Whither Advanced Therapy Medicinal Products?

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The topic of this special issue of TRANSFUSION MEDICINE AND HEMOTHERAPY is advanced therapies and tissue engineering. The legislative framework that regulates these fields in Europe is based on two Directives (and their amendments) of the European Commission [1, 2] and has been legally binding in all EC member states since December 2008. The term Advanced Therapy Medicinal Products (ATMPs) is generally used to refer to the legislation.

The regulations were introduced at a time when many regenerative therapies seemed close to translation into clinical practice. However, the level of success with the translation of gene- and cell-based therapies has not met the expectations of the pre-ATMP era. It has been argued that the demands of the regulatory framework may have contributed to a degree of stagnation in the field, but it is difficult to quantify to what extent the ATMP guidelines have hindered progress.

This foreword reviews pertinent aspects of the ATMP directives, summarizes the current landscape with respect to approvals (granted and pending), and discusses public domain information relating to withdrawal of applications for marketing authorization. It would appear that the ATMP regulations will need to evolve if the promise of regenerative medicine is to become a clinical reality.

ATMPs: The Necessity to Regulate

It should be acknowledged that regulators were correct in identifying an impending crisis. The advent of gene and cell therapies had exposed major deficits in the European medical regulatory frameworks. Therapeutic concepts, for which existing laws and guidelines were neither adequate nor harmonized, had reached or were approaching clinical use.

The ATMP regulations cover the authorization, supervision, and pharmacovigilance of ATMPs in Europe. The Committee for Advanced Therapies (CAT) of the European Medicines Agency (EMA) is responsible for assessing the quality,

safety, and efficacy of ATMPs. Three categories of product are identified in the directives:

- gene therapeutic products,
- somatic cell therapeutic products, and
- tissue engineered products.

Prior to the introduction of ATMPs, European regulation of biologics was in some disarray. The harmonized Medical Device Directive (MDD) [3] was operating reasonably well for non-biological devices but was producing inconsistencies in the area of biologics. For example, a ‘non-viable and non-human’ inclusion criterion led to illogical conflicts in the field of non-viable tissue transplants. A sterilized acellular dermis of porcine or bovine origin could be certified according to the MDD and thereafter marketed in all European member states (and often, without too many additional requirements, worldwide). At the same time, an acellular dermis of human origin must be individually approved in each member state. In Germany and Austria such transplants are covered by the national laws on medicinal products (pharmaceuticals) and require individual marketing authorizations and manufacturing licenses. In other member states an MDD-like approach is used to decide upon individual registrations for such products, or an ad-hoc approach using rules selected from national laws and from the MDD is used.

The European Tissues and Cells Directive [4] is intended to regulate non-ATMP medicinal products containing human tissues and cells but the implementations of this directive in individual member state laws has resulted in an unsatisfactory level of harmonization. The US Food and Drug Administration (FDA) also makes provision for a sub-biologic classification of Human Cell and Tissue Products (HCT/Ps) [5]. Both legislative frameworks (Europe and USA) include rules that are used to classify biological products according to the parameters ‘minimal manipulation’ and ‘homologous use’. These parameters are somewhat loosely defined, but application of the rules often plays a major role in classifying products as ATMPs and biologics. The consequences can be severe.

ATMPs: Issues Facing Developers

The decision by the European regulators to regulate ATMPs more like pharmaceuticals than like medical devices is understandable. There can be no argument against holding ATMPs to stringent quality and safety standards as far as practically feasible. However, certain medical and economical aspects of ATMP development, (in particular cell- and tissue-based therapies) do not seem to be well accommodated by the legislation.

Unlike pharmaceuticals manufactured with chemical, fermentation, or recombinant technology, much ATMP development is undertaken in universities (or small start-up derivatives) and in tissue banks [6]. These domains must operate within economic boundaries that do not apply to large pharmaceutical companies. Furthermore, much ATMP development is either focused on treatments for rare clinical conditions or on treatments for extreme cases of more commonly occurring conditions. Therefore:

- ATMP development groups are generally small and have limited resources.
- ATMP developments can be unattractive prospects for investment since return on investment (ROI) prognoses tend to be poor.
- The number of patients available for studies can be small.

In addition, particular safety and quality requirements for biological source materials, excipients, and reagents can be difficult to meet. Available purification and sterilization methods are often inappropriate.

The development course for ATMPs for regenerative therapies rarely follows a classical pharmaceutical track. One peculiarity is the absence of focus on specific indications at the outset. Instead, initial research and development tends to be focused on the establishment and characterization of ‘functional, biologically active units’ that are capable of generating or repairing tissue. In general, developers will therefore initially concentrate on tissue-related function and then on quality and safety. For novel approaches ‘proof of concept’ pre-clinical work will often be performed, whilst keeping indication options open. Data collected up to this point will suggest a range of indications in which the treatment might be both effective and necessary. An extended period of exploratory (phase II) clinical research may well be required to identify target indications for phase III studies. This chronology does not appear to have been given sufficient consideration by the regulators.

Sustaining ATMP projects throughout a prolonged exploratory phase will present serious economic challenges. Considering the anticipated ROI for such developments, business decisions will likely lead to ATMP projects being abandoned at this stage.

The treatments in question are likely to be expensive. An initial aim of guaranteed reimbursement for ATMPs was abandoned during the drafting of the directives. As a conse-

quence, in addition to the high level of clinical evidence that is required for approval of novel ATMPs, manufacturers must also consider the reimbursement implications of planned studies. It therefore becomes necessary for developers to demonstrate superiority in specific indications in discrete phase III clinical trials in order to achieve reimbursement goals. The business risks associated with running clinical trials for an ATMP approval submission that address both efficacy and superiority will often be unacceptably high. This may even be the case for developments for which quality and safety are certified and exploratory trials yield promising data.

If credence can be given to the promises of cell-based regenerative medicine it can be argued from a health perspective that better legislative and economic support should be provided.

Nevertheless, it must be acknowledged, that in addition to cell type and manufacturing quality parameters, the safety of a cell-based product can be strongly influenced by indication (e.g. site of transplantation). Given related experience in Germany [7, 8], it is appropriate that the authorities are implementing stricter rules that aid patients and doctors in resisting the allure of frontier cell therapies carrying nothing but hope [9].

ATMPs: How Well Are These Issues Addressed?

It appears that regulators attempted to ameliorate the difficulties facing ATMP developers primarily by offering discounts for consultations and submissions [10] and by providing an intermediate certification option to developers that meet the criteria for classification as a small- to medium-sized enterprise (SME).

These provisions appear to be insufficiently refined and do not alone negate the problems facing ATMP developers.

The running costs for the EMA are EUR 236 million per year [11]. This has resulted in a fee for an ATMP approval submission of a minimum of EUR 274,400.00 per pharmaceutical form (not including additional costs such as those for inspections) [12, 13]. This fee could be a major disincentive for small developers that do not meet the criteria of a SME. For example, the individual members of a coalition of small non-profit tissue banks may not meet the SME criteria.

The intermediate certification option also seems to be unnecessarily restrictive both in terms of availability and scope. Here, Article 18 of EC No 1394/2007 makes provision for attaining a CAT-certified intermediate status for quality and safety. Again, this option is only available to SMEs. Interestingly, according to the most recent CAT report [14] only 3 SMEs have decided to participate in quality and non-clinical data certification.

One can speculate as to why little use is being made of this provision. The number of registered clinical studies [6] in the field suggests that this phenomenon is not associated with

widespread abandonment of ATMP projects in early development stages. It seems more likely that the certification is not perceived as having real value when faced with the problems arising from a likely requirement for an extended period of exploratory clinical research and high-risk phase III studies.

For those developers choosing to submit approval applications, the schedule imposed by the submission system can also be problematic. Once an initial submission has been made, a system of deadlines comes into play [15] that places restrictions both on the regulators (for assessing the submissions) and on developers (for completing the submission process). No doubt this was at least in part intended to reassure developers that their submissions would be dealt with promptly.

It has led to submissions for approval being withdrawn. Both CellSeed Europe Ltd. and Anika Therapeutics S.r.l. have recently withdrawn their applications due to not being able to provide additional data towards a favorable CAT opinion 'within the agreed timeframe' [16, 17].

ATMPs: Current and Pending Approvals

Despite the incentives available during an initial transitional phase following the implementation of EC No 1394/2007, at the time of writing only three ATMPs have been granted a marketing authorization by the EMA.

ChondroCelect, an autologous cell culture product for treatment of single symptomatic cartilage defects of the femoral condyle of the knee (grade III or IV) [18] was the first ATMP to receive an approval in October 2009.

Three years later, in October 2012, Glybera was granted the second ATMP authorization. Glybera is used to treat adults with lipoprotein lipase deficiency who have severe or multiple attacks of pancreatitis despite maintaining a low-fat diet [19].

Most recently the first combination product received a marketing authorization from the European Commission. MACI is intended for treatment of symptomatic, full-thickness cartilage defects of the knee (grade III and IV of the Modified Outerbridge Scale) of 3–20 cm² in skeletally mature adult patients [20].

The approvals for all three products are limited to narrowly defined indications, and, with the exception of Genzyme (MACI), the manufacturers are required to undertake further studies and provide additional data on the use of their product in order to retain these restricted approvals.

Further ATMPs may be close to obtaining approval. In June this year, the EMA released a positive statement regarding marketing authorization for another ATMP. Provenge is indicated for the treatment of asymptomatic or minimally symptomatic metastatic (non-visceral) castrate-resistant prostate cancer in male adults in whom chemotherapy is not yet clinically indicated [21]. Two further ATMP submissions are being evaluated [22].

ATMPs: Possible Evolutionary Pathways

One potential improvement for ATMP regulation would be the provision of a more valuable intermediate approval status for products meeting quality and safety standards and for which 'proof of concept' data suggest possible therapeutic value. In the opinion of the authors, this should differ from the currently available intermediate certification. Firstly, the option should be available to all manufacturers. Secondly, a positive outcome from a review of pre-clinical and literature data should be a prerequisite for granting an intermediate certificate. Finally, the certification should support prolonged exploratory clinical investigation via registered and monitored clinical studies within defined indication limits and according to a clinical exploration plan submitted by the manufacturer.

The duration for which such an intermediate status would be valid ought to be based on reviews of incoming data with respect to the exploration plan, rather than being fixed from the outset. With appropriate safety, quality, and standards for the products (Good Manufacturing Practice) and a high standard of monitoring (Good Clinical Practice, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use), the exploratory clinical work could be conducted in a safe environment enabling the manufacturer to collect vital data for the planning of phase III studies.

Possibilities for improvements to the regulations can also be identified in the realm of product classification. The product classification approach used for medical devices could serve as an example. Here, a risk-based approach is used to sort products into a hierarchy of classes that in turn define the path to certification. A hierarchical classification system for ATMPs might also be feasible. Parameters such as dosage, cell source, mode, and site of delivery and the medical condition of patients could be used to construct such a classification matrix.

Another opportunity for evolution can be found within the current scope of the guidelines. Here we return to the aforementioned 'minimal manipulation' and 'homologous use' criteria. There are obvious possibilities for improvements in both cases.

The minimal manipulation criterion could be bound to safety-related parameters used to assess the effects of manufacturing processes on cells and tissues. For example, the expansion of a cell population might be considered minimal manipulation provided the developers could demonstrate that no relevant genotypic or phenotypic alterations arise from the expansion.

The 'homologous use' criterion is presently inadequately defined. It is generally accepted that this means 'use bone cells to treat bone defects', or 'use skin cells to treat skin defects'. However, a less dogmatic distinction may be more appropriate. An application matrix in which cell types are assessed for their use in host tissues might provide more appropriate resolution for product classification. In addition, such a

matrix could be used to determine the level of safety data required for an approval.

A rather obvious anomaly in the ‘homologous use’ criterion could be addressed by such a system. Amnion is recognized as a tissue with diverse potential in regenerative medicine. Some amnion formulations are regulated according to national implementations of the European Tissues and Cells Directive. However, according to the ATMP guidelines, due to non-homologous use, amnion must generally be considered as an ATMP (irrespective of formulation and dosage). In contrast to the situation in the USA where exclusion as a ‘biological’ lands a potential treatment based on human cells or tissues in the HCT/P category, in Europe exclusion from ATMP lands potential developments in the insufficiently harmonized tissues and cells category. This will usually be disadvantageous for the development in question.

Article 28 of the EC No 1394/2007 (the so-called ‘hospital exemption’ clause) makes a special provision for limited-scale manufacture and supply of pharmaceuticals used exclusively under the direct supervision of qualified medical practitioners in recognized specialized hospitals for named patients. Here in Germany, the national drug law implementation of this article (§4b AMG) provides ATMP developers with an important option. The Paul Ehrlich Institute is accepting submissions for

ATMP-class products under this provision as a stepping stone towards a full ATMP submission. It is said that this was initially frowned upon by the ATMP regulators. However, if the number of submissions and approvals remains low, it seems likely that both the EMA and individual national authorities will warm to approaches of this kind. The safety and quality requirements can be retained, the fees could be made more affordable, the deadline system could be relaxed, and some flexibility in terms of indication could be accommodated.

The German ‘paragraph 4b’ might turn out to be a catalyst for reinvigorating the development of regenerative therapies in Germany. Similar implementations of Article 28 of the EC No 1394/2007 might stimulate development in other member states.

The ‘translation wave’ in regenerative medicine may have been somewhat over-hyped, but regulators can play a major role in guiding and supporting development of ATMPs to ensure that the field survives and prospers in the post-boom era.

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