E&L considerations for ATMPS: challenges and possible strategies

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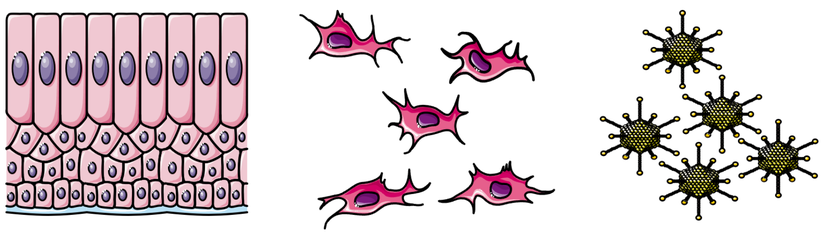
1 Introduction

ATMPs (Advanced Therapy Medicinal Products) is a broad and innovative category of biological products that encompasses GPTs (Gene Therapy Products), SCTPs (Somatic Cell Therapy Products) and TEPs (Tissue-engineered products). These therapies are notably complex and often customized to address the specific needs of individual patients or targeted patient niches which implies that developers and manufacturers have to deal with unique risks and challenges. The use of single-use systems (SUS) offers several benefits to overcome challenges in ATMPs production in terms of flexibility, modularity, costs and contamination control but, on the other hand, the impact on product quality, safety and efficacy should be carefully assessed.
Recent studies have reported that substances that leach from SUS may have a negative impact on cells. Thus, considering that cells are usually employed to manufacture ATMPs or even they are part of the final product, alteration in cell physiology and functionality raises patient safety concerns as well as drug substance (DS)/drug product (DP) quality concerns.
Thus, Extractables&Leachables (E&L) studies are required before submitting Biologics License Application (BLA)/marketing authorisation applications (MAA) but their role in early stages may be crucial for selecting the appropriate materials and preventing changes that may occur in the late stages of clinical development.
In this poster, the contrasts between traditional E&L and unique requirements of ATMPs are presented and discussed.

2 ATMPs overview

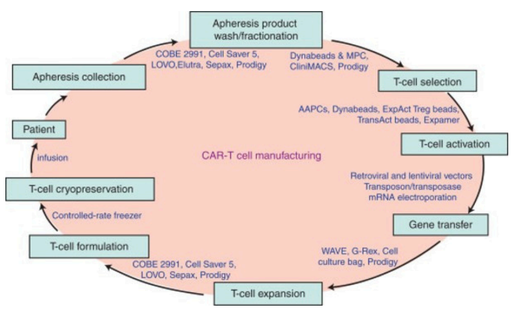


ATMPs are classified into three main groups according to Reg (EC) No 1394/2007:
1. Tissue-Engineered Products
2. Somatic Cell Therapy Medicinal Products
3. Gene Therapy Medicinal Products: Depending on whether the gene modifications are made in the laboratory or directly on the patient, these are defined as ex-vivo or in-vivo

They can be tailor-made for the individual patient (autologous: cells from patient are collected, treated, expanded and re-introduced into the same patient) or manufactured for larger population (allogenic: cells from healthy donors are collected, treated, expanded and introduced into multiple end patients).
Like all medicines, ATMPs, both for clinical trials and for commercial use, must align with the regulations related to Good Manufacturing Practice (GMP).

SUS in ATMPs manufacturing

Due to unique characteristics of ATMPs and their manufacturing process, these medicinal products demand additional requirements on manufacturing equipment.
In particular, cell-based medicinal products cannot be terminally sterilized by filtration and cells that have direct contact with manufacturing components are commonly part of the final product. Also, ATMPs are often produce in small batches and, in autologous therapy, patient's own cells are processed in a single batch.
For this reason, disposable technologies also known as SUS or SUT are largely employed in ATMPs manufacturing and for some of these medicinal products manufacturing platforms are available.
An example is CAR-T manufacturing process as shown below.



Source from, Clinical manufacturing of CAR T cells: foundation of a promising therapy, Wang X. and Rivière I., Molecular Therapy Oncolytics.

Pros and cons of SUS in ATMPs manufacturing

SUS (Single-use systems) are widely used in ATMPs manufacturing as they offer several benefits

- **Reduced contamination risk:** As SUS are disposable, the risk of cross contamination between batches is lower.
- **Flexibility and Scalability**: Easier scale-up or scale-down of manufacturing process as SUS can be adapted to different batche sizes more readily that traditional stainless steel systems.
- **Cost-effectiveness**: Initial capital investment may be lower than traditional stainless steel system. Additionally, there are savings in cleaning, maintenance and validation costs associated with resusable systems.
- **Improved time-to-market**: Reducing downtime and simplifying processes, SUS allow accelerated development and commercializtion of ATMPs.
- **Decreased downtime**: SUS eliminate the need for cleaning and validation between batches reduging downtime between production runs.
- **Enhanced process control**: Often pres-sterilized and pre-assembled, ensuring consisent product quality and minimizing risk of human error during assembly and sterilization process.

While offering numerous advantages in manufacturing, material compatibility may be one of the major risks associated to the use of SUS in ATMPs manufacturing.
In particular, leachables and particulates are a main concern for polymers which are common materials of construction for SUS, as they may impact the quality (e.g. impaired cell growth) and safety (e.g. genotoxicity, toxicity) of final products.
As a consequence, it is required that information about these impurities are provided for both process components and packaging.

3 E&L definitions & Approach

Extractables

A substance or chemical entity, extracted from a test article by an extraction medium under specified laboratory test conditions, including temperature, duration, extraction process, and dimensions of contact (e.g. ratio of test article weight or surface area to extraction medium volume).

Extractable: A substance that is transferred from a donor item to a receptor item when contact is initiated and maintained between the two items under laboratory conditions.

Extractables profile: All extractables, identified and quantified

Leachables

A substance or chemical entity, leached from a packaging system, a manufacturing component, or a medical device by a pharmaceutical product, process stream, or a body fluid/tissue, that is present in the pharmaceutical product, process stream, or body fluid/tissue because these objects contacted the system, the component, or the device during their manufacturing, distribution, storage, or clinical use

E&L – Regulatory framework and best practices

Regulatory guidelines and best practices that can be support E&L studies

Regulatory guidelines: USP 1663 · USP 1664 · USP 1665 USP 665 · ICH M7 ICH Q3D ICH Q3C

Best Practices: PQRI · BPOG

Even thoughthese may be used to support ATMPs, specific guidelines to address unique challenges of these medicinal products are currently notavailable. Indeed, leachables study requirements for ATMPs havenot been documented in published guidelines.

Dedicated guidelines should establish harmonized requirements which include aspects suchas extraction study conditions, simulation study to support E&L leachasbles risk assessments, analytical testing, material assessments, characterisation of leachables clearance/removal during processing.

Primary packaging regulatory guidelines and best practises

USP 1663 (Extractables study) → ICH M7; ICH Q3D; ICH Q3C; PQRI (Toxicological Risk Assessment) → USP 1664 (Leachables study)

USP 1663: The chapter establishes critical dimensions of an extractables assessment and discusses practical and technical aspects of each dimension

ICH M7: This guideline emphasizes considerations of both safety and quality risk management in establishing levels of **mutagenic impurities** that are expected to pose negligible carcinogenic risk

ICH Q3D: This guideline provide indications on how to assess and control **elemental impurities** in the drug product using the principles of risk management as described in ICH Q9

ICH Q3C: recommends acceptable amounts for **residual solvents** in pharmaceuticals for the safety of the patient.

PQRI: This document describes **recommendations for E&L assessments** of small volume, large volume parenterals and prefilled syringes with additional considerations for biological products.

USP 1664: This general chapter presents a framework for the design, justification, and implementation of assessments for **drug product leachables** derived from pharmaceutical packaging and delivery systems.

Process components regulatory guidelines and best practises

USP 1663, USP 665 (Risk Assessment / Extractables study) → ICH M7; ICH Q3D; ICH Q3C; PQRI (Toxicological Risk Assessment) → USP 1664 (Leachables study)

USP 1665; USP 665:This chapter is applicable to plastic manufacturing components that are used once and discarded (single-use systems) and components that are used once, rendered suitable for re-use (e.g., cleaning, sterilization) and then re-used in multiple-use systems.

Traditional E&L workflow

Risk Assessment

A risk assessment provides guidance on qualification procedures applicable to manufacturing components and systems providing a risk-based approach.

Extractables Study

The extractables study is performed under laboratory conditions in order to create extractables profile(s) of particular Pharmaceutical packaging/delivery systems, packaging components, or materials of construction.

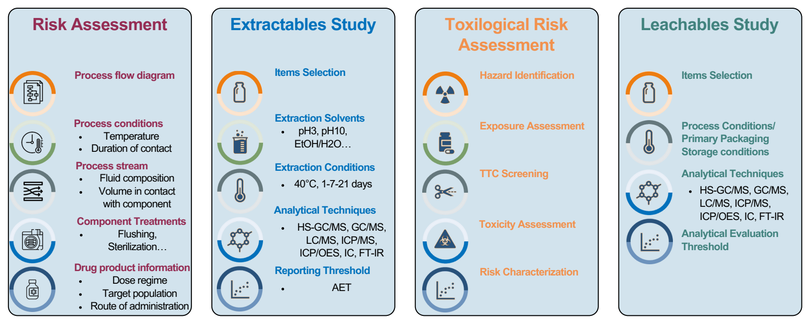
Toxilogical Risk Assessment

A Toxicological risk assessment is aimed to identify the extracted impurities that could be a concern for the patient when exposed to the Drug Product in contact with primary packaging and process component.

Leachables Study

A leachables study is generally performed directly on the product formulation in its final packaging configuration. This study is designed to characterize the overall release of actual leachable substances, degradation products and other potential impurities that could be present in the product through the product's shelf-life.

Parameters in traditional E&L workflow



Unique challenges of SUS employed for ATMPs manufacturing

Unlike small molecules and traditional biotechnology medicinal products (e.g. recombinant proteins, monoclonal antibodies), ATMPs manufacturing has unique characteristics that need to be considered when designing an E&L study.

These may be divided into two categories:
- Process-related
- Product-related

Process-related considerations

Solutions

Generally, polar solutions are used. 10-15% DMSO is used as cryoprotective agent.

Process streams are close to physiological conditions; no extreme pH and organic solvents are used as cells are employed or they are the final product.

Process step

Polar solutions with 10-15% DMSO are commonly used as a cryoprotective agent. Process streams are kept near physiological conditions, avoiding extreme pH and organic solvents because of cell use.

In vivo therapies directly administer vectors to patients, while ex vivo therapies add vectors during manufacturing.

Temperature

Cells are not compatible with extreme temperatures.

Contact time

It may vary depending on manufacturing step. During steps such as transduction, activation and expansion last several days

Product-related considerations

Treatment

Patients may receive a one-time dose to minimize exposure to leachables.

However, some treatments involve large volumes, increasing exposure to leachables. High dosing volumes can lead to low leachable concentrations, which can be challenging for analytical methods.

Storage

Final products are kept at low and very low temperature, thus mitigating the risk of leachables during storage

Cryoprotectant mayafffect the polarity of the solution and promoteleachablesaccumulation or alter the leachablesprofile.

Biocompatibility

Carcinogenic, mutagenic, or genotoxic compounds (CRMs) are rarely reported in public extractable studies. However, cells used in cell and gene therapies may be more sensitive to CRMs than whole organisms.

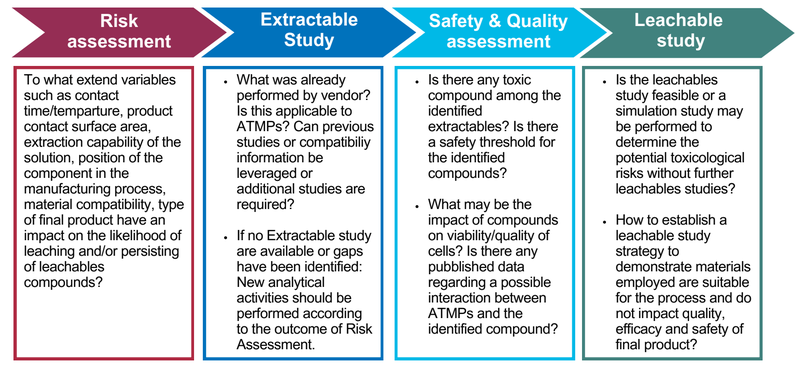
Some materials have been shown to inhibit cell growth and affect critical quality attributes (Budde and Jurkiewicz, 2021).

Type of product

Many gene therapy products require vectors, and their manufacturing process must be carefully checked for impurities.

Certain applications, such as ocular indications, may need specific safety thresholds.

4 E&L strategy for ATMPs



5 Conclusions

- SUS are extensively used in ATMPs manufacturing process as they enable manufacturer to address some of the unique challenges of such medicinal products.
- Leverage of equipment and single-use products traditionally designed and reserved for bioprocessing may not be possible due to difference in ATMPs processing and lack of specific regulatory guidelines.
- Design of appropriate E&L strategy for ATMPs should be risk based and driven by product- and process-specific considerations.
- Eurofins has the capacity to support ATMPs development cycle form discovery to commercialization thanks to the broad company network, including testing, manufacturing (Contract Development and Manufacturing Organization - CDMO) and Consulting.

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