Federal Ministry
of Health

Federal Ministry of Health, 11055 Berlin

Mrs. Ioana Siska, MD, PhD
European Commission
DG HEALTH & CONSUMERS (SANCO)
Unit D4/ Substances of Human Origin Team
Office address: Rue Froissart 101, 08/82
B-1049 Brussels/Belgium

DIVISION 115
OFFICER Dagmar Friese

ADDRESS Friedrichstraße 108, 10117 Berlin
POSTAL ADDRESS 11055 Berlin

PHONE +49 (0)30 18 441-4590
FAX +49 (0)30 18 441-4848
E-MAIL Dagmar.Friese@bmg.bund.de
INTERNET www.bundesgesundheitsministerium.de

Berlin, 30 April 2013

AZ

Exclusively via email at:
SANCO-ADVANCEDTHERAPY-REPORT@ec.europa.eu
Cc at:
Ioana-Raluca.Siska@ec.europa.eu

Public Consultation on Regulation (EC) 1394/2007

Dear Mrs. Siska,

Thank you very much for your email dating from March 7th, 2013. Regarding the therein mentioned public consultation, please find attached the comments from the Federal Ministry of Health and the national competent authority Paul-Ehrlich-Institute for your information.

With kind regards

Dagmar Friese

PUBLIC CONSULTATION PAPER ON THE REGULATION ON ADVANCED THERAPY MEDICINAL PRODUCTS

Member State: Germany

The document is based on the reporting of the Paul-Ehrlich-Institut. The Federal Ministry of Health supports the report complemented by propriatery positions.

Marketing authorisation application requirements for advanced therapy medicinal products (ATMP)

The so-called ATMP Regulation (Regulation [EC] No. 1394/2007) foresees the centralised procedure as the regular marketing authorization (MA) procedure for ATMP, intended to make ATMP immediately available in all EU member states, and to ensure assessment and evaluation of these innovative medicinal products at the highest community level. However, in the European perspective ATMP are developed mainly by SME (small and medium-sized enterprises), academia or hospitals and often will not have a huge commercial impact. Thus, it is anticipated that many of these developers have no interest and will not be capable or in the position to pursue a central MA. Experience from previous marketing authorisation applications (MAA) reveal a huge regulatory workload for applicants since the procedure may last for up to two years and may include several rounds of responding to extensive lists of questions posed to applicants. Several stakeholders argue that it should be explored whether for certain ATMPs - beyond the provisions made in the so-called Hospital Exemption (HE) - a national or decentralised MA followed by a stepwise expansion to other EU member states would be more appropriate.

Based on Art. 24 of the ATMP Regulation, specific requirements for ATMP have been established in Directive 2009/120/EC. Paul-Ehrlich-Institut contributed significantly to drafting these requirements and thus endorses these provisions. However, Paul-Ehrlich-Institut also recognises that fully complying with these requirements is very time-consuming, leading to quite a long developmental phase from the initial scientific idea and the proof of concept for a medicinal product up to a full data set suitable for submission of a MAA. This holds especially true when the ATMP is targeting a disease or condition with low prevalence, regardless if it is being designated as an orphan medicinal product or not. The evaluation of MAA for ATMP up to now has often revealed various deficiencies leading to a negative opinion or withdrawal of the application.
Furthermore, it should be reconsidered whether the actual tools at hand to address deficiencies post-approval are adequate or may be further optimised and extended.

Paul-Ehrlich-Institut considers the CAT to have an important role in the execution of the ATMP Regulation providing dedicated expertise for the evaluation of ATMP. While the ATMP Regulation sets some provisions for the composition of CAT, the area of specific expertise needed appears not

to be sufficiently defined and documented. Noting that the number of CAT members with clinical background is quite limited and on the other hand quality aspects of the application are mainly discussed at the Biologics Working Party (BWP) it may be considered to strengthen CAT by further elaborating on the desired expertises. Clinical expertise should be better tailored towards main clinical indications the CAT is dealing or will be dealing with, and should include some expertise in surgery. Moreover, Paul-Ehrlich-Institut perceives that CAT's role might be weakened by highly fluctuating attendance of members, which is likely to reduce continuity and informed decisions..

Regarding the products legally on the market before the ATMP Regulation came into force, one has to note that only one product achieved a MA by the end of the transitional period. This clearly is not in line with previous expectations and requires further analysis. Since only few MAA were submitted and in many cases were withdrawn during the procedure after deficiencies had been identified in the List of Questions, it is concluded that the available data set has not been adequate for submission and approval. On one hand, ATMP Regulation does not contain specific provisions regarding to which extent, despite its lower level of evidence, clinical experience achieved outside of prospective clinical trials but from marketing of the product may be acceptable and sufficient to support the benefit/risk evaluation in the context of a MAA. On the other hand, given the complexity of most ATMP, the difficulties to design, implement and conduct clinical trials and the duration of such a clinical development, the transitional period probably was too short to allow the generation of adequate confirmatory data on safety and efficacy for these products. Taken together with the limited options to address deficiencies post-approval, the scope of the transitional period most likely has contributed to the current situation in which only few ATMP are on the market.

In a more general perspective it has to be emphasized that experience with the evaluation of MAA for ATMP is still based on a very limited number of products. Moreover, for most of these ATMP the regulatory framework changed during development or even marketing of the ATMP and thus represents a specific situation. An appraisal based on clinical trials approved and scientific and regulatory advice given to applicants indicates that many and very heterogeneous ATMPsare in the pipeline for development. It has yet to be awaited how the system will operate and requirements will be met when MAA are submitted for ATMP that are fully developed from the start within the perspective of the current Regulation.

New concepts for the evaluation of MAA like 'adaptive licensing' are currently under discussion for medicinal products in general. These considerations may be as relevant for ATMP as for other products so that no specific discussion in the context of the ATMP Regulation may be needed.

Requirements for combined advanced therapy medicinal products

There was no experience gained with MAA for combined ATMP. Thus, it appears too early to already reflect on the provisions and to identify options for improvement. Review of this issue should be postponed until the end of 2014.

Incentives for the development of ATMP

For evaluating the effectiveness of incentives provided by the ATMP regulation it is the feedback from applicants and not from authorities that is regarded as most crucial. From Paul-Ehrlich-Institut's perspective it has to be noted that the certification procedure was applied for only in a limited number of cases. Thus, only limited regulatory experience is available for this procedure. However, applicants often point out that universities and hospitals, being not suitable to be designated as SME due to their total size/structure, are out of the scope of incentives requiring SME status.

Scope and adaptation to technical progress

The scope of the ATMP Regulation is well defined to be applicable to gene therapy medicinal products, somatic cell therapy products, tissue engineered products and to combined ATMP. However, classification of medicinal products as ATMP or non-ATMP often is depending on the evaluation whether a product is (i) 'substantially manipulated' or is (ii) not intended to be used for the 'same essential function' (non-homologous use). The experience from classification procedures suggests that further and more detailed clarification of theses definitions would be very helpful. Especially 'non-homologous use' is often discussed highly controversially. Since regulatory scrutiny may be reasonably linked to the novelty and safety of a specific use/therapeutic administration, it may be considered to restrict 'homologous use' to situations where adequate experience with the intended therapeutic use is already available.

CAT's recommendation on classification is made on the basis of documents and the rationale as provided by the applicant and thus there may be a tendency towards a biased description aiming at obtaining a desired classification as non-ATMP or ATMP. An independent evaluation of the mode of action by the EMA or consideration of other possibly conflicting scientific data is not envisaged in the procedure. This clearly impacts on the reliability of the outcome of the classification procedure, i.e. raising the possibility that one may come to a different conclusion when evaluating other/more data in the context of a MAA or a specific clinical trial application. Though this uncertainty is adequately reflected in the non-binding character of the classification recommendation, an erroneous recommendation on the classification may misguide the development of a specific product and delay achieving a MA.

Regarding progress in the field of ATMP there is one development noted which may not be easily addressed within the current framework, i.e. the development of highly personalised medicinal

products. For example, approaches are discussed and under development where a cell- or gene-based product is to be manufactured according to specific genetic changes/mutations observed in the patient's tumor. As a consequence, each lot manufactured may differ with respect to the active substance included. Regarding each lot as a distinct medicinal product seems inappropriate, as well as simply considering lots with distinct active substances as one medicinal product. For example, it appears unclear how safety and efficacy of such products should be addressed and evaluated. Consideration of adequate regulatory approaches is regarded as urgently needed.

Hospital Exemption (HE)

The so-called HE reflects the situation that from the EU perspective ATMP are developed mainly by SME, academia or hospitals, often on a patient-directed non-routine basis and thereby often will not have a huge commercial impact. Accordingly, only a few major biotech or pharmaceutical companies are currently engaged in this area. It is anticipated that many of the developers have no interest and will not be capable or in the position to pursue a central MA.

Thus, in our view the inclusion of the HE clause into the ATMP Regulation is regarded as an extremely useful and appropriate provision to bring such innovative ATMP, which inter alia are produced for an individual patient on a non-routine basis, to the patient and thereby provide additional options for treatment.

The HE may also include ATMP in the initial phase of the life cycle of a product.

For such products, it is an appropriate tool to further support the future development of the ATMP and to guide products within the EU framework from a non-routine use into a routine use and by that from the HE towards a central MA, or a potential national and intermediate solution as discussed above.

An important issue in this respect is the temporary nature of the HE with legal provisions to limit, withdraw or revoke authorisations. The HE procedure should ensure compliance with Community rules for safety and efficacy, put in place appropriate standards for quality control of the manufacturing process, including GMP, a review of all available data and include a benefit risk evaluation. It has to be avoided that HE is a way to escape regulatory control, to create two different quality standards or bypass generating valid clinical data.

As authorisation of an ATMP through the HE is under the exclusive responsibility of the national authorities, interpretation and implementation of the HE procedure is not harmonised between the member states. The CAT is not formally involved in the HE authorisation processes. As some CAT members are involved in the approval of HE at national level, CAT saw the need to organise informal CAT meetings to discuss the interpretation and implementation of the HE procedure.

Manufacturing:

Though GMP for HE products seems to be common ground in the Community, intensified cooperation and harmonisation of requirements is desirable, e.g. with respect to inspections. The revised Annex II could be the starting point for harmonisation.

Interpretation of Article 3 Nr. 7 of Directive 2001/83/EC:

As mentioned above, interpretation of the legal provisions is not harmonised. Different interpretations may lead to effects which are not in line with the intention of the HE provisions. One member state for example allows that the so called "special exemption" (bona fide unsolicited order) of Article 5 (1) of Directive 2001/83/EC is applicable for medicinal products falling under the definition of ATMP. As the requirements for HE are quite similar to the requirements of the bona fide unsolicited order, this may be a contradiction to the explicit statement in Article 3 Nr. 7 of Directive 2001/83/EC that the Directive is not applicable for HE and that HE have to be in line with this Article of the Directive.

Difficulties seem to exist for applicants when interpreting the term "on a non-routine basis". The interpretation of this term among others establishes whether a product is a HE or has to be authorised via the centralised procedure. Germany has given an interpretation in its pharmaceutical legislation (German Medicinal Products Act). A common approach for the interpretation of " a non routine basis" is desirable.

Correlation between national HE and MA on the basis of Regulations (EC) 726/2004 and 1394/2007

Since the criteria are well defined – at least in principle (see above)- pursuant to which ATMP are exempted from the centralised procedure there is a clear legal basis which ATMP have to follow the centralised procedure and which ATMP are eligible for the hospital exemption scheme. Thus, there may be no competition between both procedures, i.e. hospital exemption may not and cannot serve as an escape from a central MA.

It was criticised by some stakeholders in the field of ATMP that the national HE provisions in Germany create a strong disadvantage for manufacturers marketing centrally authorised ATMP. Their interpretation of the provisions comes to the conclusion that an authorisation for a HE is not permitted if at the same time a similar or comparable centrally authorised ATMP is on the market, and that the HE provisions offer a loophole to circumvent the hurdle of a central procedure. We do not share this interpretation . Perhaps a clearer statement would be helpful that a parallel existence of a HE product and a centrally authorised ATMP, being similar or comparable in its composition and indication, is possible –as long as the legal requirements for marketing the HE product are fulfilled.

Langen / Berlin

April 26, 2013