BPI Bundesverband der Pharmazeutischen Industrie e.V.

Friedrichstraße 148
10117 Berlin
www.bpi.de

Telefon: (0 30) 2 79 09-1 72
Telefax: (0 30) 2 79 09-3 72
E-Mail: mwilken@bpi.de

Comments

PUBLIC CONSULTATION PAPER
ON THE REGULATION ON ADVANCED THERAPY MEDICINAL PRODUCTS

Regulation (EC) 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC (hereafter "ATMP Regulation") requires the Commission to assess the application of the Advanced Therapy Regulation and to produce a report.

The Commission invited the stakeholders to provide input regarding the implementation of the Advanced Therapy Regulation and to give their views especially concerning the following topics:

- Marketing authorisation application requirements for advanced therapy medicinal products
- Requirements for combined advanced therapy medicinal products
- Hospital exemption
- Incentives for the development of advanced therapy medicinal products
- Scope and adaptation to technical progress

BPI is grateful for the opportunity to comment on the above-mentioned consultation. Doing that we would like to add some remarks concerning the overall legal framework and the experience gained with the regulatory framework in the past five years. These points are included within the comments concerning the marketing authorisation application requirements for advanced therapy medicinal products.

BPI represents the majority of Germany's industry in the field of Tissue Engineering, most of these companies being SMEs. Therefore, the comments of BPI represent the voice of SMEs that are especially invited to comment on this proposal by the Commission.

Introduction

A glance at the market shows that the transitional periods – as laid down in Article 29 of Regulation (EC) 1394/2007 for obtaining a centralised marketing authorisation for products already on the market – were not realistic. The need to extend these periods had been reiterated repeatedly and by various stakeholders during the legislative procedure. The background for the fact that so far only few marketing authorisation applications for ATMP have been submitted to the European Medicines Agency (EMA) is that the companies cannot design, perform and finalise the clinical trials required for the centralised marketing authorisation within such a short period of time. Add to this the requirements from the scope of Regulation (EC) 1901/2006 (EC Paediatric Regulation). This means that paediatric trials

need to be integrated in clinical trial concepts for medicines with new substances, and these paediatric trials need to be agreed beforehand with EMA's Paediatric Committee (PDCO). Currently, the approval process for a paediatric investigation plan (PIP) alone takes roughly 12 months. With this, the concept for paediatric trials is set initially, but the trials as such still remain to be carried out. Moreover, if adaptations to the trial design become necessary, applications for modifying the PIP must be made, and their processing by the PDCO takes further months. Without precise adherence to the PIP as approved by the PDCO, the medicine will not be authorised in the adult indication, either – not even if sufficient data for a marketing authorisation are available for use in adults, possibly after many years of use.

In many cases it is emerging that scientific advice for ATMP already on the market leads to the result that at least one prospective confirmatory clinical trial is required – additionally to clinical data gained in many years of use. Furthermore, quite frequently also data from pre-clinical trials in animals are subsequently deemed necessary for the granting of a centralised authorisation, regardless of long-standing use of products in humans. Irrespective of how this is seen in ethical terms and especially in respect of animal welfare, this causes extra cost and work and delays the moment when the complete data package becomes available for an application in the centralised procedure.

In view of the above, the BPI is not surprised that five years after entry into force of the Regulation most companies and university facilities simply cannot be able to apply for centralised marketing authorisations. In a realistic approach, clearly longer timelines must be expected. However, most recently there seem to be more such applications.

In this context, it should also be considered that manufacturers of ATMP are mostly hospitals or smaller companies who cannot – neither financially nor with their staff resources – carry out projects like a centralised authorisation in the short transitional period laid down in the ATMP Regulation; even less so because the transitional period in Article 29 of the ATMP Regulation is worded in such a way that the centralised authorisation needs to be in the hands of the manufacturer already on the date when the transitional period ended. This means that an application would have needed to be made at least one and a half years before, which factually further shortened the transitional period.

Against the above-described backdrop, the regulatory value in Article 28 (2) of Regulation (EC) 1394/2007 is immeasurable. Inter alia, it enables keeping up existing market access on a transitional basis depending on the progress of implementation in the respective Member State, because otherwise – due to the end of the period for obtaining a centralised authorisation under Article 29 of the ATMP Regulation – immediate market exclusion would have been the consequence.

ATMP development is strongly promoted with public research funds at both EU and Member State levels. It is important for the developed products to really get to the patients. For this

purpose, a regulatory framework is needed which takes into account the particular features of ATMP and of the smaller companies and university facilities who manufacture them.

From the BPI's viewpoint it is paramount that patients get safe medicines. This is given with the centralised marketing authorisation and the rules in Article 28 (2) of Regulation (EC) 1394/2007, because here, too, the link is made to the traceability and pharmacovigilance requirements and to the quality standards which apply also to centrally authorised ATMP. Moreover, manufacture needs to be approved by the competent authority. Going beyond what is legally asked for, in Germany adhering to the conditions of Good Manufacturing Practice (GMP) is demanded even for ATMP manufacture within a hospital exemption setting. Thus products, which nationally fall under the implementation of Article 28 (2) of the ATMP Regulation, are given equal status in essential regulatory aspects to medicines requiring a centralised marketing authorisation.
It is worth noting that an exemption referring to Article 28(2) of Regulation (EC) 1394/2007 needs to be applied for individually for each Member State. In the medium-term, companies need a larger market so that they can grow. Consequently, obtaining a centralised marketing authorisation will be the objective, as it enables placing on the market throughout the entire EU. But this is not realistically feasible neither in the short transitional period nor "in one fell swoop".

Where companies have provided the data necessary for a centralised authorisation, this will also be striven for. Regarding hospitals it is questionable if they would go the way to get a centralised marketing authorisation in the future as they are working on a regional level.

Regarding the general requirements for ATMP development, the Committee for Advanced Therapies (CAT) has already done valuable work. But the expectation was overly optimistic to process large amounts of centralised marketing authorisation applications for ATMP after only a few years.

<u>Marketing authorisation application requirements for advanced therapy medicinal products</u>

- In general, the ATMP Regulation has been an improvement in terms of giving a better definition and a regulatory framework for ATMP in Europe. Generally speaking, uniform standards and rules are positive for patient safety, health care and also for the planning certainty of pharmaceutical companies.

- However, figuratively speaking the ATMP Regulation has also partly turned out to be an overly rigid corset which does not drive forward development and technical progress for ATMP but, quite the contrary, hampers them.

- After long discussions, it was decided in 2007 to regulate ATMP under the medicines legislation. This decision was also preceded by discussions about regulating ATMP

Comments

within the medical devices law. The main reason behind the idea to allocate ATMP to the medicines legislation was that only the medicines legislation offered the possibility to create a completely uniform legal framework in the European Union, namely by way of a Regulation. Safety considerations were another main aspect. It is uncontested that tissue engineered products and also somatic cell therapeutic products are “somewhere in between”: in many cases, they have properties of both medical devices and medicines. Regarding technical progress that brings fast product lifecycles, they are very close to medical devices. For technical further developments with fast product lifecycles, the medicines legislation is rather static and does not always allow the necessary flexibility, as compared with the medical devices law. Should it be ensured also for the future that ATMP fall under the medicines legislation, steps would need to be taken to more strongly integrate the flexibility of the medical devices law in the regulatory framework for ATMP development. From the BPI’s viewpoint, the rigidity of the medicines legislation currently inhibits innovation in the ATMP field, because technical improvements – which are achieved practically daily for tissue engineered products and somatic cell therapeutic products – are counteracted by the rigid system of variations and line extensions. Thus technical progress is thwarted by the overly rigid marketing authorisation system for medicines in this field which is, in fact, close to medical devices. Additionally, it is pointed out that – irrespective of ATMP being allocated under the medicines legislation in Europe – under social law of the Member States especially tissue engineered products are seen as “methods”. Consequently, for their reimbursement tissue engineered products rather tend to be treated similar to medical devices.

- The transitional period for obtaining the centralised authorisation was too short. Within a period of three years – and four years in the special case of tissue engineered products – the requirements to a centralised marketing authorisation procedure with all its pre-clinical and clinical trials were not achieved for reasons of time and finance. ATMP are products which might remain in the patient’s body. Long-term studies are expected for such products. Due to overly short transitional periods ATMP, which have been used for years and obviously were not deemed a risk to patient safety, disappeared from the market after the end of the transitional period under the Regulation. They are unlikely to return.

- Another problem is that the different classes of ATMP were not given enough consideration under the Regulation. These classes cannot be compared with each other. The products involve different risks. Gene therapy medicinal products usually pose greater risks than tissue engineered products, and within the class of TEPs autologous products need to be seen differently from allogenic ones.

- Certain products should be exempted from the ATMP Regulation. This holds true in particular for autologous homologous transplant products. They should be regulated as transplants under Directive 2004/23/EC (Cells and Tissue Directive).

Comments

- The allocation in the medicines legislation gives rise to very many questions for autologous tissue engineered products generally. Their manufacture rather constitutes a service than a medicine but has equal status with chemically/synthetically manufactured mass products: due to the legal allocation. This is bound to result in an artificial linkage of biotechnologically processed tissue products – which are based on viable cells or tissues with properties to regenerate – to the classical concept of the pharmaceutical world with its view on pharmacological, immunological or metabolic effects as the principal mode of action. With this, the mode of action of skin, cartilage or bone replacement by autologous cells/tissues is not described. With the efforts to resort to analogies for these properties (e.g. by equalling pharmacology with functionality and pharmacodynamics with biodistribution) it is tried to put things together that do not fit exactly.

- Treating tissue engineered products as medicines raises further questions. Such products are defined by their entire manufacturing process, including identity and potency. Time and cost-consuming testing as to further specifications does not make these products any better. Moreover, the already considerable manufacturing costs of autologous cultivated tissue engineered products are further driven up so that such products become even more unprofitable in their manufacture and, consequently, more difficult to sell.

- Highly specialised manufacturing processes and the special way of application (often surgical operations) and the combination with other medicines and/or medical devices further increase the complexity but not necessarily the risk. General rules might be desirable but obviously, they are very difficult in this field where a high degree of flexibility needs to be ensured. In many respects, the existing regulatory framework does not allow this flexibility.

- ATMP are mostly manufactured by SMEs, university facilities or hospitals. Unlike most producers of conventional medicines, they have a relatively low budget and no or only little experience in the performing of clinical trials and in the regulatory sector. There is a need to build competencies, set up departments, and newly create methods. The short transitional periods of maximally 4 years are not enough for this. Even now, the legal framework is asking too much of many of these stakeholders. Therefore, it is imperative to think about suitable support measures for manufacturers and university facilities. The SME Office of EMA is certainly very helpful, but it cannot give assistance to university facilities and small companies which do not meet the European recommendation of a SME definition.

- Tissue based ATMP are usually applied exclusively by a specialised and trained doctor, and there is post-treatment also in close cooperation between the manufacturer and the attending physician. In most cases, the number of patients is

relatively low and the application is personalised. These therapies are mostly distributed nationally. Against this backdrop, a centralised marketing authorisation – which gives market access throughout Europe – is often over dimensioned and too costly for the concerned SMEs and hospitals. Not only SMEs but also hospitals have difficulties in effectively steering a central authorisation procedure at EMA. Beside organisational aspects, also limited regulatory expertise and language barriers are important factors. The centralised marketing authorisation procedure suits bigger companies with the adequate staff to fulfil all the different tasks and read the relevant documents. But EMA needs to understand that – especially with the inclusion of ATMP – the "clients" became smaller companies and players outside the industry sector. EMA has little familiarity with the specific characteristics of applicants for ATMP, and the readiness to adapt to the needs and the resources of these applicants is growing only slowly. It is important to bear in mind a publication of Maciulaitis et al. in 2012 saying that academia, public organisations and SME are reflecting about 96 % of the actual developers in the ATMP field. Therefore, it should be thought about the right structures to reflect this. The structures at EMA need to become much more flexible to cope with the needs of the new "clients".

- To benefit from the special expertise of the CAT, this committee should be the lead committee in the assessment of ATMP. It would be welcomed to further streamline the scientific review process by the different EMA committees, such as CAT and CHMP. This would be best achieved by increasing the dialog between these committees, in order to clarify the requirements and to reduce uncertainties for ATMP developers.

Hospital Exemption

The regulatory value in Article 28(2) of Regulation (EC) 1394/2007 is immense. Inter alia, it enables keeping up existing market access on a transitional basis for products already on the market, depending on the progress of implementation in the respective Member State, because otherwise – due to the end of the period for obtaining a centralised marketing authorisation under Article 29 of the ATMP Regulation – immediate market exclusion would have been the consequence. Therefore, the hospital exemption is also an important bridging, as the transitional period was much too short to allow the conducting of clinical trials (and the completion of a PIP in accordance with the Pediatric Regulation). So without the hospital exemption all products on the market would have to leave the market immediately. That would have caused huge damage for the whole ATMP sector.

Although it is noted that there are discrepancies between Member States regarding the national implementation of the legislation e.g. in the term "non-routine preparation", BPI is not of the opinion that the solution should lie in a generally narrow definition of this term. Quite the contrary, also industrial standardised procedures should be included if they are for preparations for individual patients or rather small patient groups.

Comments

Possibly, the term “non-routine preparation” can be worded with somewhat more precision. Here, it is observed that those Member States, which have not yet implemented, orient their interpretation to the MS which have already implemented the so-called hospital exemption. For this purpose, e.g. the demand for manufacture under GMP conditions might make sense. Very often, many ATMP currently on the market are prepared only for one specific person (comparable with magistral formulations), and their use involves very little risk. Rather, risks arise in the methodical use of the products. However, methodical use is given less attention and cannot really be fully standardised. The freedom of medicine should be preserved for individual uses.

The hospital exemption is important, in order to have a suitable tool for the first steps of the process of newly developed ATMP: the possibility to try a new therapeutic approach, to treat several patients with the ATMP. At a given point of time, the production is outside the scope of the hospital exemption – and this is the point of time when a centralised marketing authorisation is required.

Therefore, the hospital exemption is a crucial tool to try new therapeutic approaches and to earn the funds for the centralised marketing authorisation procedure – this is the big difference of the hospital exemption in relation to clinical trials: the medicinal products within the trials need to be provided free-of-charge whilst in the hospital exemption setting the products may be sold.

Consequently, a stricter approach regarding the hospital exemption will not lead to more products, as most of the ideas will never come to the market – the tool for trying a new therapeutic approach in a setting controlled by a competent authority and for starting a business would be missing. Apart from that, limiting the hospital exemption will lead to a situation where producers have to undergo the centralised procedure earlier with less money and less knowledge about the product. It is not realistic that these circumstances will help finalise the centralised procedure better or more successfully – quite the contrary.

Apart from that, there are no problems regarding the safety of patients in a hospital exemption setting where the Member States in their national laws are following the approach that is clearly stated in Article 28 of Regulation (EC) 1394/2007. Here, the legislator states: *“Manufacturing of these products shall be authorised by the competent authority of the Member State. Member States shall ensure that national traceability and pharmacovigilance requirements as well as the specific quality standards referred to in this paragraph are equivalent to those provided for at Community level in respect of advanced therapy medicinal products for which authorisation is required pursuant to Regulation (EC) No 726/2004.”*

So an authorisation is needed; and concerning the safety and quality of the products the relevant standards for centralised products shall apply. At this point of time, the law does not

ask for efficacy data. Nevertheless, e.g. in Germany the applicant is obliged to provide the competent authority with clinical data as soon as they become available.

In the assessment of medicines to be authorised within a hospital exemption, it is up to the national authorities to assess the risk-benefit ratio on the basis of available data. Needless to say that no authorisation is granted where such an assessment is not possible or the assessment has a negative outcome.

An effective pharmacovigilance system should have an important role.

We take the view that the hospital exemption – put into practice in this way – is an incentive to develop ATMP and partly makes their development possible in the first place.

Extending fields of indication can be driven forward in this manner, too.

Of course, the national authorities should have a supportive function in the cooperation with the CAT so that the products can be further developed towards a centralised marketing authorisation, where possible.

Moreover, the hospital exemption rule should be clarified in the way that manufacture is not limited to hospitals. Also, it should be clarified that “non-routine preparation” includes standardised manufacture where, however, the preparation is intended only for a certain patient or patient group. Furthermore “non-routine preparation” should not be limited to manufacture and use taking place in one Member State. The competent authority of the MS where the preparation is used should decide on the application and also supervise pharmacovigilance.

Certification Procedure

Because of the detailed analysis of data involved in the granting of a certificate, the certification procedure is bound to become a real preparation exercise in order to file a marketing authorisation application at later stage. Therefore, it would be important to lay down possible implications of the certificate in relation to a marketing authorisation application. One possibility could be that a granted certificate in relation to quality and/or non-clinical data is taken into regard in the assessment of the final dossier. As long as the certificate is not outdated, the assessment scope during the marketing authorisation procedure as such could, in fact, be limited to those parts of the dossier that have not been assessed in advance. This would save relevant resources at the Agency and the CAT and may shorten the assessment phase in general. The idea could be summarized as a **“rolling NDA-like approach”,** meaning that the whole dossier is assessed part by part as it is currently possible at the FDA.

Comments

Such an approach would be of real benefit for SMEs, giving them the possibility to do the **whole assessment procedure step-by-step**. In the case of missing data, these could be incorporated at a later stage. Such a stepwise approach would prevent SMEs from filing a premature dossier that may not be regarded as approvable.

The **stepwise approach would define milestones** during the entire process. This would be of particular importance to SMEs who are unfamiliar with the centralised procedure and would often come into contact with a very high level of regulation for the first time. The milestones could be the points where, for example, the data package concerning the quality or the non-clinical part of the product is ready. Having the certificate for these parts would show SMEs that they are on the right track. Also, the Agency would be in the position to ask for additional data or to identify outstanding issues that have to be addressed, in order to be well prepared for the marketing authorisation procedure as such.

Therefore, the certificate can certainly not be seen as a replacement for the marketing authorisation procedure. This is clearly stated by the legislator in Whereas 25 of the ATMP Regulation. But from BPI's viewpoint, this requirement would not prevent the implementation of the system of certification as outlined in Article 18 of the Regulation on Advanced Therapies: as a kind of "pre-assessment" of the already existing data in order to **simplify the marketing authorisation procedure** as such at a later stage by referencing the valid certificates granted for the product in advance.

Apart from that, the certification procedure should be opened to other small companies not meeting the European recommendation of defining an SME. This could be done by introducing a reasonable fee for the small non-SME; that is in relation to the fee that is applicable for SMEs.

Furthermore, it would be important to open the certification procedure for academia.

<u>Incentives for the development of advanced therapy medicinal products</u>

The ATMP Regulation provides for various financial incentives which, however, were largely linked with the already expired transitional periods according to Article 29 of the Regulation and thus have meanwhile come to an end. To be mentioned by name are the possibilities under Articles 19 und 29(3) of the Regulation.

Due to the earlier addressed, very short transitional periods in Article 29 of the Regulation and with only two ATMP having a centralised authorisation by the end of the transitional period (neither being medicines which were already legally on the market at the time of entry into force of the Regulation), the funds earmarked for granting such incentives were not put to any use at all. In the impact assessment, the EU Commission relied on a cautious

Comments

estimate and assumed between 7 and 11 authorisation applications which were to benefit e.g. from the incentives according to Article 29 (3).

Therefore, it would be right and useful to prolong the incentives provided by law. Linking the incentives under Article 19 of the ATMP Regulation with a “particular public health interest” is very difficult to put into practice. This should be deleted or, at least, be based on a broad definition of this term.

Existing or newly created incentives should benefit not only SMEs but also facilities of academia.

Moreover, regulatory and administrative support is urgently needed too. Most applicants have no or little experience with regulatory aspects, and the centralised marketing authorisation procedure makes high requirements to the compilation of documents and the timely cooperation of the applicants. Therefore, it would be important to get more support from the Agency. Here, some starting points are EMA’s SME office and the Innovation Task Force, but this is not sufficient and should be intensified.

Berlin, 15.03.2013 MW