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PUBLIC CONSULTATION PAPER ON THE REGULATION ON ADVANCED THERAPY MEDICINAL PRODUCTS

Comments of the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)

The European Confederation of Pharmaceutical Entrepreneurs (EUCOPE) represents via national member associations, including BPI (Germany), EMIG (UK), SwedenBio (Sweden) and the US Biotechnology Industry Organization (BIO) more than 900 mid-sized innovative - often family owned - pharmaceutical and biotech companies. In addition, many innovative companies from Austria, Bulgaria, France, Germany, Greece, Italy, the Netherlands, Sweden, and the UK are represented on the board of the association. EUCOPE membership includes innovative family owned companies such as B.Braun, Sigma-Tau, Ferring, Miltenyi or Vianex as well as innovative companies active in the field of biotechnology and rare diseases such as Alexion, Celgene, Biogen Idec, InterMune, Otsuka or Grifols (www.eucope.org).

EUCOPE highly appreciates the opportunity to review and comment on the above mentioned consultation. Please find some General Findings (I) and comments on the specific Consultation Items (II) below.

(I) General Findings:

Art. 25 of Regulation (EC) 1394/2007 (ATMP Regulation) foresees that the Commission shall publish a general report on the application of the Regulation, which shall include comprehensive information on the different types of advanced therapy medicinal products authorized pursuant to the Regulation. In this report, the Commission shall assess the impact of technical progress on the application of this Regulation. It shall also review the scope of this Regulation, including in particular the regulatory framework for combined advanced therapy medicinal products. EUCOPE remains at the disposal of the Commission for a continuous dialogue on further developments.

Art. 29 of the ATMP Regulation foresees transitional periods with 31.12.2011 / 31.12.2012 as deadlines for compliance with the rules of the Regulation for products on the market on 30.12.2008. Practice has shown that these deadlines have proven not to be feasible. So far only few marketing authorization applications for ATMP have been submitted to the European Medicines Agency (EMA). The reason is that the companies could not design, perform and finalize the clinical trials required for the centralized marketing authorization within such a short period of time, especially when taking into account the requirements of Regulation (EC) 1901/2006 (Paediatric Regulation). Paediatric trials need to be integrated in clinical trial concepts for medicines with new substances, and these paediatric trials need to be agreed on beforehand with EMA's Paediatric Committee (PDCO). Currently, the approval process for a paediatric investigation plan (PIP) alone takes some 12 months. 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 medicinal product will not be authorized in the adult indication.

Additionally, it can be expected that scientific advice for ATMP already on the market leads to the requirement of at least one prospective confirmatory clinical trial which further delays the point in time where all data necessary for a centralized authorization is complete.

A publication of Maciulaitis et al. in 2012 found that **academia, public organizations and SME reflect the major part of the actual developers in the ATMP field**[1]. Five years after entry into force of the Regulation it can be observed that most companies and university facilities were not in a position to apply for centralized marketing authorization. This applies especially to hospitals and smaller companies with limited resources both financially and regarding staff but which are the main manufacturers of ATMP. Since Art. 29 requires the completion of the centralized marketing authorization procedure by the end of the transitional period, companies were effectively in a position to having to complete all data for the centralized marketing authorization not after 5 years but after 3,5 years in order to file the application in time.

In this context, the procedure laid down in **Art. 28 (2) of Regulation (EC) 1394/2007 provides an important alternative for preserving market access for existing therapies**. Contrary to the immediate market exclusion which is the consequence of the strict deadlines of Art. 29, Art. 28 provides a transitional basis depending on the progress of implementation in the respective Member State.

ATMP development is strongly promoted with public research funds at both EU and Member State levels. This should be reflected in a regulatory framework which takes into account the needs of smaller companies and hospitals which mainly manufacture ATMP.

Both the centralized marketing authorization and the rules in Art. 28 (2) of Regulation (EC) 1394/2007 foresee traceability, pharmacovigilance requirements and quality standards. 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 Art. 28 (2) of the ATMP Regulation, are given equal status in essential regulatory aspects to medicines requiring a centralized marketing authorization.

EUCOPE would like to underline that the procedure of Art. 28 (2) doesn't lead to a circumvention of the requirement of a central authorization. In the medium-term, companies need a larger market so that they can grow. Consequently, obtaining a centralized marketing authorization will be the objective, as it enables placing on the market throughout the entire EU. However, building up the necessary requirements takes time.

For the time being, the situation outlined above requires the use of the Art. 28 (2) procedure given the limitations of smaller entities. Regarding hospitals it is questionable if they would go the way to get a centralized marketing authorization in the future as they are working on a regional level.

[1] Romaldas Maciulaitis et al., Clinical Development of Advanced Therapy Medicinal Products in Europe: Evidence That Regulators Must Be Proactive, http://www.nature.com/mt/journal/v20/n3/full/mt201213a.html.

(II) Comments on specific Consultation Items:

Marketing authorization application requirements for advanced therapy medicinal products

- In general, the ATMP Regulation has been an improvement in terms of providing a better definition and a regulatory framework for ATMP in Europe. Uniform standards and rules are positive both for patient safety and for the planning reliability of pharmaceutical companies.

- Regarding some aspect, however, 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 hampers them.

- When assessing the marketing authorization requirement for ATMP it has to be taken into account that in some regards such products have characteristics comparable to medical devices. A main reason for allocating ATMP to the pharmaceuticals legislation were safety considerations. It is uncontested that tissue engineered products and also somatic cell therapeutic products 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 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. A future ATMP legislation should strongly integrate the flexibility of the medical devices law in the regulatory framework for ATMP development. From our point of view, the rigidity of the medicines legislation currently perturbs innovation in the ATMP field because technical improvements – which are achieved in fast succession for tissue engineered products and somatic cell therapeutic products – are counteracted by the rigid system of variations and line extensions.

- 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).

- For autologous tissue engineered products the allocation in the medicines legislation gives rise to many questions. 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 pharmaceuticals focusing on pharmacological, immunological or metabolic effects as the principal mode of action. Resorting to analogies for these properties (e.g. by equaling pharmacology with functionality and pharmacodynamics with biodistribution) seems inadequate.

- Treating tissue engineered products as pharmaceuticals 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 less profitable in their manufacture.

- As stated above, ATMP are mostly manufactured by SMEs, university facilities or hospitals. Given their limited resources and the requirements of the ATMP Regulation it is imperative to think about suitable support measures for manufacturers and university facilities. The SME Office of EMA is helpful, but it is not foreseen that the SME Office gives 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 specialized 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 personalized. These therapies are mostly distributed nationally. Against this backdrop, a centralized marketing authorization – 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 managing a central authorization procedure at EMA. Beside organizational aspects, also limited regulatory expertise and language barriers are important factors. As mentioned above most of the actual developers in the ATMP field are academia, public organizations and SME . It should be ensured that the EMA provides structures which are adequate and flexible to meet the need of these smaller organizations and their capacities.

- 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

As set out above in the General Findings, Art. 28(2) of Regulation (EC) 1394/2007 has an important bridging function in the context of the short transitional period of Art. 29, which didn't leave sufficient time to conduct clinical trials, especially regarding the completion of a PIP in accordance with the Pediatric Regulation. Thus, without the hospital exemption products already on the market on 30.12.2008 would have to leave the market immediately.

The term "non-routine preparation" should be interpreted in a broad way. Member States, which have not yet implemented the hospital exemption, should orientate their interpretation to Member States where the implementation has taken place. E.g. the requirement for manufacturing under GMP conditions should be observed. Very often, 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 standardized. The freedom of medicine should be preserved for individual uses.

The hospital exemption is important in order to have a suitable tool in the development of ATMP: the possibility to try a new therapeutic approach or 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 centralized marketing authorization is required.

Therefore, the hospital exemption is a crucial tool to try new therapeutic approaches and to earn the funds for the centralized marketing authorization 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 wouldnot lead to more ATMP products. On the contrary, most of the ideas would never come to the market once this important 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 centralized procedure earlier with less money and less knowledge about the product. It is not realistic that these circumstances will help finalize the centralized procedure better or more successfully.

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 as well.

The national authorities should have a supportive function in the cooperation with the CAT so that the products can be further developed towards a centralized marketing authorization, where possible.

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 standardized manufacture where 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 authorization application at later stage. Therefore, it would be important to lay down possible implications of the certificate in relation to a marketing authorization 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 authorization 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. An assessment of the dossier in several parts is currently possible at the FDA.

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 centralized 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 authorization procedure as such.

As clearly stated in Recital 25 of the ATMP Regulation, the certificate cannot be seen as a replacement for the marketing authorization procedure. Nonetheless, this requirement would not prevent the implementation of the system of certification as outlined in Art. 18 of the ATMP Regulation as a “pre-assessment” of the already existing data in order to **simplify the marketing authorization 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.

Incentives for the development of advanced therapy medicinal products

The ATMP Regulation provides for various financial incentives, e.g. in Art. 19 or 29 (3). However, these were largely linked with the already expired transitional periods according to Art. 29 of the Regulation and thus have meanwhile come to an end.

Due to the earlier addressed very short transitional periods in Art. 29 of the Regulation and with only two ATMP having obtained a centralized authorization 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 estimate and assumed between 7 and 11 authorization applications which were to benefit e.g. from the incentives according to Art. 29 (3).

Therefore, it would be useful to prolong the incentives provided in the Regulation. Linking the incentives under Art. 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 centralized marketing authorization procedure sets high requirements for the compilation of documents and the timely cooperation of the applicants. Therefore, it would be important to get more support from the Agency. The work of the EMA’s SME office and the Innovation Task Force should be intensified in this regard.

In case of any comments or questions please don’t hesitate to contact us (+32.475.902448).

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