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**REPORT FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT AND
THE COUNCIL**

**in accordance with Article 25 of Regulation (EC) No 1394/2007 of the European
Parliament and of the Council on advanced therapy medicinal products and amending
Directive 2001/83/EC and Regulation (EC) No 726/2004**

(Text with EEA relevance)

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1. INTRODUCTION

Scientific progress has brought about a new type of medicinal products based on gene therapy, somatic-cell therapy or tissue engineering. To provide for a common framework for the marketing of so-called advanced therapy medicinal products (hereinafter "ATMPs"), Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products (hereinafter "ATMP Regulation") was adopted in 2007¹

The ATMP Regulation was designed to ensure a high level of human health protection as well as the free movement of ATMPs in the EU. The cornerstone of the Regulation is that a marketing authorisation must be obtained prior to the marketing of ATMPs. In turn, the marketing authorisation can only be granted if, after a scientific assessment of the quality, efficacy and safety profile, it is demonstrated that the benefits outweigh the risks. The application for a marketing authorisation must be submitted to the European Medicines Agency (hereinafter "Agency") and the final decision is taken by the Commission. This procedure ensures that these products are assessed by a specialised body (the Committee for Advanced Therapies; hereinafter "CAT") and that the marketing authorisation is valid in all the EU Member States.

The ATMP Regulation empowered the Agency to make scientific recommendations as to whether a given product should be considered an ATMP (hereinafter "classifications"). Additionally, it provided for a new instrument, the so-called certification procedure, designed as an incentive for small and medium sized enterprises (hereinafter "SMEs") that were involved in the first stages of the development of ATMPs but lacked the resources to conduct clinical trials. Specifically, the certification that the quality and preclinical aspects of the development are in conformity with the relevant regulatory requirements was expected to help SMEs attract capital and to facilitate the transfer of research activities to entities with the capacity to market medicinal products.

The ATMP Regulation applies since 30 December 2008. However, a transitional period was foreseen for ATMPs that were already in the EU market when the Regulation was adopted. Specifically, gene therapy and somatic cell therapy were required to comply with the Regulation by 30 December 2011, while tissue-engineered products were required to comply with the new requirements by 30 December 2012.

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Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L324, 10.12.2007, p.121).

By means of this Report, prepared in compliance with Article 25 of the ATMP Regulation, the Commission takes stock of the situation of ATMPs in the EU and analyses the impact of the Regulation on advanced therapies. The report takes account of the outcome of the public consultation on the application of the ATMP Regulation conducted by the Commission services (hereafter "public consultation").²

2. RESEARCH AND DEVELOPMENT ACTIVITIES ON ADVANCED THERAPIES IN THE EU: THE CURRENT LANDSCAPE

There is significant research in advanced therapies in the EU. Specifically, up to 250 distinct ATMPs were reported in the EudraCT³ during the period 2004-2010.

The majority of research in advanced therapies is conducted by small companies and entities that operate on a non-for-profit basis. Thus, almost 70% of sponsors for clinical trials on ATMPs reported in EudraCT are non-for-profit organisations or SME's; big pharmaceutical companies accounting for less than 2% of all sponsorships. Likewise, the majority of applications for scientific advice to the CAT are also submitted by SMEs (*see* Section 3.5).

The translation of research activities into medicinal products available to patients is generally challenging. Only a small fraction of the molecules investigated as potential medicinal products eventually obtain a marketing authorisation. The majority of the molecules investigated do not even make it to the stage of testing in humans for a variety of reasons (*e.g.* that the assumed activity of the molecule or the mechanism of action is not confirmed, or that pre-clinical studies demonstrate that the safety profile is not acceptable). In addition, it is estimated that, on average, less than a quarter of the molecules that are tested in clinical trials obtain a marketing authorisation. Typically, the path from identification of an active substance to the authorisation of the medicinal product can take more than ten years.

Due to the specific characteristics of advanced therapies, developers of ATMPs are confronted with additional difficulties. For example, the variability of the source materials makes it difficult to demonstrate the homogeneity of the product. Likewise, the small batch sizes which are typically available and short shelf-lives thereof (ranging from few hours to few days) can render extensive testing impossible. Moreover, the realisation of randomized controlled clinical trials may not always be feasible, for instance, if the administration of the product requires a surgical procedure (*i.e.* the majority of tissue engineering products), or where no alternative treatments are available.

In addition, the development of ATMPs is further hindered by the fact that researchers usually lack appropriate funding and regulatory expertise to successfully navigate through the marketing authorisation procedures. In turn, the uncertainties in the return for investment are a major deterrent to investors.

3. OVERVIEW OF THE APPLICATION OF THE ATMP REGULATION FROM 1 JANUARY 2009 TO 30 JUNE 2013

The regulation of ATMPs has been an important step to protect patients from scientifically unsound treatments. In addition, the ATMP Regulation has created a common framework for the assessment of advanced therapies in the EU.

² http://ec.europa.eu/health/files/advtherapies/2013_05_pc_atmp/2013_04_03_pc_summary.pdf

³ Database of all clinical trials that have started in the EU after 1 May 2004.

We are still at the early days of the development of advanced therapies and only four ATMPs have been granted a marketing authorisation. However, the much higher activity of the CAT in the area of scientific advice and classification, as well as the high number of clinical trials involving ATMPs, is a signal of a dynamic research sector.

3.1. A specialised body and adapted regulatory framework

The establishment of the CAT, as provided for in Article 20 of the Regulation, has been a chief milestone in the implementation of the ATMP Regulation. This committee gathers some of the best available experts in the EU to assess the quality, safety and efficacy of ATMPs. It held its first meeting in January 2009. In addition, a collaboration group between the CAT and the notified bodies for medical devices was set up in November 2010 as an advisory group to the CAT on combined ATMPs.⁴

The ATMP Regulation empowered the Commission to adopt specific requirements regarding the content of marketing authorisation applications, good manufacturing practices, good clinical practice, and the traceability of ATMPs. An amendment to the Part IV of the Annex to Directive 2001/83/EC adopted on 14 September 2009 adapted some of the requirements in terms of the content of marketing authorisation applications for ATMPs.⁵ In addition, a revised Guideline on good manufacturing practice containing specific adaptions for ATMPs applies since 31 January 2013.⁶ However, the adoption of specific requirements regarding good clinical practice and traceability is still pending as additional experience was deemed necessary to better understand the type of adaptations required.⁷

Specific provisions governing the certification procedure were adopted by means of Commission Regulation (EC) No 668/2009 of 24 July 2009.⁸

3.2. Marketing authorisations

Ten marketing authorisation applications for ATMPs had been submitted to the Agency by 30 June 2013. Five of them concerned products that were previously on the EU market.

Out of the ten marketing authorisation applications, four have successfully completed the procedure and have been granted a marketing authorisation by the Commission:

- *ChondroCelect*, a tissue engineered product indicated for repairing single symptomatic cartilage defects of the femoral condyle of the knee in adults;⁹

⁴ http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/12/WC500099532.pdf

⁵ Commission Directive 2009/120/EC amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products (OJ L 242, 15.9.2009, p.3).

⁶ http://ec.europa.eu/health/files/eudralex/vol-4/vol4-an2_2012-06_en.pdf

⁷ Some recommendations regarding good clinical practice for ATMPs have been however published by the Commission services (http://ec.europa.eu/health/files/eudralex/vol-10/2009_11_03_guideline.pdf)

⁸ Commission Regulation (EC) No 668/2009 implementing Regulation (EC) No 1394/2007 of the European Parliament and of the Council with regard to the evaluation and certification of quality and non-clinical data relating to advanced therapy medicinal products developed by micro, small and medium-sized enterprises (OJ L 194, 25.07.2009, p.7).

⁹ Marketing authorisation granted by Commission Decision C (2009) 7726 of 5 October 2009.

- **Glybera**, a gene therapy medicinal product indicated for adult patients diagnosed with familial lipoprotein lipase deficiency (LPLD) and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions;¹⁰
- **MACI**, a combined ATMP indicated for the repair 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.¹¹
- **Provenge**, a somatic cell therapy medicinal product 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.¹²

In contrast, four marketing authorisation applications have failed. One of these applications corresponded to a product that was on the market prior to the entry into force of the ATMP Regulation.

Two marketing authorisation applications were under assessment by the CAT on 30 June 2013.

3.3. Classifications

The CAT had received 87 requests and it had issued 81 classification recommendations by 30 June 2013.¹³ Almost half of all classification requests received originated from SMEs and an additional 15% of the requests came from the non-for-profit sector. Classification requests from large pharmaceutical companies represented approximately 5% of all submissions.

3.4. Certifications

Only three certification requests had been submitted to the Agency by 30 June 2013. Two of the requests concerned exclusively quality data, while the third request related to quality and non-clinical data. The CAT granted the certification in all three cases.

3.5. Scientific advice

By 30 June 2013, the Agency had provided scientific advice regarding ATMPs on 93 occasions; the advice referring to 65 different products. Over 60% of the requests for scientific advice had been submitted by SMEs and an additional 6% was from academia. Requests from big pharmaceutical companies represented less than 10% of all requests.

Additionally, it is noted that seven out of the ten applicants for marketing authorisation had previously requested scientific advice.

4. ANALYSIS

The contribution of the ATMP Regulation to public health could be measured against two parameters: (1) the extent to which new ATMPs have become available in the EU; and (2) the extent to which authorised ATMPs are efficacious and safe.

¹⁰ Marketing authorisation granted by Commission Decision C (2012) 7708 of 25 October 2012.

¹¹ Marketing authorisation granted by Commission Decision C (2013) 4190 of 27 June 2013.

¹² Marketing authorisation granted by Commission Decision C (2013) 5841 of 6 September 2013.

¹³ The classification procedure was on-going for the remaining six applications.

While there are no indications suggesting that the requirements of the ATMP Regulation are not sufficiently robust to ensure the good quality, efficacy and safety profile of authorised products, it needs to be considered if the high level of public health protection that the Regulation was designed to achieve is being undermined by the marketing of products exhibiting the characteristics of ATMPs marketed outside the framework of the ATMP Regulation (*e.g.* under the regulatory framework applicable to tissues and cells, medical devices, or others).

Additionally, it needs to be considered if there is room to facilitate that more ATMPs can become available to patients.

4.1. The impact of the ATMP on the availability of existing ATMPs

4.1.1 Advanced therapies available in the EU prior to the ATMP Regulation

It has been difficult to obtain precise figures about the number of advanced therapy medicinal products that were on the EU market prior to the entry into force of the ATMP Regulation. This may be partially explained by the intrinsic difficulties linked to the application of the definition of "ATMP" (*see* Section 4.3).

Member States have reported 31 ATMPs as being legally on the EU market prior to the entry into force of the ATMP Regulation.¹⁴ This figure must be taken with caution as, on the one hand, the same product may have been reported by more than one Member State and, on the other hand, not all Member States have been able to report. Even among the reporting Member States, it is not excluded that the reported figures are incomplete as some products may have been put on the market as tissues/cells or medical devices despite having the potential to fall under the definition of ATMP.

It is worth noting that a number of Member States have indicated that no ATMP was available in their territory prior to the entry into force of the ATMP Regulation, the non-availability of these products being more common in the smaller Member States.

4.1.2 Advanced therapies after the entry into force of the ATMP Regulation

The low number of marketing authorisation applications received by the Agency (*see* Section 3.2) shows that a significant number of developers of ATMPs that were on the market prior to the entry into force of the ATMP Regulation did not apply for a marketing authorisation.

According to data reported by the Member States, approximately 60 derogations from the obligation to obtain a marketing authorisation prior to the marketing of advanced therapies had been granted until April 2012.¹⁵ Derogations were granted under Article 3(7) of Directive 2001/83 (so-called "hospital exemption") as well as under other provisions of the Directive, notably Article 5.¹⁶

It follows that the effects of the entry into force of the ATMP Regulation on the availability of previously available treatments is difficult to establish in practice:

¹⁴ Pooled data from surveys conducted by EMA in 2007 and 2009.

¹⁵ http://ec.europa.eu/health/files/advtherapies/2013_05_pc_atmp/07_2_pc_atmp_2013.pdf

¹⁶ Article 5(1) of Directive 2001/83 provides that a Member State may exclude from the provisions of the Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility.

On the one hand, a significant number of existing ATMPs continue to be used in the absence of a marketing authorisation under derogations granted by Member States (the hospital exemption or otherwise).

On the other hand, the majority of the ATMPs that have been reported by the Member States as being marketed in their territories before the ATMP Regulation entered into force were chondrocyte-containing products (16 out of 31). As the marketing authorisation under the ATMP Regulation is valid in all Member States and given that two marketing authorisations have been granted for chondrocyte-containing products, the application of the ATMP Regulation may have actually led to wider coverage of the EU territory for these products.

4.2. Hospital exemption

The ATMP Regulation gives Member States the power to authorise the use of custom-made ATMPs prepared on non-routine basis in the absence of a marketing authorisation, provided that the product is used for individual patients in a hospital and under the professional responsibility of a medical practitioner.¹⁷ The so-called hospital exemption requires the application of national requirements on quality, traceability, and pharmacovigilance equivalent to those required for authorised medicinal products.

The hospital exemption enables patients to receive an ATMP under controlled conditions in cases where no authorised medicinal product is available. Additionally, it facilitates research and development in advanced therapies by non-profit organisations (such as academia and hospitals) and it can be a valuable tool to obtain information prior to seeking a marketing authorisation.

However, the experience accumulated since the entry into force of the Regulation shows that there is a risk that a too broad use of the hospital exemption may deter the submission of marketing authorisation applications. Specifically, ATMPs with a marketing authorisation face higher developmental and maintenance costs than ATMPs that are made available through the hospital exemption, as the marketing authorisation is linked to stricter data requirements and post-marketing obligations. Developers seeking a marketing authorisation are therefore put in a competitive disadvantage vis-à-vis those that market the products through the hospital exemption.

If the hospital exemption became the normal route to market advanced therapies, there would be detrimental consequences for public health. First, clinical trials remain the main means to obtain reliable information about the efficacy and safety profile of a medicinal product and the systematic administration of complex medicinal products to patients in the absence of appropriate clinical trials could put patients at risk. Secondly, the collection of data on efficacy and safety of the treatment would be seriously undermined as each site would only generate information on a small number of patients and there would be no transmission of information to the authorities of another Member State where the same type of product may be used under the hospital exemption also. Additionally, the treatment would not be available to all patients across the EU.

It is therefore necessary to find a balance between the need to ensure that ATMPs are made available to patients only after the quality, efficacy and safety thereof has been adequately demonstrated, and the need to facilitate early access for new treatments in case of unmet medical needs.

¹⁷

Article 28(2) of the ATMP Regulation which, in turn, amended Article 3 of Directive 2001/83.

The lack of harmonisation regarding the conditions required by Member States for the application of the exemption has also been identified as a concern in the public consultation. The usage that is made of this derogation is very different across Member States, partly because of different approaches as to the meaning of "non-routine". For example, while the concept of "non-routine" is narrowly construed in some Member States where a maximum number of patients is fixed, in others there is no limit and the derogation is applied case by case.

Clarification of the conditions under which the hospital exemption is possible and of the requirements attached could contribute to improving the functioning of the internal market in advanced therapies. In this context, appropriate consideration should be given to the reporting of results, particularly negative results, so that patients are not unnecessarily exposed to unsafe/ineffective treatments.

Other issues that could benefit from additional clarification include:

- the role of derogatory provisions of Directive 2001/83/EC other than the hospital exemption (in particular Article 5(1) thereof) in the context of ATMPs, and
- the role of data generated from the use of a product under the hospital exemption in the context of an application for a marketing authorisation.

4.3. Scope of the Regulation and classification of ATMPs

4.3.1. Scope of the ATMP Regulation

Three types of medicinal products are considered ATMPs: gene therapies, somatic cell therapies, and tissue engineered products. The assessment whether a product falls under any of these categories may involve complex scientific judgements. Specifically, the question whether a manipulation of a living material is to be considered as substantial may be difficult to answer. Even the question whether the cells or tissues are intended to fulfil the same function in the donor and in the recipient can be challenging in some cases (*e.g.* bone marrow material).

Experience in the application of the definitions of the various categories of ATMPs by the CAT shows that some aspects of the definition could be further clarified to ensure a better match of the legal definitions with the underlying scientific reality.

Additionally, advanced therapies being a field subject to rapid scientific progress, it is necessary to keep the definitions of gene therapies, somatic cell therapies, and tissue engineered products under continuous review. New innovative products, which are not clearly captured by existing provisions, are emerging. For instance, the development of devices which allow the collection of cells or tissues, the processing thereof in a closed environment and its reinjection into the donor within the same procedure raises questions as to how these treatments should be regulated (particularly in case of non-homologous use).

4.3.2. Classification

An increasing number of innovative biological products exhibits characteristics that could potentially fall under various regulatory regimes (*e.g.* medicines, medical devices, cosmetics, or tissues and cells). Clarity on the regime that is applicable to new products is essential to achieve an adequate level of public health protection. Moreover, developers also need a clear understanding of the regulatory framework that will apply to their products so that the development process can be adapted to the relevant requirements.

However, cases have been reported where the competent authorities of the Member States had reached divergent conclusions as to whether a product should be considered as ATMP or not. The disparities that exist across the EU regarding the classification of ATMPs have also been identified as a concern in the public consultation undertaken by the Commission services in preparation of this report.

The possibility that the same product may be subject to different requirements across the EU implies that the level of public health protection is different according to the place of residence of the patient. That the same product can be marketed under different regulatory regimes is not only undesirable from a public health standpoint but it also undermines the incentives to develop ATMPs. First, the uncertainty as to the market potential for a product discourages investments. Secondly, divergent classification of the same product distorts competition between developers. Finally, the application of different regulatory requirements across the EU hinders the free movement of these products.

The ATMP Regulation gave the Agency the task of providing scientific recommendations on advanced therapy classifications. The advice is provided free of charge and it is non-binding.

The classification mechanism provided for in the ATMP Regulation has shown two strengths. First, a centralised assessment ensures a single view point throughout the EU and provides certainty. Secondly, that the service is provided at no cost has prompted small companies to use this mechanism (see Section 3.3). In the Commission's view, this is a positive outcome as it can help ensure that the development process of these products is designed at an early phase in a way that maximises the chances of obtaining a marketing authorisation.

However, the current classification mechanism also exhibits some weaknesses. First, the conclusion of the CAT that a product is an ATMP may be disregarded by a developer that decides to market the product without generating efficacy and safety data, and/or without complying with the quality and pharmacovigilance requirements that are typical of medicinal products. Another limitation of the current system is that the competent authorities of the Member States do not have the possibility to seek the view of the CAT when they are confronted with the question whether a product should be considered as ATMP.

4.4. Requirements for the marketing authorisation of ATMPs

4.4.1. General considerations

The ATMP Regulation builds on the procedures, concepts, and requirements designed for chemical-based medicinal products. However, ATMPs present very different characteristics. Additionally, in contrast to chemical-based medicinal products, research in advanced therapies is -for the most part- conducted by academia, non-for-profit organisations, and SMEs, which only have limited financial resources and often lack exposure to the regulatory system that governs medicines.

Commission Directive 2009/120/EC provides for adapted requirements in terms of the information that applicants must provide when applying for a marketing authorisation of an ATMP. The possibility to apply a risk-based approach to determine the extent of quality, non-clinical and clinical data is also envisaged.

However, the public consultation shows that it is widely felt that additional flexibility should be applied, particularly in the area of quality, with a view to ensure that the marketing authorisation application requirements take due consideration of scientific

progress and specific characteristics of ATMPs. This view has been shared by respondents representing industry, patients, hospitals, academia and non-for-profit organisations.

In addition to possible specific adaptations of quality or efficacy/safety data requirements, it has been suggested that, to allow advanced therapies to kick off, alternative approaches to reduce regulatory costs should also be explored. Thus, several respondents in the public consultation suggested the introduction of a marketing authorisation granted on the basis of limited data to be used in a restricted setting, particularly in cases of unmet medical needs. The data collected on the uses in the restrictive settings could be subsequently used to expand the marketing authorisation up to the point of becoming a standard authorisation.

4.4.2. *The case of autologous ATMPs*

In the case of autologous products the cells/tissues are harvested from a patient, then treated or expanded, and finally they are introduced back into the same patient. The starting material (*i.e.* the cells/tissues) is different for each patient and, as a consequence, the manufacturing process of these products has specific features as compared with other medicinal products.

Nevertheless, not all autologous products face the same manufacturing challenges. In this regard, it is appropriate to distinguish two different scenarios. On the one hand, there are autologous products where the patient's cells/tissues are transported to a pharmaceutical company and the final medicinal product is delivered back to the hospital for implantation/injection in the same patient. ChondroCelect, MACI and Provenge, which received a centralised marketing authorisation, are examples of such autologous ATMPs. On the other hand, there are cases where the patient's cells/tissues are manipulated in the hospital (*e.g.* by means of medical devices that are developed for cell separation and manipulation) prior to re-administration to the same patient.

In the public consultation some respondents considered that autologous ATMPs should not be regulated as medicines. While this approach would reduce the developmental costs associated with the use of these products, in the Commission's view, the need to ensure an adequate level of public health protection should prevail over economic considerations.

The regulation of these products as medicines ensures that the risk-benefit thereof has been found positive by an independent and highly-specialised body, that patients are followed-up after treatment, and that the lasting effects of the treatment can be known to health care professionals (in terms not only of safety but also of efficacy).

However, it is important that the requirements that apply to autologous products are proportionate and adapted to the specific characteristics thereof. Requiring autologous products that are manufactured at the hospital prior to the administration to the patient to comply with the quality controls and manufacturing requirements of standardised chemical-based medicinal products would prevent the development of these treatments in practice as a batch release certification would be required per treatment and a manufacturing license would be required per hospital.

4.4.3. *The case of combined ATMPs*

A combined ATMP is an ATMP that contains viable cells or tissues and that incorporates one or more medical device(s) as an integral part of the product. ATMPs incorporating a device but containing non-viable cells or tissues are also

combined ATMPs if the action of the cells/tissues on the human body is primary to that of the device.

Under the current rules, the final scientific assessment of the combined ATMP is undertaken by the CAT. However, for the device part, the Agency is to rely on the assessment of the notified bodies (if available). If no assessment is available from the notified bodies, the Agency is in principle required to consult one, unless the CAT considers it is not necessary.

The public consultation showed that the separate assessment of the medical device and the medicinal product is widely perceived as an excessive burden when the device is not marketed separately. Thus, there was strong support to the principle of a single assessment (by the CAT) for ATMPs where the device is an integral part of the product (*i.e.* all combined ATMPs). Additionally, the public consultation showed that stakeholders have difficulties to understand the interaction between the Agency and the notified bodies in practice.

The risk has also been identified that the current framework gives incentives to developers to use medical devices already licensed (even if for a use different to the intended use in the combined ATMP) rather than developing new, better targeted devices. This course of action may be prompted by the perception that choosing a device with the CE-mark will facilitate the regulatory procedure.

4.5. Marketing authorisation procedure

The ATMP Regulation requires that marketing authorisation applications for advanced therapies are submitted to the Agency. The scientific evaluation thereof involves up to five committees. Specifically:

- (i) the CAT assesses the marketing authorisation application and gives its opinion to the Committee for Medicinal Products for Human Use ("CHMP");
- (ii) the CHMP adopts an opinion which is transmitted to the Commission;
- (iii) the Pharmacovigilance Risk Assessment Committee ("PRAC") provides recommendations to the CHMP on pharmacovigilance matters;
- (iv) the Paediatric Committee ("PDCO") intervenes on aspects related with the obligations imposed under Regulation (EC) No 1901/2006 of the European Parliament and of the Council;¹⁸ and
- (v) the Committee on Orphan Medicinal Products ("COMP") provides scientific opinions to the Commission on aspects related to the application of the orphan incentives (this committee is only involved therefore if the applicant seeks orphan status).

The current marketing authorisation procedure has proven complex to manage in practice and it is also challenging for prospective applicants, which are typically entities with no exposure to the centralised procedure of marketing authorisations. In this regard, the public consultation showed that the procedure for evaluation of ATMPs at the Agency is perceived as too cumbersome, particularly for SMEs and non-for-profit organisations.

¹⁸

Regulation (EC) No 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L378, 27.12.2006, p.1).

In sum, the experience acquired since the entry into force of the ATMP Regulation shows that there is room for streamlining the procedure for the evaluation of ATMPs. Simplification of this procedure should not only bring benefits for prospective applicants but should also ensure that there is a robust assessment of these complex products and clear allocation of responsibility within the Agency for this task.

4.6. Certification

The certification of the quality and non-clinical data by the Agency was a novel instrument designed to help SME's attract investments/obtain revenue for the development of ATMPs. By analogy with the reductions applied in the case of scientific advice, the Agency applied a fee reduction of 90% to certification requests submitted by SMEs.¹⁹

However, the very low number of certifications applications received is a disappointing outcome. The low usage of the certification procedure may be partially explained by the exclusion of non-commercial entities from the certification scheme. Expanding the category of applicants that could apply for a certification could therefore help increase the value of this instrument.

Additionally, the outcome of the public consultation and the enquiry carried out by EMA²⁰ suggests that the value of the certification could increase if some changes were made, such as a clarification of the link between the certification and the marketing authorisation procedure, or the extension of the certification scheme to cover other parts of the dossier (*i.e.* clinical aspects).

4.7. Scientific advice

Early contacts between developers of ATMPs and the authorities are important to ensure that the development activities are designed in the best possible way to maximise the chances of obtaining a marketing authorisation. Understanding at an initial stage of development the requirements that are necessary to demonstrate the efficacy and safety of the product is particularly important for developers that are not familiar with marketing authorisation procedures.

As an incentive to prompt developers of ATMPs to discuss the development of their products with the Agency, the ATMP Regulation provided for significant fee reductions for requests for scientific advice. The discount went up to 90% in the case of SMEs.

The large number of requests for scientific advice that have been received by the Agency in the period under consideration in this report is a positive development that can contribute to the successful translation of research into medicinal products. Of particular relevance is that the majority of the requests for scientific advice emanated from SMEs (*see* Section 3.5). The heavy discount applied to SMEs has proven therefore effective.

In contrast, the exclusion of certain non-profit organisations from the fee incentives has been identified in the public consultation as a shortcoming. The low percentage of requests for scientific advice from academia (6%) suggests that a fee reduction analogous to that applied to SMEs could encourage researchers working in an academic (or other non-for-profit setting) to seek scientific advice from the Agency.

¹⁹

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/07/WC500146978.pdf

²⁰

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/02/WC500138476.pdf

4.8. Fee incentives regarding marketing authorisation application and post-marketing obligations

Fees linked to the application for marketing authorisation and post-marketing activities (during the first year after the granting of the authorisation) were reduced by 50% for SMEs and hospitals if there was a public health interest in the concerned ATMP. These fee reductions were however limited in time and no longer apply.

It is difficult to make general conclusions on the impact of these fee incentives as only two marketing authorisations had been granted during the term of validity thereof. However, in general terms, the costs linked to post-marketing activities can be very significant, particularly if a large number of post-marketing obligations is imposed. These costs can be unaffordable for small companies, particularly until such time as the medicinal product is capable of generating income (*i.e.* pending the agreement of the national bodies competent for reimbursement procedures).

5. CONCLUSIONS

Advanced therapies have the potential to bring major benefits to patients. However, there are still many unknowns and it is therefore important to put in place adequate controls to prevent detrimental consequences for public health.

The ATMP Regulation protects patients by requiring that an independent review of the ATMP is done by the best available experts in the EU according to high standards of quality, efficacy and safety before the product is made available to patients.

However, too burdensome requirements could have detrimental consequences for public health as it could prevent the appearance of valid treatments for unmet medical needs. Regulation in this area should contribute to creating conditions that facilitate the appearance of new medicinal products, while ensuring a high level of public health protection. It is likewise important that the regulatory framework is adapted to rapid scientific progress.

On the basis of the experience accumulated since the entry into force of the ATMP Regulation, some possibilities to help the translation of research into ATMPs available to patients across the EU while maintaining a high level of public health protection can be identified, including:

- clarification of the scope of the ATMP Regulation by fine-tuning the current definitions of ATMPs and by reflecting on the appropriate regulatory framework for new innovative products that may not be captured by existing provisions;
- considering measures to avoid disparities in the classification of ATMPs in the EU;
- clarification of the conditions for the application of the hospital exemption, as well as the role of data obtained therefrom in the context of marketing authorisation procedures;
- revising the requirements for the authorisation of ATMPs with a view to ensure that applicable requirements are proportionate and well-adapted to the specific characteristics thereof, having specific consideration to autologous products;
- streamlining the marketing authorisation procedures;

- extending the certification procedure and clarification of the link between the certification and the marketing authorisation procedure;
- creating a more favourable environment for ATMP developers working in an academic or non-for-profit setting, including by promoting early contacts with the authorities through the application of the fee reduction for scientific advice and by extending the certification scheme to these developers;
- considering possible fee incentives to reduce the financial impact of post-marketing obligations.