Executive Summary

IFPMA Position Paper on:

IN-COUNTRY TESTING OF ADVANCED THERAPY MEDICINAL PRODUCTS

INTRODUCTION

Advanced Therapy Medicinal Products (ATMPs) are medicines based on cells, genes or tissues.

They offer ground-breaking new opportunities for the treatment of disease and injury. Regulatory requirements have not kept the same pace as advancements in ATMP innovation. As a consequence, ATMPs are regulated in various manners in international markets and in many cases lack specific regulation. Existing in-country testing requirements for traditional biological products may be applied without acknowledging the specific considerations for these new therapies.

This paper discusses specifics of ATMPs, where traditional in-country testing is challenging, outlining existing control strategies to detect potential issues, with recommendations to waive in-country testing without compromising product safety, quality and efficacy and in compliance with requirements, i.e., by recognition of certificates from countries with mature National Regulatory Authorities (NRAs).*

KEY MESSAGES

- Compared to traditional biological products, ATMPs may have smaller batch sizes, lower yield, shorter shelf-life, require faster turn-around-time, have a different distribution model, storage conditions, and specific and complex analytics. These differences require a change in mindset by all stakeholders.
- Considering ATMPs with small batch size, test samples consume a disproportionate percentage of a batch and compete with material available for patient treatment.
- In-country testing unnecessarily delays patient access to products and may make the return-to-patient not possible in the case of disease progression.
- In-country testing of ATMPs is extremely challenging (e.g., when they are directly supplied to treatment centers) or not fully representative (i.e., separately packed and distributed side-samples for individualized products or patient kits).
- Existing reliance pathways should be strengthened to realize a timely and predictable ATMP registration and importation processes. The reliance on inspections and approvals from mature NRAs is important to achieve a reliable global supply of quality medicines.
- NRAs should introduce a process for waivers from in-country testing for products manufactured in facilities inspected for GMP compliance by mature NRAs.
- NRAs should rely on Certificates of Analysis (CoAs) issued by manufacturers of products manufactured in facilities inspected for GMP compliance by mature NRAs.

* Mature NRAs refers to Stringent Regulatory Authorities, SRAs [1-3]. A list of SRAs has been published by the WHO here.
Once the WHO listed authority (WLA) system is fully implemented the term WLA will replace the term SRA.

IMPACT OF UNCERTAINTY

The lack of ATMP specific regulations in many markets causes uncertainty of requirements needed for regulatory approval and import testing requirements.

There are only a few regions in the world where a regulatory framework exists for ATMPs and within these regions it is recognized that import testing is not generally feasible. These markets do not require import testing (e.g., Brazil) or are applying a flexible approach (e.g., EU [4]). Specifically, the EU does acknowledge the need to rely on controls conducted outside of the EU, where no relevant mutual recognition agreement (MRA) on GMP is in place and describes the exceptional conditions as follows: 1) limited amount of product or 2) short shelf-life and testing in the third country is conducted in GMP certified facilities [4].

The flexible definition of ATMP testing requirements is an important improvement compared to testing requirements for traditional pharmaceutical products. However, it should be noted that the discretionary nature of (case-by-case) decisions leads to uncertainty until the end of the registration process. Such uncertainty hinders the applicants to prepare the commercial supply, for example, to ramp up testing capacity, supply and qualify product specific instruments, realize technology transfer or forecast and produce testing materials (e.g., reference standards, control solutions).

INCREASING INTERNATIONAL RELIANCE

More and more countries utilize reliance approaches throughout the entire product lifecycle (regulatory review, inspections, post-approval changes).

Additional examples of reliance are risk-based approaches that NRAs apply to accelerate marketing authorizations and patient supply with new medicines. Based on these so-called reliance pathways, the product approval is accelerated by the reliance on or recognition of prior reviews by other countries, e.g., mature NRAs or ICH countries [5-8].

The WHO supports such an approach by stating [9]: “The risk of poor quality should be assessed before deciding to request analysis of a particular product. For example, if the manufacturing site has been found to comply with GMP principles, the manufacturer is under regular supervision of a NRA applying international standards, and there is no specific reason for additional testing of the product (such as a quality complaint or a suspicion of quality deterioration during distribution or storage). The manufacturer’s batch certificate may be relied upon to indicate the quality of the product.” Thus, WHO proposes that all NRAs use reliance approaches and make them an integral part of regulatory operations [10].

The reliance on inspections and certificates from mature NRAs is important to achieve a reliable global supply of quality medicines [4].

CONCLUSIONS

ATMPs have delivered positive outcomes for patients living with life-threating genetic conditions.

Acknowledging this transformational therapeutic potential, there is also a need to acknowledge a paradigm shift required for this new class of medicinal products. Despite many similarities to traditional products, ATMP specifics (as further laid out in the Annex) warrant unique considerations.

Several NRAs have eliminated or reduced import testing for traditional products. Real data suggest that import testing procedures do not add benefits for the patients, provided that the products are uninterruptedly controlled according to globally harmonized manufacturing and distribution standards.

RECOMMENDATIONS

- The quality of imported ATMPs can be ensured without additional testing by relying on the Certificates of Analysis (COAs) issued by manufacturers of products that are inspected and approved by a mature NRA.

The recognition by mature NRAs ensures that the manufacturer:

- provides evidence (e.g., by GMP certificates) that the product manufacturing, testing and storage/distribution systems are well controlled and validated;

- has implemented a QMS to assure compliance; and

- is under regular control of independent auditing and globally recognized inspectorates (e.g., mature NRAs or PIC/S members), e.g., as described in the WHO Certificate of Pharmaceutical Product (CPP) procedure [11]

There is a need for international collaboration and reliance, moving further towards global harmonization, with the common goal of delivering safe and effective products to patients. Most ATMPs serve (very) small patient populations. With all their inherent challenges, ATMPs require a streamlined, effective and predictable importation process ensuring the authenticity, quality, suitability, and registration compliance. Flexibility is needed to allow faster and better access to these treatments for waiting patients. The reliance on inspections and certificates from mature NRAs is strongly recommended. By relying on CoAs issued by manufacturers in facilities, which are inspected by mature NRAs, import testing for these products should be waived.

WHAT MAKES ATMPs DIFFERENT

Background

In-country testing is, inter alia, performed for two testing categories: (1) registration testing, including lifecycle management** and (2) import testing, which is still required for traditional pharmaceutical products (small molecule, biological/biotechnology and vaccine products) in specific countries [12,13]. This paper focuses on import testing; additional considerations for registration testing are discussed in a dedicated chapter. Testing requirements have existed for decades, for example, in the EU as of 1975. Historically, retesting requirements may have been added to regulations because Good Manufacturing Practice (GMP)/Good Distribution Practice (GDP) oversight and regulations were not harmonized and did not exist in all regions. Further motivation for import testing is summarized in **Table 1**. Import testing was implemented to monitor and confirm the quality of finished products when introduced into the local supply chains, i.e., to detect counterfeit products, confirm products remained compliant to the CoA and licence, ensuring product identity, efficacy and safety.

Table 1. Rationales for the implementation of import testing modified from [14].

Past motivation for import testing	Current state for ATMPs: How the past motivations for import testing have been addressed
GMP/GDP oversight and regulations were less harmonized or established	Harmonized GMP and GDP guidelines are in place and engrained as part of robust Quality Management Systems (QMS). Regulatory oversight and information exchange across NRAs (e.g., MRA, MOU, CDA) and inspection schemes (e.g., PIC/S) are established. Thus, the quality of supplied products is controlled and secured through the entire supply chain by the industry and regulators.
Incomplete development of regulations and enforcement procedures	
Mistrust of having poor quality products imported	Registration processes are advanced (e.g., CTD structure) and information on foreign suppliers is available. Product transport is controlled/monitored and End-to-End traceability and serialization put in place. Shipping system quali-fication addresses distribution cycle, schedule, duration (evalu-ating forces, conditions, and sequences of transport environ-ment, horizontal impact and rotational flat drop, vibrations and compressions). Today's dominant threat, leading to mistrust, is counterfeit drugs, which cannot be identified by registration or import test-ing, but by surveillance testing or specific testing programs.
Limited opportunities of counterfeit detection	Technical capabilities for fast and mobile identification of counterfeit products (e.g., near infrared spectroscopy, NIR, and global product databases) are standard and part of post-marketing surveillance activities.

CDA: Confidentiality Agreement, CTD: Common Technical Document, **MRA:** Mutual Recognition Agreement, **MOU:** Memorandum of Understanding, **PIC/S:** Pharmaceutical Inspection Co-operation Scheme

** The term "registration testing" is used in this paper to refer to testing in conjunction with registration procedures (new registrations, license renewals, line extensions, post-approval changes).

Since import testing was implemented, significant convergence between NRAs and international harmonization has occurred. For example, regulatory standards (e.g., CTD structure), Pharmaceutical Inspection Co-Operation Scheme (PIC/S) and International Council for Harmonisation (ICH) have been broadly adopted. With the implementation of harmonized standards for GMP and GDP, product quality is controlled and maintained in the supply chain and confirmed by continuous regulatory oversight. More and more countries have acknowledged the limited value of import testing compared to the benefit of full or partial exemption of in-country testing, including Australia [15], Brazil [16], China [17,18], Kazakhstan [19], Mexico [20], the Russian Federation [21], the United States of America [22] and the Ukraine [22]. However, it still remains a mandatory requirement in many markets in Asia, Europe and Latin America.

Benefits of ATMPs and what makes them unique

ATMPs have introduced the opportunity to address previously untreatable conditions and to cure patients rather than ameliorating symptoms. Multiple approved products have been launched globally and the number of clinical trials continues to grow. As with any new and innovative technologies, ATMP developers face many regulatory challenges, one of which is import testing.

ATMPs cover a very diverse set of modalities and product types (**Figure 1**). These modalities require unique approaches that may differ from those applied to more traditional biopharmaceutical products. ATMPs are medicines for human use that are based on cells, genes or tissues, specifically:***

- Somatic cell therapy medicinal products (sCTMP, hereinafter referred to as CT): these contain cells or tissues that have been manipulated to change their biological characteristics or cells or tissues not intended to be used for the same essential functions in the body. They can be used to cure, diagnose or prevent diseases.
- Gene therapy medicinal products (GTMP, hereinafter referred to as GT): these contain genes that lead to a therapeutic, prophylactic or diagnostic effect. They work by inserting 'recombinant' genes into the body, usually to treat a variety of diseases, including genetic disorders, cancer or long-term diseases.

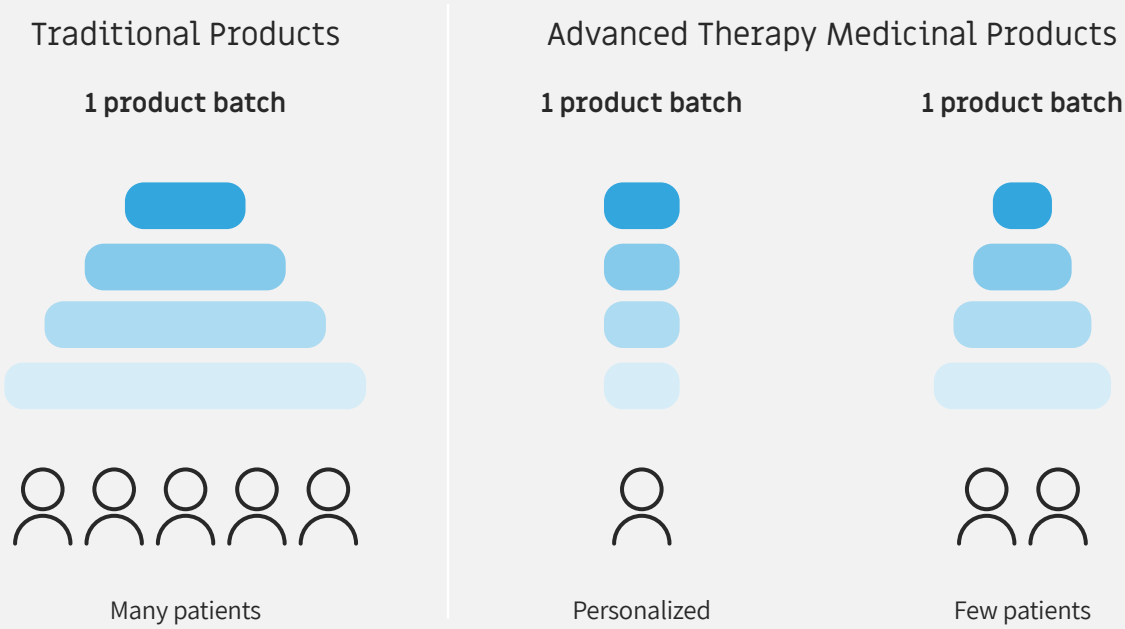
  Two types of GT can be distinguished: The direct insertion of genes into the cells of a particular tissue is referred to as ***in-vivo*** **GT.** ***Ex-vivo*** **GT** comprises of an initial gene transfer in cultured cells (e.g., stem cells), which are then returned to the patient.
- Tissue-engineered products (TEPs): these contain cells or tissues that have been modified so they can be used to repair, regenerate or replace human tissue.

Beyond these definitions, ATMPs can be divided based on patient population and production model: (1) **Make-to-Stock (MTS)** (also referred to as off-the-shelf) for few patients and (2) **Make-to-Order (MTO)** for a single patient (also referred to as individualized therapeutics) (**Figure 1b**).

While MTS products are more similar to traditional production planning, largely matching the inventory with anticipated consumer demand, there is, however, a paradigm shift as compared to traditional products. Most MTS ATMPs treat rare or ultra-rare diseases, meaning the patient population is small to very small (rare < 5 people in 10,000 [24] and ultra-rare < 1 per 50000 persons [25]). This combined with other inherent supply differences such as smaller batch size, lower storage temperature requirements, and in some cases custom built dose per patient (called 'kitting', i.e., individualized packaging) requires a different approach to product management and allocation to regions. MTO individualized products are produced upon order; each batch is manufactured for a single patient and can only be delivered to treat the specific patient with no allowance for error or shortage. The supply chain requirements for both product branches share specific characteristics and deviate from traditional products.

*** This paper uses the ATMP classification of the European Medicines Agency [23]. Abbreviations are used throughout the paper (cell therapies, CT; gene therapies. GT and tissue-engineered products, TEPs). The paper focusses on CT and GT; TEPs are introduced for completeness.

(A)



(B)

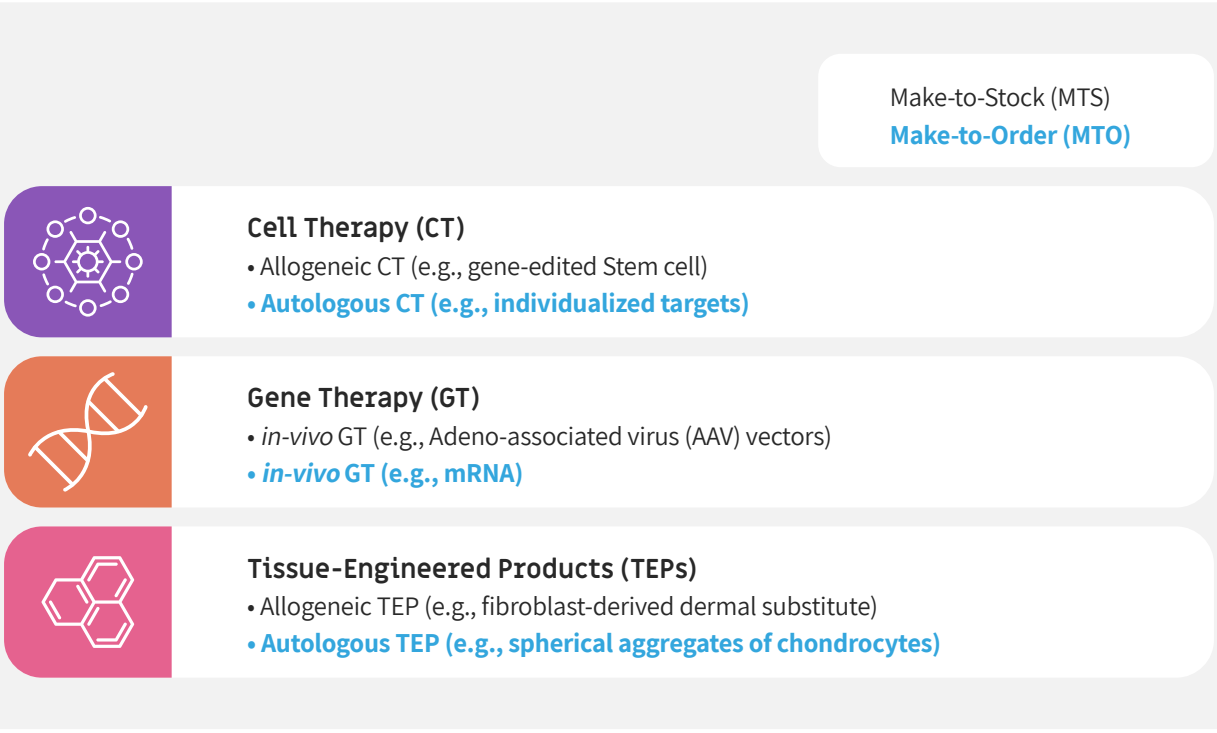


Figure 1. ATMPs—a class of medicinal products that require specific considerations. (a) Patient Supply Paradigm: the differences between traditional product supply and ATMP supply from a patient population perspective (modified from Oh [25]). **(b)** ATMPs are divided into three main types: cell therapies (CT), gene therapies (GT) and tissue-engineered products (TEPs). Based on the production model, each type can be subdivided into (1) Make-to-Stock, MTS and (2) Make-to-Order, MTO. **MTS:** Allogeneic CT is single-source cells (donor) to treat many patients. There are cases where donor cells are specific for one patient (matched-donor scenario). *In-vivo* GT products are administered to patients for treatment of a genetic condition. Allogeneic TEPs can be used to treat many patients, e.g. fibroblast-derived dermal substitute. **MTO**: Autologous CT products are where a patient's own cells are removed and genetically modified *ex-vivo*, and then returned to the patient for treatment. *In-vivo* GT products are manufactured for an individual patient, based on an individual genome for treatment of their condition. Autologous TEPs are prepared from the patient's own tissue, e.g., to repair defects to the cartilage.

Small Batch-Size and Product Scarcity Considerations

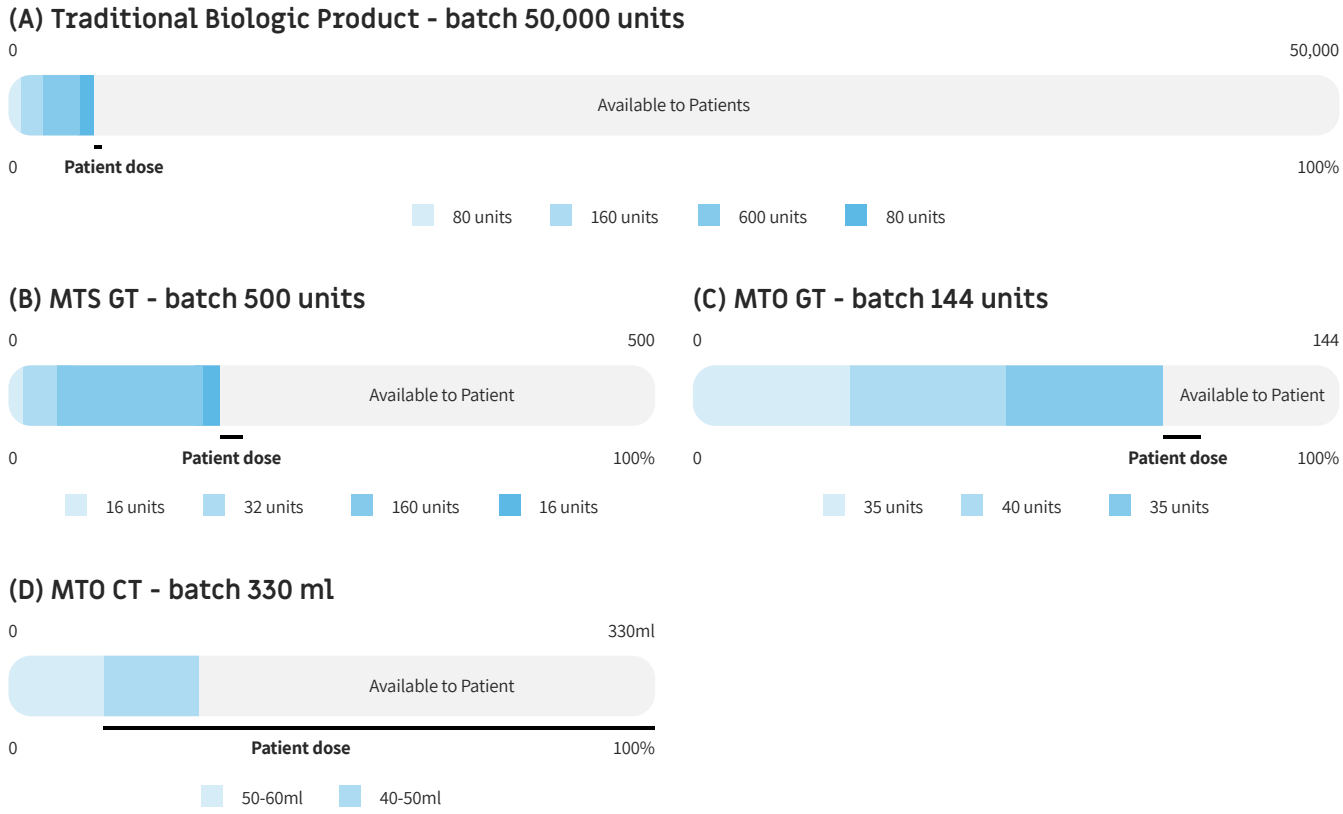
While batches can vary in size, in general, ATMP batch sizes are significantly smaller compared to traditional products (**Figure 2**).

- The majority of MTS products are for rare genetic conditions, requiring few batches manufactured annually for a small patient population. This small product volume requires global distribution for patient treatment; a single batch may be imported to several countries.
- Even with more frequent production, ATMP manufacturing capacity is smaller, leading to smaller batch sizes compared to traditional products. With a smaller batch size and fixed batch sampling requirement (e.g., release testing, stability, reference and retention samples), there is less product available for patients.
  - For MTS allogeneic products (matched-donor scenario) and MTO autologous products, the starting material is taken from a donor or patient. The patient material is very scarce and precious; it is very variable in size dependent on patient health (*ex-vivo* cells are limited in the ability to expand, or have low 'patient yield' based on dosing requirements). There is a need to evaluate each sampling requirement to maximize available product and patient treatment.
  - MTO products manufacture one batch for a single patient. There is a limited amount of product available, especially with a multi-dosing schedule.
- Many MTS products require individualized packaging determined by patient weight (so-called patient kits). Product constraints drive the combination of more than one batch into patient kits (e.g., one patient kit may consist of two separate batches to derive the therapeutic dose needed per patient weight) (**Figure 3**).
- Traditional product manufacturing is higher in yield per batch, so there is less impact with the quantity of units consumed for import testing. Considering the small ATMP batch size, these unit quantities would consume a disproportionate percentage of a batch (**Figure 2**).

Time is a Key Factor

Time is key for production, distribution and administration of ATMPs. The therapeutic form of ATMPs requires specific storage conditions and often administration shortly after being manufactured. The supply chain is set-up and controlled to rapidly deliver products to the patients. These requirements result in the need for a streamlined, effective and predictable importation process.

- **Shelf-life:** ATMPs typically have to be stored at ultra-low temperatures (e.g., -70°C or in the vapor phase of liquid nitrogen) to maintain shelf-life. If cryopreservation and, thus, storage at ultra-low temperatures is not possible, shelf-life may be too short for import testing (e.g., Alofisel: 72 hours shelf-life at 15-25°C [27]), i.e., shipments to local testing laboratories, test execution, data logistics. The testing process depletes the remaining product shelf-life and may impact supply and availability to patients.
- **Turn-around-time** (TAT): For MTO ATMPs, the total TAT is an important aspect of the production and treatment process and is critical for the overall process. Manufacturing can only begin once patient samples (e.g., blood, tissue) are collected, with the patient then waiting for the product to become available. Over the 'wait time' (e.g., vein-to-vein approximately 3 to 5 weeks), the patient's health may decline and the patient may no longer be able to benefit from treatment or even to receive it. It is important to establish a consistent and reliable TAT timeframe to manage this uncertainty and to minimize the chances for the patient to become ineligible for treatment.



	(A) Traditional Product	(B) MTS-GT	(C) MTO-GT	(D) MTO-CT
Batch size	50,000 units - 100%	500 units - 100%	144 units - 100%	330 - 404 ml (variable) - 100%
(1) Release Testing	80 units - 0.16%	16 units - 3.2%	35 units - 24%	50-60ml[C] - 18%
(2) Reference/Retention	160 units - 0.32%	32 units - 6.4%	40 units - 28%	
(3) Stability Program[A]	600 units - 1.2%	160 units - 32%	N/A	N/A
(4) In-country Testing[B]	80 units - 0.16%	16 units - 3.2%	35 units - 24%	40 - 50 ml [c] - 15%
Remaining Units	49,080 units - 98%	276 units - 55%	34 units - 24%	210 - 284 ml (67 -70%)
Max Patients treated	16,360[D]	9.2[E]	1	1

[A.] Sampling for on-going stability study (annual requirement, not routine) [B.] Each additional re-test requires same units number used
[C.] In this example, QC sample volume must be known and aliquoted prior to DP filling; sampling from DP bags not possible. Variable batch size (2-4 bags dependent on starting volume. [D.] Assume 80 kg patient weight (3 units per patient) [E.] Assume 30 kg pediatric patient weight (30 units in patient kit)

Figure 2. ATMP batch size is smaller than for traditional products. This figure contains examples of typical batch sizes for each category of products. **(a)** Compared to traditional products, such as monoclonal antibody batches, most ATMPs have smaller batch sizes. **(b)** Make-to-Stock Gene Therapy (MTS GT); in this example, the batch has 500 units and with fixed sampling requirements. Hence, there is less product available for patients. **(c)** Make-to-Order Gene Therapy (MTO GT); manufacturing is for one individual, the scale is smaller (in this example 144 units). Smaller batch size with fixed sampling requirements results in very limited batch availability to the patient. The batch is only manufactured once and every unit is critical for patient treatment. **(d)** Make-to-Order Cell Therapy (MTO CT) batches are highly variable and dependent on patient health and cell ability to grow. Import testing is not possible for individualized therapy.

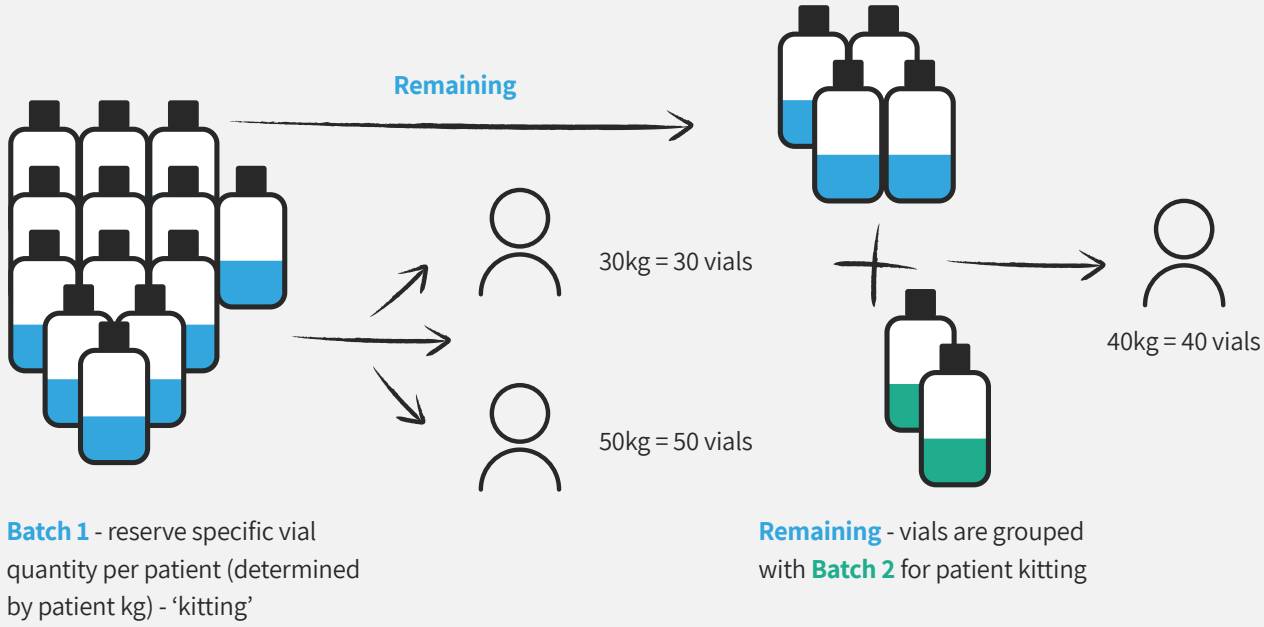


Figure 3. Make-to-Stock (MTS) products may require kitting. Patient kits are defined by patient weight. Remaining units from batch 1 must be combined with batch 2 to provide sufficient product for patient treatment.

Transport, Distribution & Storage

ATMPs may be manufactured for individual patients and/or require kitting (refer to **Figure 3**). To ensure short TAT and patient-specific distribution, there is a need for a different distribution model compared to traditional products (**Figure 4**).

- In most cases, ATMPs will not be distributed from a national distribution center, but directly from the manufacturing site to the treatment center, skipping normal distribution channels. Patients benefit from the much shorter direct distribution chain under full oversight of the manufacturer/license holder. In addition, the 'order to payment' information systems are fully designed and specific for ATMPs, eliminating risk of counterfeit/fraud.
- The stability of ATMPs often requires storage in a frozen state at ultra-low temperatures and makes it necessary for the receiving body (e.g., customs warehouse, governmental laboratory) to have adequate receiving and storage procedures as well as a suitable infrastructure.
- Allocation of batches to multiple countries. Given the comparatively small number of patients that can be treated with these products, the country/region demand for the product may be difficult to predict with accuracy. One batch may be sent to many countries or may even need to be reallocated from one country to another, resulting in the potential for one batch to require multiple testing, further depleting the amount available to treat patients.
- Short shelf-life products and short TAT require direct delivery to a treatment center, ensured by stringent control of supply chain logistics. Import testing would require additional interventions because samples must be taken from integer shipping units. This introduces risks of temperature excursions (e.g., partial thawing) that may impact product quality and consequently cause product rejection. Product replenishment is not readily possible (no safety stock in case of product limitation and short shelf-life). Alternatively, side-samples would have to be sampled from the same batch and separately packed and distributed to the testing site. Side-samples would not be fully representative for the imported product and decrease product availability for patients.
- Sampling for import testing is not possible for MTO products or not fully representative for MTS patient kits:
  - MTO autologous product supply chain begins with the acquisition of patient samples (e.g., blood, tissue, cells, tumor biopsy) and the product is returned to the patient;
  - MTS kits correspond to an individual patient weight. Side-samples, representing all contained batches in the patient kit, would be required.

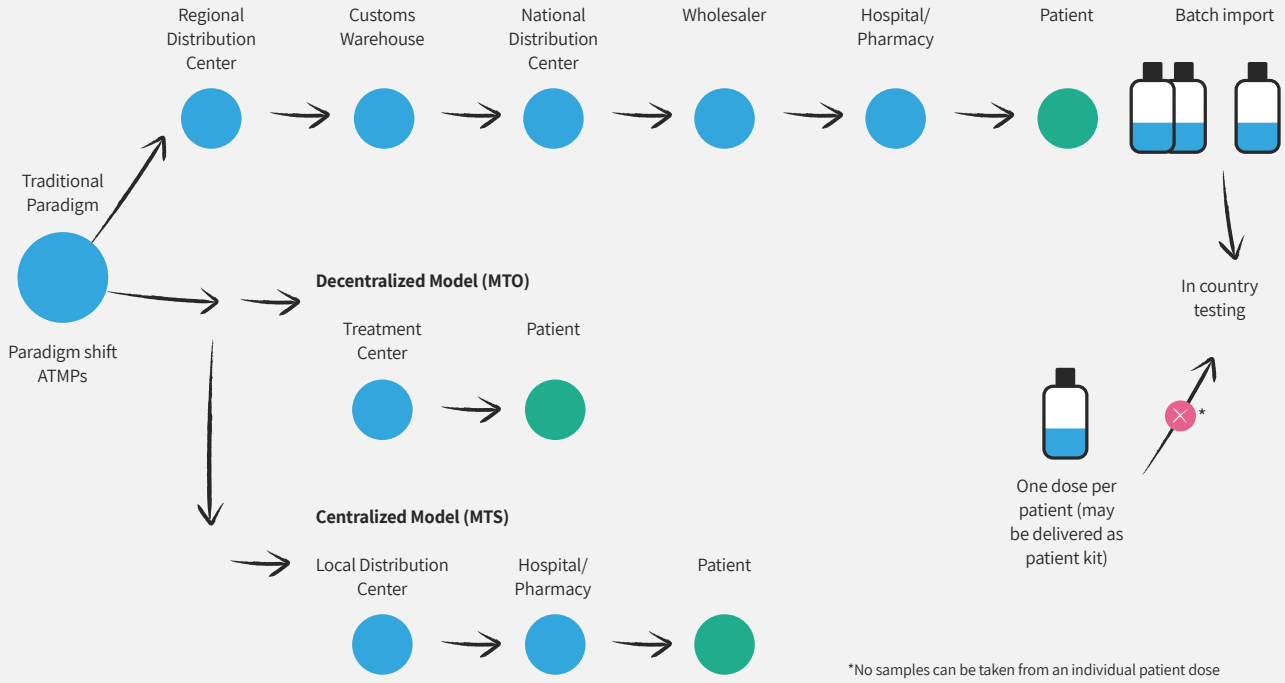


Figure 4. ATMPs have different supply chain requirements compared to traditional products. Traditional products follow the model where - in this example - they first are shipped to a regional distribution center, a custom warehouse, and then to a national distribution center, wholesaler, and finally a hosp ital or pharmacy for patient treatment. This process is followed for an entire batch, and there are individual units sampled for import testing. In contrast, ATMPs can be patient-specific, MTS products require kitting, and MTO products are per individual and, in combination with short turn-around-time, there is a need for a different distribution model. ATMPs will not be distributed from a national distribution center, but from a specialized regional or international center directly to a treatment center, skipping normal distribution channels. No samples can be taken from an individual patient dose for import testing; separate sample packs would be required.

Implementation and Execution of Import Testing

ATMPs require non-traditional analytical technologies and may also need real-time release testing, where testing is executed on process intermediates. Additionally, the implementation of analytical methods often requires a long lead time to set up the methods.

Analytical Methods

- Methods used for traditional biological products are not sufficient and other technologies are required (e.g., light scattering, analytical ultracentrifugation, sequencing technologies), requiring specific instrumentation and expertise.
- There is an increased risk that methods may not perform the same from country to country, if not accompanied by a proper analytical technology transfer or differing equipment is used, generating disparate results that need investigation before patients can receive treatment.

Product Limitations

- Any use of the product should be minimized to ensure that sufficient product is available for patient treatment. Sample size and test duration typically used for traditional biological products may not be appropriate for ATMPs (especially MTO products).
- Product limitations may lead to a drift from pharmacopeial sample size requirements, or new methods being established as a suitable replacement (e.g., rapid microbial methods).

Testing of Intermediate Product

- Not all tests are performed at the finished product level, but at different intermediate process steps. For example, CoA tests may be performed prior to the final formulation with cryopreservative and cannot be repeated on the distributed product.
- Real-time release testing (RTRT) at in-process level may be applied to shorten TAT, especially for products with short shelf-life.

Time Consumption

- Import testing requires long method establishment times and stringent planning of product release. Innovation (e.g., methodologies, instruments) is continuously evolving with the aim of further optimizing TAT and to allow patient access to products more rapidly. Import testing counteracts the gains from innovation and unnecessarily delays patient treatment.
- Real data show that method establishment and in-country testing of traditional products require significant time and may delay patient assess [12,13]. It can be expected, that this issue will be amplified by the particular nature of the ATMP methods.

Table 2 summarizes the ATMP specifics affecting import testing feasibility as discussed in this publication.

Product Scarcity	Small batch size limits product availability to patients. There is a direct impact on supply if MTS products require import testing; a disproportionate part of the batch is consumed for testing. MTO product manufacturing is not feasible with import testing; the focus should be set on patient treatment and all sampling should be restricted to the manufacturing process.
Time Considerations	The consideration that ATMPs may have a short shelf-life, combined with time required for import testing narrows the window for patient treatment. Import testing will cause delays in patient supply with even increased impact if patient material is used as starting material (MTO products) and patients are critically waiting for their treatment. The time efforts should remain focused on manufacturing and return-to-patients since delay caused by import testing may make the patient treatment not feasible due to disease progress.
Transport, Distribution & Storage	ATMP supply chain is established to minimize product risks (temperature excursions) and interventions (supply chain interruptions). Import testing would require additional product movement, introducing risks to the patient supply.
Implementation & Execution of Import Testing	ATMPs may require non-traditional analytical technologies and may need real-time release testing, where testing is executed on key intermediates. The testing and longer implementation of different technologies at international locations will delay patient access to treatment.

End-to-End Control Strategy Offsets Need for Import Testing

Where a company has demonstrated appropriate controls of manufacturing and distribution processes (e.g., by means of certificates of mature NRAs), additional import testing is not warranted.

Import Testing of Traditional Pharmaceutical Products

Import testing for small molecule, biological/biotechnology and vaccine products at the country level is unlikely to increase public health protection, can delay batch release and therefore access to these products, and creates an unnecessary burden for the public health care system and the global pharmaceutical industry [12]. Moreover, import testing does not detect counterfeit or substandard products, nor does it reduce the additional risks related to local distribution channels because testing occurs at the point-of-entry into a country. Post-marketing surveillance testing is better suited to control the quality of medicines much closer to the patient, addressing highly relevant concerns: counterfeits and supply interruptions [14,28].

ATMPs are tightly controlled and tracked throughout the entire supply chain as well as or better than traditional products

Industry and NRAs have developed processes and quality oversight systems including inspection practice [13,22]. The quality of the product is confirmed at the site of manufacture and documented in the CoA and/or Certificate of Conformance. Manufacturers ensure GMP with appropriate Quality Management Systems (QMS) and are under regular control by mature NRAs inspectorates using widely harmonized inspection schemes.

Modern QMS have moved from only the quality control of the finished product to a concept of quality determined throughout the whole GMP manufacturing process:

- Product quality is determined by numerous manufacturing controls throughout the manufacturing process and not only by the release test. The control strategy of modern manufacturing processes comprises numerous non-/critical process parameters (non-/CPP) and non-/critical quality attributes (non-/CQA). The quality of a batch cannot be assessed based on the final product, but must consider the whole control system.
- Release testing represents a robust system, integrated with quality infrastructure and regulatory oversight. Product quality is dependent on process validation, process controls, applying product knowledge to manufacturing (e.g., quality by design principles) maintaining consistent output from batch-to-batch.****

Likewise, control is maintained throughout product distribution under GDP:

- The systems and processes developed to manage and control Chain-of-Custody (CoC) and Chain-of-Identity (CoI) are designed with rigorous controls: unique, often patient-level, identifiers ensure positive identification throughout a series of supply chain handoffs. This system unambiguously guarantees the bidirectional tracking of patient-specific products. The CoC allows end-to-end traceability up to the product administration. This includes data points such as handover information, temperature and storage conditions, actions performed, by whom, and the associated location, date, and time of those actions. For MTO therapeutics, the supply chain begins with the collection of patient samples (e.g., blood, tissue, cells, tumor biopsy) and, thus, a close interface with the hospital or clinic is essential.

The global regulatory environment has evolved considerably over recent years, where the integrity of shipments can be adequately controlled and verified upon receipt, providing assurance that product quality has not been compromised. With this oversight in place, patients can receive medicines in real time, and repeated testing is considered redundant because it provides no additional assurance of quality or identity of the product. A risk assessment demonstrating that product quality is continuously controlled through the entire supply chain supports this conclusion [29].

Garbe *et al.* [12] substantiate this perspective based on real data collected from multinational pharmaceutical companies. Specifically, efficacy and duration of import testing were analyzed. A batch rejection rate of 0.005% was found (= 18'616 batches were re-tested and 1 batch thereof was rejected). The maximum testing duration of 22 weeks was reported. These figures suggest that import testing does not add significant benefits to the quality or safety of drugs and that the testing may cause significant delay of product supply and significant loss of remaining product shelf-life.

Understanding the value of the successive controls across the entire supply chain, several governments, including those in Australia [15], Brazil [16], China [17,18], Kazakhstan [19], Mexico [20], the Russian Federation [21], the United States of America [22] and the Ukraine [22] have eliminated or reduced redundant testing.

**** It is acknowledged that the robustness and understanding of some ATMP manufacturing processes is still limited and ATMPs are not generally considered "well characterized". Even ATMP processes tend to have higher variability compared to traditional product processes, the product quality is controlled and determined throughout the validated GMP manufacturing process.

Registration Testing—Additional Considerations

Registration testing and import testing are widely comparable, with both being performed upon product import. The justifications presented are similarly applicable for registration testing. For registration testing, still required in about 70 countries for traditional products [13], there are additional considerations:

Product Scarcity

- To support national registration testing campaigns, a disproportionate part of ATMP batches would be consumed, especially if spare samples are required. Moreover, certain countries require testing of several batches. As a consequence of a small ATMP batch size (e.g., MTO products), several drug substance and drug product batches will have to be produced and dedicated to comply with all registration testing requirements.
- Evidence of traditional products shows testing quantities required range from 2 to 100 samples for marketing authorizations, from 2 to 50 for renewals, and from 3 to 50 for post-approval changes [13]. For variations, some countries may require the same amount of sample regardless of the classification of the change (minor or major classification).

Time Considerations

- Real-life data show that the time required for implementation of test methods and execution of registration testing for traditional pharmaceutical products can take up to 12 months [13]. For ATMPs, even longer periods up to 18 months were reported. In certain cases, the testing is not possible at all due to limitations in instrumentation.
- Lead times for manufacturing and importing samples to regulatory authorities can differ across regulatory processes. For traditional products, this could range from 60 to 180 days for marketing authorizations and 60 to 365 days for both major and minor post-approval changes. These lead times in providing samples to the authorities have a direct impact on the approval timelines for new medicines as well as for post-approval changes [13].

Taken together, registration testing depletes product supply, from an already small batch size, and unnecessarily prolongs patient access to new medicines without adding value when a product is certified by a mature NRA.

ATMPs Used in Clinical Trials Require a Development Stage Adapted Approach

PIC/S [30] and the EU [4] are strongly supporting a development stage adapted and risk-based approach for ATMPs used in clinical trials acknowledging that it is not always feasible to perform all specified tests or to use the usual sample size. Limited samples may be available, for example, in case of autologous products, allogeneic products in a matched-donor scenario, products for ultra-rare diseases, and for products for use in first-in-human or Phase II clinical trial with a small-scale production. As a consequence, a modified testing and sample retention strategy may be developed and documented.

Import testing of investigational ATMPs imported from third countries shall not be mandatory for the reasons indicated above (as applied, for example, in the EU [31]). The importer should ensure that the quality of the batch is in accordance with the terms of the clinical trial authorization and that it has been manufactured in accordance with quality standards at least equivalent to the GMP requirements of the importing country. For this purpose, a GMP certification of the development manufacturing or testing site by the NRA in the third country is not required (GMP certificates are not always available).

In addition, systems and processes to manage and rigorously control both CoC and CoI are fully applied during development and allow for end-to-end traceability up to the product administration. Consequently, relying on testing performed under GMP in the third country is justified.

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