Drug Development Decisions

New approaches to product development are currently being explored as a means to control costs, with companies encouraging automated production and decentralised manufacturing as a means to do so

Zeb Younes and Zaklina Buljovcic at PharmaLex

There has been great progress in the development of cellular, tissue, and gene therapy products/advanced therapy medicinal products (ATMPs) in the last decade. To date, 14 ATMPs have been approved in Europe (though four have been withdrawn now) and 10 cellular and gene therapy products are approved in the US. A summary of the approvals to date is presented in Table 1 and 2. Given the potential of these products, improved understanding of the regulatory hurdles, and potential to reduce costs in next-generation versions, the number of such products in development is increasing rapidly.

Many developers of cellular, tissue, and gene therapy medicinal products have orphan drug designation and/or a form of priority/accelerated review status. This allows the developers to speed up various aspects of the development programme. However, this fast development has a significant impact on the area of chemistry manufacturing and controls (CMC), where some activities can be accelerated, but many of the critical activities cannot. This results in the requirement to complete complex CMC development activities in a tighter timeframe and often in parallel to nonclinical and clinical development.

Product	Classification	Description	EMA authorisation year
ChondroCelect*	Tissue-engineered	Viable autologous cartilage cells expanded ex vivo	2009
MACI*	Tissue-engineered	Autologous cultured chondrocytes	2012
Provenge*	Cell therapy	Autologous peripheral blood mononuclear cells activated with pulmonary alveolar proteinsosis granulocyte-macrophage colony-stimulating factor (PAP-GM-CSF) (sipuleucel-T)	2013
Glybera*	Gene therapy	Human lipoprotein lipase (LPL) gene variant LPLS447X in a vector	2013
Holoclar	Tissue-engineered	Ex vivo expanded autologous human corneal epithelial cells containing stem cells	2015
Imlygic	Gene therapy	Oncolytic virus generating GM-CSF	2015
Strimvelis	Gene therapy	Autologous CD34+ cells transduced to express adenosine deaminase	2016
Zalmoxis	Cell therapy	Genetically modified allogenic T Cells	2016
Spherox	Tissue-engineered	Autologous spherical aggregates of chondrocytes	2017
Alofisel	Cell therapy	Allogeneic mesenchymal adult stem cells	2018
Yescarta	Cell therapy	Genetically modified allogenic T Cells	2018
Kymriah	Gene therapy	Autologous T cells encoding anti-CD19	2018
Zynteglo	Gene therapy	Autologous CD34+ cells encoding βA-T87Q-globin gene	2019

*No longer on the market

Table 1: Summary of approved ATMPS in the EU

Product	Description	FDA first authorisation year
Carticel	Autologous cultured chondrocytes	1997
Provenge	Autologous peripheral blood mononuclear cells activated with sipuleucel-T	2010
Laviv	Autologous suspended fibroblasts	2011
GINTUIT	Allogeneic cultured keratinocytes and fibroblasts in bovine collagen	2012
Imlygic	Oncolytic virus generating GM-CSF	2015
MACI	Autologous cultured chondrocytes on a porcine collagen membrane	2016
KYMRIAH	CAR T	2017
Yescarta	CAR T	2017
Luxturna	Adeno-associated virus vector containing modified RPE65 cDNA	2017
Zolgensma	AAV vector-based gene therapy containing a SMN1 transgene	2019

Table 2: Summary of approved cellular and gene therapy medicinal products in the US

From a CMC perspective, it has become apparent that, although the types of products are diverse with varying degrees of complexity and inputs, certain challenges are more common than others. These have been summarised in the following as key points for consideration.

Drug Substance and Drug Product Designation

Often, the manufacture of such products is not aligned with the traditional approach of a distinct drug substance (DS) stage, which is followed by manufacture of the final finished drug product (DP). In many cases, the manufacturing process is continuous and often considered by developers inappropriate to assign distinct DS and DP stages. However, for regulatory purposes, the process must be assessed by experienced experts and appropriate DS and DP stages defined. This, as well as starting material, allows developers to define appropriate control strategies and structuring of regulatory dossier content.

Another factor that may explain the reluctance of developers to assign DS and DP is that a battery of tests is traditionally

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expected on both the DS and DP. However, with these products, the assigned DS is, in some cases, simply not sufficiently stable to support testing on DS stage or the manufacturing process is too short. This could be due to the impact of freeze/thaw, device integration, components that interfere with the analytics, or simply because the tests take too long compared to the stability of the product. Additionally, test methods may not be suitable for the DS or even the DP, and test data from different steps in the manufacturing process may be required instead.

In many cases, the required DS and DP testing will be performed as part of in-process control testing during manufacturing and will then be listed in DS and DP specification. One very common example is sterility testing. When dealing with cell- or blood-derived starting materials, the product sterility control strategies should be agreed with the authorities upfront. For products with a short shelf-life, sterility testing at different stages of the manufacturing process can be proposed, applying the positive-to-date release concept, and, in some cases even rapid polymerase chain reaction testing might be suitable.

It should be noted that, currently, a shift has occurred from purely autologous to allogeneic product developments. In allogeneic cell products, some of the classical concepts known for biotechnology products may be applied, such as cell banking, generation of bulk substance, or product. The same is true for *in vivo* gene therapies (applying viral vectors or microorganisms). In any case, a risk assessment-based approach with scientifically sound justification for the final approach may be put forward for Agency agreement.

Source, History, and Qualification of Starting/Raw Materials

Depending on the complexity of the manufacturing process, there are numerous starting and raw materials, which may include human tissue, cells from peripheral blood or other sources, and process components such as vector, plasmid, host cell line, growth factors, and proteins.

Starting/raw materials are often established during early development, and documentation, traceability of the sources, testing, certification, storage, tracking, and control are not always maintained as required. Although some of this data can be obtained retrospectively later in development, not all the information is always available. This puts the drug developer in a compromising position during later development and can result in direct delays to the programme if not resolved.

The sources of tissue or blood-derived starting/raw materials must be compliant with regional requirements (donor selection/screening/testing/collection/storage/transport/traceability). A rigorous quality control process should be in place to ensure only acceptable materials enter the process.

Furthermore, changes to critical raw/starting materials may result in unexpected and unwanted levels of variability in the finished cell/gene product. This is obvious with cells or blood as starting materials, especially in autologous products. However, also for other raw and starting materials like viral vectors or enzymes, changes that can have such an impact are not only change of type, source, and supplier, but, in some cases, even use of different batches or lots of the same starting/raw material from the same supplier can have an impact on finished product quality. The impact of such changes for critical starting/raw materials should be assessed and, if required, appropriate qualification criteria established, as this can cause serious drawbacks in development with respect to comparability (see later).

Establishment and Control of Banks

Any materials that are banked in the process, such as viruses or cells, should be banked in accordance with GMP, qualified, and released for use. Stability data on these banks should also be monitored.

During development, many of these viruses or cells are either not formally banked or, if they are, it may not be with optimum materials/processes. Further to this, due to the low quantities initially prepared, new banks may be required to support development activities.

Change in these critical components results in the requirement of additional comparability assessments. Therefore, establishing appropriate controls and a qualification process is important. This will allow drug developers to reduce

the risk of impact to DP quality upon change of bank material. Any banks (such as viral banks or cell banks, including pooled primary cells from allogeneic donors) and substances that are held for a significant period during the manufacturing process must be assessed under the worst-case scenarios for stability and adventitious agent contamination and confirmed to be appropriate for use.

Comparability

During all phases of development and post approval, CMC changes may be required, such as changes to the manufacturing components/materials, process steps, and facility. To confirm that the finished product before and after change has no significant impact to the critical quality attributes (CQAs) of the product, a comparability assessment must be completed.

The type of comparability assessment will be simpler in early development and more comprehensive as developers move through the later stages. This is best achieved using a development stage-specific product category aligned risk-assessments. Establishment of CQA comparability will allow developers to leverage clinical data generated using pre-change material moving forwards.

Facilities Quality Status

Drug developers should clearly map out their manufacturing process from starting material collection through to DP. From early development, this should include clarity of the quality status of all facilities involved. Blood and tissue procurement facilities, as well as testing facilities for starting material, must have the appropriate regional registration/accreditation either to the 2004/23/EC and/or 2002/98/EC directives or to comply with human cells, tissues, and cellular and tissue-based products requirements in the US. For cell and gene product manufacturing, nonclinical and clinical CROs need to apply appropriate good practice standards, and the manufacturing facilities must operate in accordance with GMP for ATMPs.

Automated and Decentralised Production

In addition to the trend of developing allogeneic rather than autologous products, companies are increasing efforts to include automated production and decentralised manufacturing. An example of decentralised manufacturing is where a manufacturing unit (rather than a single centralised site of manufacture) is established at every hospital that provides treatment, leading to multiple local manufacturing sites.

Automated production and decentralised manufacturing increase standardisation, control costs, and improve availability for the patients. Decentralised manufacturing poses new challenges, such as establishment of machines enabling production with easy and aseptic handling directly at the hospital site together with a feasible approach for batch release at the specific sites. Strategic CMC approaches, including worst-case scenarios, comparability assessment, and risk assessments, will be vital to ensure patients receive the required product quality.

Planning for Commercialisation

As indicated in Table 1 (page 60), several authorised products were withdrawn. The major reasons cited for withdrawal were commercial, manufacturing facility, and infrastructure (transport/viability of product) related issues.

From a CMC perspective, later in development, facility capabilities to support long-term commercial requirements must be in place. Additionally, all critical reagents should have qualified alternative suppliers in the event they can no longer be sourced. The same is true in cases of combined products for the device component.

A trend is clearly increasing among the products currently in development to control costs and use novel approaches towards the end goal to have commercially viable products. Upfront development activities and use of risk assessments are critical in reducing CMC risks during and after development. This investment will save time and resources in the long term.

About the authors

Zeb Younes has around 20 years of experience in biological products, including a range of cell, tissue, and gene therapy products, from proof of concept through and beyond commercialisation. She has prepared numerous regulatory documents and scientific advice procedures in Europe, the US, Brazil, and Canada. Zeb set up and managed research teams and GMP laboratories, developed and implemented risk-based approaches, and has led EU national/FDA GMP audits. She holds a first-in-class BSc (Honours) in Medical Biochemistry.
Email: zeb.younes@pharmalex.com

Zaklina Buljovcic is a regulatory specialist with more than 10 years' experience in tissue, cell, and gene therapies and 15 years in regulatory. Her main focus is in regulatory strategy, programme management, and pharmaceutical quality. Zaklina manages projects within interdisciplinary teams on expedited programmes, scientific advice, and preparation for central marketing authorisations. Her experience includes biotech, blood, microbiota, and veterinary products. Zaklina is a biologist and holds a PhD from the University of Stuttgart-Hohenheim, Germany.
Email: zaklina.buljovcic@pharmalex.com