ATMPs: How to Successfully master Challenges and foster the Regulatory Success Rate?

When facing the fairly poor success rate of ATMP authorization applications and despite game changing potential of ATMPs the following questions arise: Where do we stand with ATMPs? What are the challenges faced during different stages of development and during authorization of ATMPs? How can challenges be prevented or successfully mastered? And how can the regulatory environment foster the success rate? The following article provides answers.

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ATMPs comprise four distinct product categories, i.e. gene therapy medicinal products (GTMP), somatic cell therapy medicinal products (sCTMP), tissue-engineered products (TEP) as well as combined ATMPs.

Combined ATMPs contain one or more medical devices as an integral part of the medicine. An example of this is cells embedded in a biodegradable matrix or scaffold.

Though an EU regulatory framework is in place since 2008 and more than 900 ATMPs are in clinical trials, the number of authorized ATMPs with currently less than 10 is very low.

Approximately 50 percent of the ATMP authorization applications are successful. This success rate is disappointing and significantly lower compared to other new therapeutic entities. Based on recent internal research data the overall success rate for new therapeutic entities at the time of approval is higher than 80 percent.

In this article the following four key questions are discussed:

1. Where do we stand with ATMPs?
2. What are the challenges faced during different stages of development and during authorization of ATMPs?
3. How can challenges be prevented or successfully mastered?
4. How can the regulatory environment foster the success rate?

1. Where do we stand with ATMPs?

Between January 2009 and August 2016, 8 ATMPs were granted a marketing authorization (MA) in the EU or were recommended to be approved. The approvals refer to 3 GTMPs (Glybera, Imlygic, Strimve-
lisis), 2 sCTMs (Provenge, Zalmoxis) and 3 TEPs (ChondroCelect, MACI, Holoclar), of which two have been additionally classified as combined ATMPs (MACI, Imlygic).

An overview of the marketing authorization applications (MAA) evaluations at European Medicines Agency (EMA) is provided in Figure 1. During the period of January 2009 and mid 2016 8 ATMP applications received a positive opinion, 4 applications received a negative opinion and 4 applications were withdrawn during the authorization procedure by the applicant. Withdrawal typically indicates that the issues raised by regulators during the authorization procedure could not sufficiently be addressed by the applicant. Two applications are currently under review: (1) a TEP containing allogeneic adipose-derived stem cells for the treatment of fistulas and (2) a combined TEP containing autologous chondrocytes in a collagen scaffold for treatment of cartilage defects.

ATMPs which were approved or received a positive opinion are listed in Figure 2. However, from the 8 products where the approval hurdle was successfully taken, two are no longer authorized. With regard to the ATMP MACI, the marketing authorization holder closed the EU manufacturing site. Consequently, the licence of the manufacturing site was withdrawn and the product authorization was suspended [1]. For the ATMP Provenge the marketing authorization was withdrawn. Further details are provided in section 3. As a consequence, only a total of 6 ATMPs are approved or received a positive opinion until August 2016 (Figure 2 on page 134).

2. What are the challenges faced during different stages of development and during authorization of ATMPs?

When facing this fairly poor success rate and despite game changing potential of ATMPs the question arises: what are the underlying reasons?

While some reasons are certainly associated with the individual product and its particular characteristics, there are other and more general issues that can be attributed to the ATMP product class. The general challenges are further addressed in section 2.1. and product specific examples are provided in section 2.2.

2.1. General challenges

Shortcomings in all parts of the dossier

Compared to other product classes where issues are in the majority of cases in the clinical part of the dossier, ATMP show shortcomings in all parts of the dossier, from product quality to the non-clinical program up to the clinical program and data.

This leads to a high number of objections including major objections during the evaluation of the MAA. In order to respond to regulators’ questions and to address major objections, long clock stops are needed during the evaluation procedure. For some products and programs the issues are so severe that they cannot be sufficiently addressed during the procedure. As consequence, applicants either withdraw their application or regulators issue a negative opinion.

Quality challenges

The challenges frequently observed in the quality part of ATMP applications comprise issues with the characterization of these complex types of products including deficiencies in the potency assay. Thereby the determination of the consistency of products derived from an established manufacturing process is impaired. Changes in the manufacturing process are frequently made to improve product quality over time, to adjust to the current scientific and regulatory standards or to cope with changes in supply of materials needed for the production. The assessment of the comparability of products pre- and

| Initial Evaluation of Marketing Authorisation Applications (MAA) for ATMP |
|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| Submitted MAAs   | 3    | 1    | 2    | 3    | 2    | 2    | 1    | 1    | 15    |
| Positive draft opinion | 1    | 0    | 1    | 1    | 2    | 1    | 1    | 2    | 9     |
| Negative draft opinions | 1    | 0    | 1    | 0    | 0    | 0    | 2    | 0    | 4     |
| Withdrawals      | 1    | 1    | 0    | 0    | 2    | 0    | 0    | 0    | 4     |
| Ongoing MAAs     |      |      |      |      |      |      |      |      | 2     |

i Same product (Cerepro); ii Same product (Glybera)
* EMA’s Committee for Advanced Therapies (CAT) adopted two negative draft opinions for the same product (Heparesc)

Figure 1: Overview of submitted MAAs for ATMPs between 2009 and 2016 including outcome [CAT monthly report, July 2016].
post-change represents a further quality challenge for complex types of products.

Even the setup of an ATMP manufacturing process including the qualification and validation thereof is not a trivial undertaking. In particular for autologous, cell-based ATMPs the sourcing of starting material to develop a manufacturing process presents a significant hurdle.

**Non-clinical challenges**

For the non-clinical development there are rarely off-the-shelf solutions available. Sufficiently sensitive and relevant models are frequently lacking to assess safety and pharmacodynamic properties and to guide the clinical development. Consequently, the sponsors have to identify alternative strategies. Deficiencies are frequently observed in the identification and also justification for alternative strategies.

The following non-clinical areas present particular challenges for ATMP developers: biodistribution, germline transmission studies as well as tumorigenicity studies.

**Clinical challenges**

An important challenge for clinical development is the fact that ATMPs frequently present with a pleiotropic mechanism of action (MoA). These MoAs are not necessarily directly linked to the nature of the product but can be influenced by patient related factors. This complicates patient selection and prediction of response.

Many ATMPs are developed for orphan indications for which there are rarely established clinical development paths available. Therefore, the design of studies including valid endpoints, comparator selection, and the required statistical rigor given the limited number of patients present additional development hurdles.

For many ATMPs, in particular autologous cell-based products, the patient safety profile is not only defined by the administered product but also driven by concomitant treatments or measures related to the collection of autologous starting material for the production of the ATMP, such as surgery or leukapheresis.

**ATMP sponsors**

ATMPs are traditionally developed by academia and small and medium-sized enterprises (SMEs). Given the complexity of the products the development and approval is demanding per se, even for experienced pharmaceutical companies. This is even more true for companies who have less experience in product development and regulatory strategies combined with the limited financial resources.

**2.2. Challenges – two examples**

The ATMPs Provenge and Heparesc were selected to exemplify product specific challenges at different stages.

**The Provenge case**

Provenge is the first approved personalized cancer vaccine for the treatment of metastatic hormone refractory prostate cancer (mHRPC). The product obtained approval from the FDA in 2010 and marketing authorization as a sCTMP in the EU in 2013.

Provenge is produced from autologous cells obtained by leukapheresis which are subsequently activated.

<table>
<thead>
<tr>
<th>ATMP</th>
<th>Category and Indication</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>ChondroCelect</td>
<td>TEP, Repair of symptomatic cartilage defects of the knee (1–5cm²)</td>
<td>approved</td>
</tr>
<tr>
<td>Glybera</td>
<td>GTMP, Treatment of lipoprotein lipase deficiency (1–5cm²)</td>
<td>approved</td>
</tr>
<tr>
<td>MACI</td>
<td>TEP, combined ATMP Repair of symptomatic cartilage defects of the knee (3–20cm²)</td>
<td>approved, now suspended</td>
</tr>
<tr>
<td>Provenge</td>
<td>sCTMP, Treatment of prostate cancer</td>
<td>approved, no longer authorized</td>
</tr>
<tr>
<td>Holoclar</td>
<td>TEP, Treatment of limbal stem cell deficiency due to ocular burns</td>
<td>approved</td>
</tr>
<tr>
<td>Imlygic</td>
<td>GTMP, combined ATMP Oncolytic virus for treatment of melanoma (3–20cm²)</td>
<td>approved</td>
</tr>
<tr>
<td>Strimvelis</td>
<td>GTMP, autologous genetically modified CD34+ cells for treatment of ADA-SCID</td>
<td>approved</td>
</tr>
<tr>
<td>Zalmoxis</td>
<td>sCTMP, allogeneic T cells genetically modified to express suicide gene for treatment of GvHD</td>
<td>Positive opinion, pending EC decision</td>
</tr>
</tbody>
</table>

Figure 2: Overview of ATMPs obtaining marketing authorization in the EU and current status.
in vitro by an immune stimulatory fusion protein (PAP-GM-CSF). The resulting CD54+ cells activate the patient’s immune system after infusion and prolong overall survival (OS) by approx. 4 months. In the US the regulatory hurdles were finally met during the second approval procedure in 2010. As part of the submission further results from studies with overall survival as primary endpoint were provided. In 2007 the product was initially rejected due to uncertainty in terms of clinical efficacy coming out of the selected study design with time to progression as primary endpoint.

In the EU, the regulatory approval hurdle was met in 2013. However due to commercial challenges and market access issues triggered by the high cost of goods the EU based sponsor went bankrupt [2] [3] [4]. In 2015 the marketing authorization of Provenge was withdrawn due to commercial reasons [5].

The Heparesc case
Heparesc is a sCTMP consisting of manipulated living liver cells from a healthy donor. The product was developed for the treatment of young children with specific urea cycle disorders. The authorization for Heparesc was refused in 2015. During the evaluation procedure EMA’s Committee for Medicinal Products for Human Use’ CHMP had concerns about the design and conduct of the studies, which cast doubt on their results and whether these could have occurred by chance.

In addition, there were concerns about the clinical relevance of the results of the tests that measured the ability to produce urea. Although taking into account the challenges of developing the medicine, including the difficulty of enrolling patients due to the rarity of the disease, the CHMP therefore concluded that the benefits of Heparesc did not outweigh its risks and recommended the refusal of the marketing authorisation. This assessment was confirmed during a re-examination procedure involving experts in the treatment of urea cycle disorders [6].

An overview of the Heparesc case is provided in Figure 3.

3. How can challenges be prevented or successfully mastered?

For ATMPs our experience is that “regulatory challenges“ faced during approval or even thereafter are in fact development issues originating from early development stages. For example, with the Heparesc case the approval issues were related to a large extent to the design and conduct of the clinical study as well as an insufficient bioanalytical strategy. With the Provenge case, though the product obtained approval, the issues were related to the price which was driven by the high cost of goods. As a consequence, challenges and issues need to be addressed early on during the development. At later stages only rescue strategies are possible with mixed results.

In the following points to consider are provided to address ATMP challenges at dedicated development stages (see figure 4–7).

3.1. Points to consider at R&D stage (Figure 4)
At the transition from research to the development stage it is important to reflect and understand the reasons of previous ATMPs failures. Though

![Figure 4: Points to consider at research and development (R&D) stage.](attachment:figure4.png)
failures can have different reasons, for ATMPs it becomes more and more obvious that the issues go like a red line through the entire development chain. Understanding the reasons of previous failures clearly helps to prevent falling into the same trap. Due to the complexity of the products a clear understanding of the MoA is not a trivial exercise. However, it is absolutely key to success to characterize the MoA as thoroughly as possible by complementary means. Likewise important is the identification of a suitable potency assay or a complementary set of assays to assess or predict product functionality. It is highly recommended to consider cost of goods already early on, i.e. when the initial GMP process is being designed.

Figure 5: Points to consider for manufacturing (for abbreviations see figure 4).

Figure 6: Points to consider for non-clinical development (for abbreviations see figure 4).

Due to the complexity of the products a clear understanding of the MoA is not a trivial exercise. However, it is absolutely key to success to characterize the MoA as thoroughly as possible by complementary means. Likewise, a clear understanding of the pathophysiology of the target disease is essential. Understanding both will facilitate the selection of a lead indication where the pathophysiology matches the MoA. Thereby the chance for success is increased.

Begin with the end in mind: Already at this early stage drafting a target product profile is helpful to guide lead candidate selection. With the target in mind drafting the integrated development plan across all disciplines is a very useful instrument to guide a focussed development program.

3.2. Points to consider for manufacturing (Figure 5)
The issues related to Chemistry, Manufacturing and Control (CMC) certainly differ among the different ATMP classes. Substantially modified cell-based (autologous) products represent from our perspective the most challenging category. Unlike for other proprietary products the manufacturing process can start already at the patient’s bedside which is not necessarily a qualified Good Manufacturing Practice (GMP) unit.

Process qualification and validation represents another hurdle as patient-derived material is a scarce source. Though material from healthy donors can be used for this purpose if properly justified, it is not always possible in the EU to source this material for e.g. ethical reasons. The identification of key quality attributes of an ATMP is critically important. This helps to set up the process properly, to ensure consistency and supports comparability exercises associated with manufacturing changes.

Likewise important is the identification of a suitable potency assay or a complementary set of assays to assess or predict product functionality. It is highly recommended to consider cost of goods already early on, i.e. when the initial GMP process is being designed.

Figure 7: Points to consider for clinical development (for abbreviations see figure 4).
(FIH) study. For this exercise the potential risks and uncertainties associated with an ATMP or related procedures are listed, assessed and appropriate measures are identified for the planning and conduct of the clinical study. A proper risk mitigation strategy combined with an in-depth knowledge of the MoA and pathophysiology guides the selection of the most appropriate patient population. Thereby the success rate can be increased early on in development. The identification of appropriate biomarker can facilitate and streamline the development. At late stage clinical development and after manufacturing changes it is important to carefully assess comparability to ensure that the clinical performance is not impaired by a changed quality profile of the ATMP.

The EMA is aware of the particular challenges that ATMP developers are facing. As a consequence thereof a multi-stakeholder meeting took recently place to discuss regulatory measures to foster innovation and the development of ATMPs [7].

4. How can the regulatory environment foster the success rate? What regulatory tools are available?

On the EMA website there are dedicated scientific guidance documents available to support companies developing ATMPs [8]. In addition to the scientific guidelines there are dedicated regulatory tools and benefits available to support ATMP development. These benefits comprise for example:

4.1. classification procedure – classification of the ATMP,
4.2. certification procedure – certification of CMC and non-clinical documentation,
4.3. scientific advice at reduced fees or
4.4. EMA Innovation Task Force – support from the EMA innovation task force.

4.1. Classification procedure
As far as the classification procedure is concerned, companies can consult the EMA to determine whether a medicine they are developing is an ATMP and if so, under which category of ATMP the product would fall. The EMA established the procedure to address questions on borderline classification with other areas, such as medical devices, as early as possible. EMA publishes the outcome of the assessment of the classification of ATMPs as summary reports [9].

4.2. Certification procedure
For SMEs the EMA’s Committee for Advanced Therapies (CAT) provides a certification procedure for ATMPs. This is an opportunity for SMEs to get an assessment of the data they have generated and check that they are on the right track for successful development. Such a pre-assessment of data is currently not available for any other product classes.

The certification procedure involves the scientific evaluation of quality data and, when available, non-clinical data that SMEs have generated at any stage of the ATMP development process. It aims to identify any potential issues early on, so that these can be addressed prior to the submission of a marketing-authorisation application.

After assessment, the CAT may recommend issuing a certification confirming the extent to which the available data comply with the standards that apply for evaluating a marketing authorization application. Following the CAT recommendation, the Agency issues a certification [10].

4.3. Scientific advice at reduced fees
The EMA can give scientific advice and protocol assistance (in the case of orphan medicinal products) to a company on the appropriate tests and studies in the development of a medicine.

Scientific advice helps the company to make sure that it performs the appropriate tests and studies,
so that no major objections regarding the design of the tests are likely to be raised during evaluation of the marketing authorization application. Such major objections can significantly delay the marketing of a product, and, in certain cases, may result in refusal of the marketing authorization [11]. Following the Agency’s advice increases the probability of a positive outcome.

Scientific advice at EMA level is associated with a fee of up to 83,700 Euro in case of an initial multidisciplinary advice covering quality, non-clinical and clinical aspects. For ATMPs the following fee waiver scheme currently applies: 65% for a non-SME applicant, 90% for an SME applicant and 100% reduction for ATMPs falling under the Priority Medicines (PRIME) scheme.

Scientific advice is also offered by several agencies at national level.

4.4. EMA Innovation Task Force

The EMA Innovation Task Force (ITF) is a multidisciplinary group that includes scientific, regulatory and legal competences. The objectives of the ITF are to establish a discussion platform for early dialogue with applicants, in particular SMEs to proactively identify scientific, legal and regulatory issues of emerging therapies and technologies [12].

In addition to the ATMP dedicated procedures mentioned above the ATMP developing companies can also benefit from the PRIME scheme and the Adaptive Pathways Initiative. In principle, these procedures are open to all product categories, provided that the defined criteria are fulfilled.

Adaptive pathways

The adaptive pathways initiative is part of the EMA’s efforts to improve timely access for patients to new medicines. It is a scientific concept for medicine development and data generation which allows for early and progressive patient access to a medicine. It applies primarily to treatments in areas of high medical need where it is difficult to collect data via traditional routes and where large clinical trials would unnecessarily expose patients who are unlikely to benefit from the medicine. Adaptive pathways are based on the following three principles:

1. Iterative development,
2. Gathering evidence through real-life use to supplement clinical trial data and
3. Early involvement of patients and health-technology-assessment bodies in discussions on a medicine’s development.

The approach builds on regulatory processes already in place within the existing EU legal framework such as scientific advice, compassionate use, the conditional approval mechanism, patient registries and other pharmacovigilance tools [13].

PRIME scheme

The PRIME scheme was launched by the EMA to enhance support for the development of medicines that target an unmet medical need. This voluntary scheme is based on enhanced interaction and early dialogue with developers of promising medicines, to optimize development plans and speed up evaluation so these medicines can reach patients earlier [14] [15].

PRIME builds on the existing regulatory framework and tools such as scientific advice and accelerated assessment but has also new elements, such as early appointment of a rapporteur from the CHMP or CAT in case of an ATMP. Early rapporteur appointment is intended to provide continuous support and help to build
knowledge ahead of a marketing authorization application.

While PRIME is open to all companies on the basis of preliminary clinical evidence, applicants from the academic sector and SMEs can apply earlier on the basis of compelling non-clinical data and tolerability data from initial clinical trials.

SMEs and academia generally have less experience with the regulatory framework and therefore would benefit from earlier scientific and regulatory advice.

References

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