (see EU GMP Part IV paragraph 7.33 [2] and Directives 2004/23/EC [22] and 2002/98/EC [23]). Donor eligibility procedures include a medical assessment and donor health history assessments are performed against a series of exclusion criteria before collection. Cells can be analyzed for potential pathogens and are characterized sufficiently for processing (e.g., screening for pathogens, HIV, and other viruses). Cells that are not screened for pathogens are risk assessed for processing and labeled accordingly. Traceability is initiated at the point of cell collection (e.g., apheresis), and the process is started without delay. Fail-proof identification and traceability controls are used to ensure that the final cell therapies are fully traceable to the donor and that the chain-of-custody is secured.

2.10.2 Raw Materials

Raw materials are a significant source of variation in the process, and therefore should be well understood and controlled. Examples of materials are cell culture media, buffers, cell separation reagents, and single-use components. Materials intended for cell therapies should be selected and characterized during the development process. Materials identified as *research grade* may be used for early stages in product development if properly qualified and sourced from approved suppliers. Commercial grade materials should be used as soon as feasible to minimize changes later in the process. Human-derived materials (e.g., serum albumin) should be sourced from licensed products and facilities. Animal-derived materials need to be avoided or screened for TSE (Transmissible Spongiform Encephalopathy), BSE (Bovine Spongiform Encephalopathy), and other adventitious agents.

GMP for materials applies to autologous cell therapy applications. These include following written procedures, receipt and storage of materials, material identity, testing against approved specifications, evaluation and qualification of suppliers, and material qualification activities [24]. Well-characterized materials from reliable suppliers are key elements to ensure consistent product quality.

The quality of materials is important in the manufacturing of cell therapies. Special attention is placed on material contamination and its inherent variability. The risks for contamination are assessed and control measures are established to mitigate them to acceptable levels. Materials should be certified as free from bacteria, fungi, and mycoplasma prior to use to eliminate contamination risks.

Starting materials are those materials that end up as a component of the final product (cells, tissue, etc.) and are subject to strict quality controls to ensure they meet viral and microbial safety specifications. They also have strict release criteria for quality and safety prior to use. Risk analyses are recommended for exceptional cases where starting materials are managed or manipulated outside a GMP environment. The relevant regulatory authorities should agree with the overall control strategy.

2.10.3 Analytical Methods and Quality Control Testing

Analytical methods produce reliable data to support product development, the establishment of CQAs, regulatory submissions, and lot release decisions. Assays are required to be validated to support late phase clinical and commercial stages of manufacture. QC testing needs to match product release turnaround requirements to ensure the process is completed and delivered to patients in a consistent manner. This may require fast methods (e.g., rapid microbial methods) or staggered release approaches. Functional assays are needed to identify appropriate biomarkers, validate rapid-release tests, and provide for in-process monitoring. QC methods used in development are frequently not compatible with rapid release. A QC strategy to move from in vivo assays to cell culture assays to biochemical assays is typically required to achieve appropriate release times.

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2.10.4 Product Release

There are multiple requirements for product release such as batch record reviews, material release confirmation, investigation and closure of quality relevant deviations, confirmation of lot traceability controls, verification of Chain-of-Custody documentation, EU Qualified Person Certifications [1], and completion of release testing. Usually, the last product release step is to confirm compliance with sterility, microbial, and mycoplasma specifications due to the time it takes to complete the tests. Rapid microbial testing methods can be used as part of release strategies for time sensitive treatments. Staggered (e.g., two-level release) may be considered to overcome long testing times to meet product delivery requirements. Partial release decisions can be staged at product filing stage and product shipping stage. Final product release is normally required prior to patient use. A robust product release process with effective notification triggers is required to ensure product can be intercepted if conflicting product quality information is identified prior to patient use. Some regulatory agencies describe exceptional circumstances where a product that is out of specification may still be necessary to be administered to avoid immediate harm to the patient, after taking into consideration all alternatives (e.g., EU GMP Part IV, section 11.5 [2]). A risk-benefit analysis and justification are required in addition to notification requirements as detailed in the regulation.

2.10.5 Vein-to-Vein Traceability (Chain-of-Custody)

Traceability is a critical feature for autologous cell therapies and must be established throughout the product lifecycle. Vein-to-vein traceability ensures the correct product is used by the patient.

2.10.6 Product Transportation and Supply Chain

Autologous cell therapies may not remain viable at ambient temperature over extended periods, requiring cold storage between processing phases. Shipping and distribution (transportation routes) should be qualified and temperature logged to ensure proper conditions (e.g., temperature, pressure, physical integrity). The patient's cells are transported to the manufacturing facility for processing and then back to the clinic/hospital site for patient use. For short shelf-life products, the transportation controls should ensure that the stability lots experience the shipping conditions to be used. Cryo-preservation systems and controls are used during storage and across the supply chain as needed to preserve the products until delivery and patient use. See also Chapter 8.

2.10.7 Long-Term Follow-Up

Cell therapies can be monitored for an extended period of time to evaluate delayed adverse events. This follow-up is conducted formally when needed as described in regulatory guidance documents and involves several aspects such as the assessment of risks for delayed adverse effects, creation of formal protocols, and establishment of duration of follow-up observations (e.g., 15 years). The schedules for patient clinic visits are prepared for each case, and a detailed history file is maintained. Annual reports are filed with regulatory agencies during the life of the protocol. Record retention procedures should be in place to ensure long-term retention of data.

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3 Technology Transfer and Scale-Out

3.1 Introduction

Technology transfer and scale-up are relatively well-established processes in the traditional pharmaceutical industry. The industry often contracts services out to third parties for both technology transfer and scale-up/scale-out of product. These contracts may be from development to manufacturing or between manufacturing units/sites within one country or across different countries. The transferee (receiving unit) may therefore be subject to different regulatory guidance than the transferor (sending unit).

While technology transfers for ATMPs may differ in some ways from traditional pharmaceutical products, the same principles of meeting the requirements of product safety, quality, and efficacy apply. Technology transfer relates to the philosophy of transferring a process from the sending unit to the receiving unit while maintaining process performance characteristics and adhering to local regulations. The product CQAs need to be achieved at the receiving unit based on the knowledge from the sending unit.

For autologous cell therapies, one of the major challenges in manufacturing is that it cannot be scaled-up. The autologous process involves one-patient to one-batch, which limits batch volumes. For example, Chimeric Antigen Receptor T-cell (CAR-T) therapies are less than 12 L per batch. Each unique batch is made to order rather than manufacturing large batches of a therapeutic protein, for example. Finding ways to increase the number of patients that can be served, while maintaining quality, is critical. Thus, scale-out (increase in capacity by increasing quantity of equipment) rather than scale-up (increase in capacity by increasing capacity of equipment) is the approach for autologous cell therapies.

Scale-out is similarly about ensuring CQAs are achieved within agreed acceptance criteria. For autologous ATMPs, the effort is primarily focused on organizational, facility, or utility changes. Increasing facility capacity now means creating more cleanroom footprint to do the work and shifting the mindset from scaling-up to scaling-out. Scale-up of equipment is not a factor since the equipment is likely to be identical. The major challenges with scale-out are related to the amount of manufacturing space needed to handle multiple batches at one time, causing scale-out to be more expensive.

The major hurdle in ATMP technology transfer is taking the therapies from the research laboratory to commercial manufacturing. There are manual process steps that do not transfer well to the specifications needed for commercial manufacturing; this is being addressed by newer automation equipment and processes. Due to the complex manufacturing process (as illustrated in Figure 1.2) coupled with the lack of standardized operations, technology transfer of autologous cell therapies requires keen oversight and continual improvement. The following aspects are key to a successful technology transfer:

- Robust and thorough validation and control strategy, e.g., validation plan, QTPP, and document development history prior to technology transfer
- Complete understanding of product/process CQAs and CPPs
- A diverse and highly skilled team
- On-site laboratory scientists supporting the manufacturing team
- Subject Matter Experts (SMEs) to support engineering runs
- Clear and detailed Standard Operating Procedures (SOPs)
- Management reviews performed to understand how the developed product and process can be manufactured at commercial scale

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- Finalized closure risk assessment to indicate where the process is at risk for contamination and cross-contamination

For detailed information regarding technology transfer, refer to *ISPE Good Practice Guide: Technology Transfer (Third Edition)* [25].

Refer to Appendix 1 for regulatory considerations related to technology transfer/scale-out.

The remainder of this chapter covers technology transfer/scale-out quality aspects and implications on the supply chain and facilities/utilities. A case study is also provided.

3.2 Quality Aspects of Technology Transfer/Scale-Out

3.2.1 Quality Risk Management and Risk-Based Approach

ICH Q9 [13] defines QRM as *"a systematic process for the assessment, control, communication, and review of risks to the quality of the drug (medicinal) product across the product lifecycle."* It lists the following applications of QRM as part of development:

- As part of development: *"To assess the need for additional studies (e.g., bioequivalence, stability) relating to scale up and technology transfer"*

- As part of change management/change control: *"To evaluate the impact on product quality of changes to the facility, equipment, material, manufacturing process or technical transfers"*

Autologous cell therapies, as compared to allogeneic therapies, do not lend themselves to a scale-up manufacturing strategy because of patient-specific treatments. Manufacturers of autologous therapies must rely on QRM to ensure that each step of the manufacturing process is evaluated and reviewed during technology transfer and scale-out.

The EMA guideline on risk-based approach [15] states:

> *"The risk-based approach is based on the identification of various risks associated with the clinical use of an ATMP and risk factors inherent to the ATMP with respect to quality, safety and efficacy.*
>
> *The risk factors associated with a specific risk (e.g., . . . treatment failure) are likely to be product specific and multifactorial . . . Risk factors are related to, for example, the biological characteristics of the product, the manufacturing process, and the specific therapeutic use of the ATMP. For each risk factor, its contribution to an identified risk associated with the product under development will need to be evaluated in order to conclude on each risk."*

3.2.1.1 Risks Associated with Technology Transfer and Scale-Out

The following aspects should be considered during technology transfer and scale-out of autologous cell therapies:

- Monitoring of CPPs: The CPPs need to be monitored closely during the production process because of changes when scaling-out.

- Supply Chain: In the case of the sending unit manufacturing raw materials and finished products in the same location, the receiving unit will need to understand the risks with shipping and coordinating the raw materials and finished products between facilities. See Chapter 8.

- Comparability: Demonstrating true comparability requires proper planning to ensure the drug product and ancillary materials meet the same requirements between the sending and receiving units.

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- Technology Transfer: Ensuring quality and GMP standards are upheld at Contract Manufacturing Organizations (CMOs), changes in process timing, extra timing is needed for real-time activity verification.

- Equipment Type and Size: During a technology transfer, the risks with using better and more efficient systems, such as equipment for washing cells, can impact the processing environment.

- Knowledge Transfer: It is important to ensure differences in CQA testing, training, and automation and IT technologies are documented.

3.2.1.2 Mitigation of Risk

The ATMP industry is moving towards incorporating automation wherever possible to speed up delivery of therapies to the patients. With patient focus as a primary focus, implementation of digital manufacturing practices (e.g., implementation of a Manufacturing Execution System (MES)) must be incorporated wherever possible in the design of new facilities to optimize timelines and reduce human error. The following aspects should be considered:

- Automating standard processes wherever possible leads to eliminating human interaction and open processing

- Utilization of electronic batch records leads to the high-level goals of eliminating paper in cleanrooms and allows for quality review by exception, resulting in expedited release times which result in faster vein-to-vein times

- No manual data entry

- No open operations

3.2.2 Control Strategy

The following aspects relate to control strategy and the importance of understanding CQAs, CPPs, and Critical Material Attributes (CMAs):

- ICH Q8 [19] states *"A control strategy is designed to ensure that a product of required quality will be produced consistently. The elements of the control strategy . . . should describe and justify how in-process controls and the controls of input materials (drug substance and excipients), intermediates (in-process materials), container closure system, contribute to final product quality. These controls should be based on product, formulation and process understanding and should include, at a minimum, control of the [critical quality attributes,] critical process parameters and material attributes."*

- ICH Q10 [16] defines control strategy as *"A planned set of controls, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control."*

  This definition can be broken down into its elements, so taking each in turn:

  - Materials:

    > The understanding and control of CQAs, CPPs, and CMAs, along with having a clear product and process flow, are fundamentally important to ensuring that an effective control strategy is in place for an ATMP.

    > Examples of CQAs include cell quality/viability, potency, bioburden, impurities such as viral vector protein, particulates, etc.

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> Examples of CPPs include pH, centrifuge controls, etc.

> Examples of CMAs include media composition, Water for Injection (WFI) quality etc.

- Components:

> Example parameters/attributes include control of the quality of vials, stoppers, bags, etc.

- Facility and equipment operating conditions:

> Example parameters/attributes include air classification, material specifications where there is product contact, room quality and design to ensure material and people can operate securely from a product quality point of view, etc.

- In-process controls:

> ATMP facilities depend on controlling many manual interactions (at the time of publication). In-process controls are often in-process CQAs, i.e., a measurement of a process output that is critical for the final product CQA. As experience is gained, these steps perhaps will become more automated to enable more process controls.

- Finished product specifications:

> Specifications have to be met, but the development of these specifications is important to ensure there is strong focus on the patient and also that they are practical to implement.

- Associated methods and frequency of monitoring and control:

> This is one of the most important requirements for ATMPs as there can be many steps and controls involved. Also, steps may have to be adapted as the individual product knowledge is gained. Many controls are manual, examples include documents signed and witnessed, manipulation of materials in clean air hoods, storage of materials within a laboratory setting or warehouse, control of all documents to meet individual patient requirements, ensuring the operational and facility requirements are met, etc.

- ATMPs often suffer from heterogeneity/variability in the cellular starting material, which may have a further impact on the consistency of the production process and of the final product. The cellular starting material (patient biopsies/blood) could include variability associated with demographics or other medical indicators, such as a patient's age, ethnicity, gender, and comorbidities (e.g., diabetes). These factors should be evaluated to determine if a correlation with cell line performance can be established.

- Identifying and controlling sources of variability:

  - Take a comprehensive pharmaceutical development approach to generate process and product understanding and allow for identifying sources of variability. Product and process understanding support the control of the process such that the variability can be compensated for in an adaptable manner to deliver consistent product quality.

  - It is important to identify sources of variability that can impact product quality, appropriately understanding and subsequently controlling them.

  - These sources of variability can be greatly affected when scaling-up or transferring due to changes in volume and/or environment.

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3.3 Implications of Technology Transfer/Scale-Out on Supply Chain

With autologous therapies, biological material is collected directly from the patient (e.g., apheresis). The material is transferred to the manufacturing site, where the cells receive genetic or other modifications and are produced in expanded quantities. The therapy is then shipped back to the clinic and administered to the patient. Both the initial material and therapy must be shipped under temperature-controlled conditions in a very short period of time. The therapy transfer requires strict temperature and chain-of-custody monitoring. For more details related to supply chain, refer to Chapter 8.

The technology transfer/scale-out challenges associated with autologous cell therapy supply chain include the following:

- Many autologous products are produced at a CMO or a remote manufacturing facility, which increases the difficulty of collection, transport, and receiving of ATMPs as there is an additional variable in the supply chain.
- The patient is part of the supply chain process, and scheduling times for collection, manufacturing, and administration can be challenging.
- Cell therapies are often vein-to-vein treatments; there are generally no backup supplies if a batch is rejected. Ensuring product quality requires careful supply chain planning.
- As product demands increase, the demand for input materials increases. For example, viral vectors are needed for gene or other modifications and require a complex manufacturing process, which could pose a potential bottleneck in the overall supply chain. This also applies to other materials, components, or even parts for equipment.
- Autologous therapies require quick turnarounds especially with fresh or frozen product (typically less than 48 hours) in transportation time from patient to manufacturing.

3.4 Implications of Technology Transfer/Scale-Out on Facilities and Utilities

When transferring or scaling-out to a different facility, the following aspects should be considered:

- Proper location of facility, e.g., near airports to ensure easier/faster access to supplies, regulatory incentives, or access to sufficient talent.
- The size of the facility available versus the scale of process and the size, quantity of equipment needed to perform the process, number of personnel needed to support production, flow of personnel and materials, gowning areas, liquid nitrogen freezer space, etc.
- Whether it is a multi-product or single product facility. If multi-product, consider how to avoid impacting current operations with the new technology transfer/scale-out.
- Whether the facility will be used for producing clinical phase materials or commercial manufacturing.
- The type of electronic systems that are planned for installation. Planning during the design phase could be required for systems tied into the infrastructure of the facility.
- What utilities are readily available and how they differ from current facility.
- Cleanroom design, for instance, modular or stick built, etc.

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- Ample space for all support aspects including manufacturing, QC testing, raw material storage, product storage, cold storage, and Product Quality support.
- The right equipment for the scale and the right quantity of each unit.
- Warehouse space: Large enough to store raw materials, product, and close to the production area for quick access.
- Whether redundant suites are required to ensure an uninterrupted production schedule is available, i.e., can maintenance be performed as necessary without the need to stop production?
- Future facility considerations such as flexibility, redundancy, and evolving technology, e.g., adequate QC expansion space to support increased therapy production.

Process modeling and simulation are highly recommended (note that this does not include sterility validation):

- Using a model of the process to define predicted throughputs helps to guide the team to properly size the facility.
- Take into consideration that the time to manually transfer product-in-process through each task and between suites is greatly lengthened when scaling-out. This can potentially affect personnel availability, equipment occupancy, materials staging, or decontamination cycle times.
- Using models and simulation can help to identify pain points and right-size facilities for present needs, but also helps toward future expansion.

Refer to Chapter 5 for more details regarding multi-product use facilities, CCS, and process simulation.

3.5 Case Study – Building a Cell Therapy Facility

Scenario: Building a cell therapy facility.

- Company X manufactures a personalized CAR-T therapy.
- Company X was looking to expand to a larger facility to increase their ability to manufacture a variety of CAR-T therapies to support future market demands. At the same time, Company X was looking to upgrade their existing facility.
- Company X was seeking to create a new automated, closed cell therapy manufacturing process to reduce costs while substantially improving quality and driving manufacturing efficiency.

Task: Upgrade Company X's existing manufacturing facilities while building a large, automated CAR-T manufacturing site.

- Provide multidisciplinary, cross-functional teams to ensure timely equipment installation, commissioning, and qualification. Drive the procurement process for the new facility from user requirements generation to asset induction including equipment procurement, capital expenditure management, asset tracking, vendor relations, and legal.
- Implement and execute a lean validation strategy leveraging intended use and family approaches for building commissioning, utility qualification, laboratory systems and equipment qualification, GMP manufacturing equipment, and computer system integration and validation.

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- Collaborate with client, equipment, and vendor teams to develop a novel cell therapy manufacturing process to be installed at the new facility in parallel with construction.

Actions: Create cross-functional teams to retrofit an existing facility for a variety of CAR-T therapies, validate existing clinical and commercial facilities, and create a first-of-its-kind greenfield cell therapy facility.

- CAR-T Startup: Utilized 15+ resources to support retrofit of an existing facility for viral vector and media manufacturing.
- Novel Cell Therapy Manufacturing Process: Utilized 5+ resources to support the development and qualification of a new cell therapy manufacturing process and equipment.
- Existing Facility Validation Support: Utilized 5+ resources for validation management and execution at existing CAR-T therapy commercial site.
- New Facility Support: Established commissioning and qualification strategy, strategy execution, and work stream project management. Supported the development of novel equipment and process for the new greenfield facility.

Results:

- For both the existing facility and new facility, created the validation master plan, risk assessment, commissioning plan, and facility User Requirement Specification (URS). Provided commissioning and qualification strategies to simplify the execution, reducing cost and scope for the client.
- Provided project management for multiple client work streams for the new facility including project schedule, scope, and analytical reporting. Mobilized several tactical teams and created various swim lanes to divide, organize, and manage quality control, building readiness, and automation of process control systems (including a monitoring system, site historian, and electronic batch record software).
- Utilized innovative single-use disposable platforms at the new facility to improve consistency and reduce risk to the patient.
- Collaborated with cell therapy equipment manufacturers to engineer and design an automated solution replacing manual processing. Modified scope to mitigate project delays and ultimately delivering first-of-its-kind equipment to commercial cell therapy manufacturing.
- Executed off-site equipment commissioning and qualification strategy allowing commissioning and qualification to be done in parallel with the utility and building startup, providing significant cost and schedule savings.
- Recognized that just because the project ends, it does not mean the work stops. Continual support of process maturity is important.

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4 Autologous Cell Therapy Manufacturing Process

4.1 Introduction

This chapter covers key aspects of the autologous cell therapy manufacturing process related to process closure, sampling and QC, and process understanding.

Because autologous cell therapy is derived from a single patient and then used to treat only that patient, the production size is usually limited to a few lots and the manufacturing process develops as a scale-out rather than a scale-up. During the bioprocessing of autologous cells, it is also required to keep cells that are derived from different patients rigorously separated to avoid cross-contamination. Therefore, autologous therapies require a significant amount of manual small-scale operations due to repetition of the *in vitro* operations (cell isolation, centrifugation, expansion, etc.). The implications are less standardization can be applied and more trained personnel have to be employed, raising the cost of the cell therapy production.

The protocols and methodologies for cell therapies were developed by scientists working at the bench scale in academic laboratories, research institutes, etc. A big step and challenge in the production of ATMPs resides in the translation of the manual basic laboratory procedures (usually performed in BSCs in open laboratories) into strictly standardized, safety and quality-controlled operations to be performed in aseptic containments, such as clean rooms and isolators. The manufacture of patient-specific ATMPs is also challenging in terms of media and buffer manufacturing, given the need for small volumes at various time points and the limited applicability of standard methods for large-scale manufacturing, release, storage, and transfer.

The majority of the current installations for ATMP manufacturing are done in traditional BSCs with ISO 5/Grade A air and ISO 7/Grade B surrounding, with manual operations and transfers. While performing open operations under the BSC offers for the process a higher flexibility to transfer and operate materials, components, utilities, etc., it presents a higher risk of contamination, cross-contamination, and product mix-up, compromising sterility. The same consideration should be given to the control of the manufacturing process as it is often currently done with written procedures. For considerations on the use of barrier technology, see Section 4.2.3 and Chapter 5.

This chapter provides a holistic approach to QRM and CCS for the use of advanced technologies. Contents include process closure, sampling & QC, and process understanding. For information on regulatory requirements related to started materials, refer to Appendix 1.

4.2 Process Closure

Autologous cell therapies have primarily been developed with open process steps for several reasons including manual manipulation of small tissue samples, small liquid volumes, small patient populations, and lack of specialized commercial systems. Taking innovative biological engineering techniques and turning them into commercial, scalable processes is going to require a reduction in risk (contamination and process variability) and cost control to manufacture. Closing process steps can help with the successful maturation of cell therapies.

Several considerations are 1) process development/equivalency between open and closed, 2) raw material supply format (e.g., bottles, vials), 3) developing robust in-process controls/transition to on-line analytics.

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4.2.1 Processing Requirements and Considerations

Autologous cell therapy manufacturing is required to meet aseptic processing requirements from start to finish. Open operations performed under an ISO 5/Grade A BSC require an ISO 7/Grade B background environment. In contrast, closed operations can be performed in an ISO 8/Grade C (or Grade D based on EU GMP [2]) environment depending on the CCS. The capital and operating costs linked to the higher classification required for open operations are substantial. Typically, a larger square footage requires additional airlocks, gowning areas, and corridors. A higher cost per square foot is attributed to the high air change rate requirement and other facility design considerations required to meet the classification. Continuous EM, utility cost, and additional gowning and cleaning also contribute to the increased operating cost. In addition, highly trained operators that have mastered aseptic practices and other techniques involved in the manual steps of the process are required to consistently perform open processes.

The starting material for an autologous process typically needs to be processed in a short timeframe after cell collection. It is collected or surgically removed at a medical facility (with potential variation between facilities) and shipped to the manufacturing facility for processing. In some cases, the preparation step of the process must be performed immediately upon receipt, without having received the analytical test results required to confirm absence of infection or contaminant. Therefore, all material must be processed in a manner that protects the environment of the manufacturing facility from potential contaminants in addition to preventing the introduction of external contaminants to the in-process material.

An autologous manufacturing facility needs to process lots for multiple patients per day. Physical segregation of these patient lots is required to prevent cross-contamination. In the case of open manipulations, this is often achieved by segregating the process into separate rooms or areas within a larger room. The technicians, equipment, and instruments could also present a risk of cross-contamination between patient lots in the case of open processing. Thorough change over, disinfection, and cleaning procedures are required for the environment, equipment, and instruments in between patient lots. Additional procedures and controls around personnel flow must also be put in place to prevent a technician from working on a different patient lot without change of gowning. These controls are especially critical when processing multiple patient lots in the same room. A risk-based approach should be followed to determine the engineering and procedural controls required to mitigate mix-up and cross-contamination risks. Segregation strategies are further discussed in Section 5.2.3.

The autologous process is developed during the early clinical stages when a low volume of patient material is processed. The challenge when proceeding to a commercial scale is that a typical bioprocess scale-up process cannot be performed. The lot size remains the same and the scale-out process of a manual and open aseptic process will result in large facilities requiring a high number of highly trained technicians.

Most autologous processes occur over multiple processing days with an incubation period in between to allow for cell expansion. Special considerations must be taken around the system that contains the cells and the growth media to allow storage of multiple patient lots inside the same incubator; the criticality of closure and technologies is discussed in Section 4.2.3.

4.2.2 Process Development Considerations (Transitioning from Clinical Development to Commercial Scale)

ATMPs can quickly move from clinical to commercial scale, requiring a rapid ramp up of production capacity. This challenge can be overcome by careful selection of the technology or systems used in the process during the clinical stage.

Once a product is approved, changing the manufacturing process or systems used in the process will involve repeating lengthy process development steps (e.g., characterization, stability, extractables and leachables studies, supplier qualification, process validation, and process comparability) to allow regulatory approval of such change.

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Selection of closed technologies at the initial process development stage will improve a company's agility when moving into commercial production. The time and cost required to perform process changes that are implemented to either mitigate issues brought on by the high risks of manual open manipulations or to allow easier scale-out and capacity ramp up will impact a company's ability to respond to the market demand for the therapy.

4.2.3 Process Closure Technologies and Strategies

Most processes can be closed by utilizing various commercially available technologies and strategies. The design of a closed process can be achieved by laying out the process into specific steps. Strategies for process closure include:

- Using a closed device, container, or bag to contain the cells, in-process product, media, or buffers, where possible
- Taking the particle limit and the typical extractables and leachables into consideration while evaluating closure systems as most products cannot be filtered
- Adding or removing liquids through disposable tubing using gravity, pressure, or small pumps
- Taking samples using manifolds that are connected to sampling containers
- Using multiple aseptic connections and disconnections throughout the process

When a process step cannot be closed, an environment enclosure (such as an isolator or rapid access barrier system) can be utilized to isolate the product from human interaction and the outside environment. This strategy reduces the surface area required to be maintained at a higher classification and reduces the risk of introducing external contamination.

4.2.3.1 Isolators

For operations that must be performed in an open environment (e.g., tissue preparation, open product sampling, and sterile filling) or where non-sterile connectors cannot be used, isolator technology can be utilized. An isolator maintains an ISO 5/Grade A environment without interaction with the room environment. It is decontaminated with vaporized or sprayed hydrogen peroxide (H_2O_2) prior to introducing any material, and typically has a material airlock chamber that allows for the removal of protective layers or decontamination of raw materials or instruments prior to entry into the processing zone.

Potential exposure to the vaporized or sprayed hydrogen peroxide may have an impact on the cells or product. Containers should be assessed for leaks and diffusion of hydrogen peroxide into the container under operating conditions. Technical solutions include, for example:

- Material transfers with extremely short time and low concentration of hydrogen peroxide exposure
- Material transfers airlock where the outer surfaces of the containers are sanitized with Isopropyl Alcohol (IPA) before entering the isolator

The total number of cell culture movements in/out of an isolator should be considered when evaluating the feasibility and design of the isolator.

Material transfer chambers allow for fast material transfer from ISO 7/Grade B, ISO 8/Grade C, or Grade D into ISO 5/Grade A in less than 10 minutes (e.g., transfer airlocks) and in less than 5 minutes (e.g., rapid transfer ports).

Glove ports are typically required to perform operations within the isolator. Manipulation through gloves can cause a loss in dexterity and potentially increase operator fatigue. A risk assessment needs to be performed to evaluate the selection of glove materials and what operations can be executed within the isolator. Additional safety and ergonomics can be achieved through robotic arms to reduce or eliminate glove intervention by technicians.

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Barrier technology is discussed further in Section 5.2.5.

4.2.3.2 Disposable Aseptic Connectors

Aseptic/sterile connectors can be utilized to join lines of tubing without compromising the sterility of the fluid path. These connectors are built into the disposable assemblies which are designed based on each specific process considering the amount of connections required during the unit operations. Many options are commercially available for all sizes of tubing.

Disposable disconnectors are also available to aseptically disconnect pieces of tubing. These connectors are easy and quick to use, but most can only be used one time. They can be cost prohibitive for processes requiring a large number of connections and disconnections. Not all sterile connectors are suitable for a room environment of ISO 8/ Grade C or Grade D. Specifically, Luer fittings and IV bag spikes are routinely used as sterile connectors within a clinic/hospital setting but may not be acceptable within a manufacturing setting. The use of those connectors should be risk assessed.

4.2.3.3 Tube Welders

Tube welders (or sealers) are commonly used in small-scale disposable processes. They allow for aseptic connection and disconnection of two pieces of disposable tubing. The connections and disconnections are used in real-time during the manufacturing process and thus allow for more flexibility regarding the number of connections and process variability. They have a higher rate of failure and leak generation compared to single-use connectors, which may require risk mitigation. Appropriate controls should be implemented via qualification and routine challenges. The test welds should cover the expected uses (e.g., dry/dry, dry/wet, wet/wet) and across the range of tubing sizes and materials utilized. The test welds should be subject to leak checks (e.g., pressure decay, bubbles) and/or tensile strength tests. Tube welders are typically tabletop equipment that requires manual operation, making them harder to use in an enclosure. The particle generation associated with the use of a tube welder may have a significant impact on area environments with low particle limits.

4.2.4 Unit Operation Alignment

4.2.4.1 Media, Buffer, and Cryo-preservative Agent Preparation

The supplementation of media and preparation of process buffers and cryo-preservative agents are generally manual processes that involve small volumes, sometimes in the µL range. This can be further complicated by batch specific formulation and/or short hold times after formulation. At the development and clinical scale, these small formulations or supplementations of purchased sterile solutions are conducted in BSCs. The use of small bags, vials, or tubes with tubing connections for the aliquots can address the processing need if the addition quantity is consistent. For variable/factored formulations, the use of micro/serological pipettes or syringes in an isolator can provide closure, and rapid transfer ports may be used to remove time sensitive formulations.

4.2.4.2 Starting Material Handling

Several operational steps are derived from medical practices that involve standard medical techniques to control contamination under the proper training and supervision of a licensed medical professional. In the point-of-care manufacturing model, these operations will continue to happen under that practice. However, risk assessment and process impact studies are needed to understand how to provide a consistent level of control across a network of enrolled clinics. When integrating process closure (single-use systems or isolators), considerations need to be made for the operation being performed and the contaminants from the patient collection. For example, when the isolation of cancerous tissue from a biopsy is used as the starting material, an excisional open biopsy procedure using sterile implements in a sterile field could be used to attain the tissue. If the isolation of cancerous tissue from the biopsy is immediately in the sterile field of the operating suite, then it is considered a lower product risk as compared to the additional manipulation to transfer it into a closed system for isolation. This same consideration needs to be addressed in the regionalized or centralized manufacturing model, but with the understanding that the handoff has crossed regulatory and expertise boundaries when the starting material is delivered to a manufacturing facility.

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To facilitate this handoff, considerations should be made to supply enrolled clinical sites/hospitals with donation collection materials. During clinical trials, this may not be set up and the ability to handle variable starting materials (e.g., an apheresis bag that requires a spike to access the starting material from the patient) should be considered.

4.2.4.3 Cell Expansion

While cell expansion of human cells has traditionally been done in T-flasks, several different vessels/structures are being used to culture adherent cell lines for autologous cell therapies. Some of these vessels are provided with connections that utilize vent caps.

Closed processing with vent capped devices requires that the vessel be opened and manipulated within an isolator. Unless the incubator is directly connected to the isolator, the transfer of the culture vessel into an isolator requires consideration for the time outside of the incubator environment and the potential impact of the sterilizing agent used to decontaminate the exterior of the vessel.

Fully closed systems that utilize aseptic connectors or tube welds for transfer provide a simpler operation and are offered as an option for most adherent cell culture structures. Example systems include traditional rigid containers adapted with tubing (shown in Figure 4.1), rocker bioreactors, and microcarriers in agitated bioreactors. Additionally, vent filters other than the vent cap type (e.g., disk, capsule, internal membrane) allow for post-use integrity testing if warranted by risk assessment.

Figure 4.1: Example Closed Systems with Tubing and Disk Style Vent Filters
Image courtesy of Corning Incorporated, www.corning.com/lifesciences.



4.2.4.4 Viral Vector Addition (Transduction)

For cells modified by transduction, the addition of viral vector in a closed manner poses similar challenges as media supplementation (previously discussed in Section 4.2.4.1). Coordination with the viral vector supplier to provide tubing connections is only part of closing this operation. As many processes utilize a factored amount of vector, dosing accuracy needs to be considered. Volumetric dosing can utilize syringes with tubing or small peristaltic pumps but are limited to milliliter (mL) level dosing. Gravimetric dosing can be easier to verify accuracy with a post-dosing weight check. Viral vectors pose a biosafety risk as they can be transferred as small aerosol droplets and potentially contaminate the surroundings and the technicians working in that area.

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4.2.4.5 Non-Viral Vector Addition (Transfection)

For cells modified by transfection, i.e., using a non-viral vector, different technologies are available. The leading technologies (at the time of publication) include liposomal nanoparticles, electroporation, and chemical competency. Liposomal nanoparticles are dosed to a mixing vessel similar to supplementation operations. Electroporation operations traditionally use open cuvettes, although several manufacturers have developed disposable closed cuvette/cartridge systems that are available pre-sterilized.

Rendering cells chemically competent for cell therapy is a novel process undergoing development. Manual draining and resuspension are a challenge to demonstrate repeatability within a closed system. At least one manufacturer has developed an automated pre-sterilized closed system for making chemically competent cells.

4.2.4.6 Cell Selection (Apheresis/Leukapheresis)

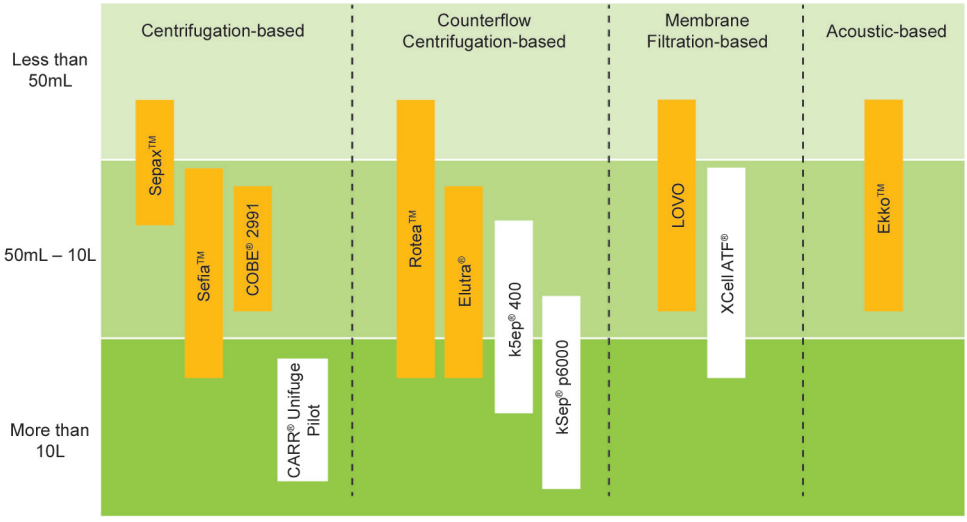
Several closed systems are available for apheresis/leukapheresis cell selection. These systems utilize centrifugation, filtration, acoustical, and microfluidic means. These technologies are limited in the enrichment of cells carrying a targeted biomarker (e.g., CD4+, CD8+) unless bound to a marker. Immuno-selective resins or immunomagnetic beads provide a means to select a cell for separation by size/mass. The use of immunomagnetic beads (monoclonal antibodies conjugated to superparamagnetic iron dextran particles) also allows for cell selection via magnetic separation which is typically less stress inducing than the typical technologies. The immune-selective resins or immunomagnetic beads are typically supplied in vials and need to be transferred into a bag before attachment to a closed processing unit.

4.2.4.7 Cell Washing/Formulation

Cell washing and formulation can utilize centrifugation, filtration, acoustical, and microfluidic means. The same equipment used for cell selection is sometimes used for washing immediately after selection. Since formulation is typically done later in the process, the tendency is to use equipment dedicated to wash/formulation. It is important to consider the holdup volume as the product is typically the most concentrated during this operation. In some designs, formulation is coupled with the filling operation.

Figure 4.2 shows a cell washing technology summary.

Figure 4.2: Cell Washing Technology Summary [28]



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4.2.4.8 Filling

One-patient, single-batch is a drastic change from the scale that the pharmaceutical industry is accustomed to. While the presentations for these therapies vary depending on the ultimate administration, bags and vials are the most commonly used forms of containers. There are industry-proven solutions for small-scale vial filling, but personalized therapies such as autologous products redefine small-scale. Clinical lots for traditional therapies are in the low-hundreds vial range, but for autologous filling, the lot may be only a handful of vials.

Closed-vial filling allows the flexibility of hand-filling but adds a layer of sterility protection during the filling operation. Using closed-vial technology is ideal, as the setup, weight checks, fill, and cleanup are simple. The cleanup consists of tear out and throw away. The vials for closed-vial filling are typically constructed of polymer (specifically cyclic olefin copolymer), allowing for cryogenic freezing. Traditional glass vials with rubber stoppers have been shown to have seal integrity concerns at cryogenic temperatures [27] and should be avoided, if possible, for cryogenic applications.

Since the autologous therapies are typically infused, bags that can be directly attached to an IV set are another common option. A best practice is to fill volumetrically using an automated, closed system driven by a peristaltic pump with an inbuilt weight check and active cooling system. Figure 4.3 shows an example closed system for filling IV bags. The filling can be done manually or as part of a semi-automated or fully automated system. Bags are typically loaded into cassettes to provide a uniform thickness for freezing and to protect the bag from mechanical damage. Even bags with films designed for cryogenic temperatures become more damage-prone at those temperatures. Protective packaging is also needed for products shipped cold. Final products may be regulated as biohazardous. Biohazardous products require spill-proof and absorbent secondary packaging.

Figure 4.3: Example Closed System to Fill Intravenous Bags
Used with permission from Terumo Blood and Cell Technologies, www.terumobct.com.



Inspection and labeling typically coincide with filling. This avoids the intermediate bright stock tracking[2] challenges and can allow for quicker processing. The processing time between formulation and cooling/freezing is typically a CPP and can be only a few hours.

[2] Bright stock manufacturing involves producing products in large efficient batches, storing them in unlabeled individual containers, and labeled just prior to shipment. [29]

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