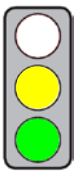
EXPERIENCE WITH THE ATMP REGULATION

cep**PolicyBrief** No. 2014-34

KEY ISSUES

Objective of the Report: The Commission describes the experience gained so far with the Regulation on advanced therapy medicinal products (ATMP Regulation) and considers changes to this Regulation.

Affected parties: Pharmaceutical companies engaged in research, non-profit-making establishments and hospitals.



Pro: Extending the certification procedure to cover universities and other non-commercial bodies is appropriate because they require better access to financing in order to convert their ATMPs into marketable products.

Contra: Revision of the hospital exemption, which allows ATMPs to be used without a marketing authorisation in domestic hospitals, is not necessary for the purpose of reducing negative incentives.

CONTENT

Title

Report COM(2014) 188 from the Commission to the European Parliament and the Council of 28 March 2014 **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.

Brief Summary

Article numbers refer to the Regulation (EC) No. 1394/2007.

Context

– Advanced therapy medicinal products ("ATMPs") are products based on gene therapy, somatic-cell therapy or tissue engineering.
– Since 30 December 2008, the Regulation on advanced therapy medicinal products (ATMP Regulation; Regulation (EC) No. 1394/2007) has regulated marketing authorisations, monitoring and pharmacovigilance with regard to these products. It contains special rules in this regard with respect to
  - the Directive on the creation of a Community code relating to medicinal products for human use (Directive 2001/83/EC) and
  - the Regulation laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (Regulation (EC) No. 726/2004).

  These two pieces of legislation also apply to ATMPs.
– The main elements of the ATMP Regulation are
  - the mandatory marketing authorisation procedure (Art. 8 and 9),
  - the optional certification procedure (Art. 18),
  - the classification procedure (Art. 17),
  - scientific advice (Art. 16) and
  - various fee reductions (Art. 19).
– The European Medicines Agency (EMA) is responsible for all procedures.
– Where no advanced therapy medicinal product (ATMPs) has been authorised for a concrete treatment, Member States may approve the use of a non-authorised ATMP ("hospital exemption", Art. 28 (2). It may be used if it
  - is prepared for an individual patient,
  - is used under medical supervision in a hospital in the said Member State and
  - complies with national pharmacovigilance and quality requirements.

Authorisation procedure

– The authorisation procedure is mandatory for the marketing of ATMPs. Authorisation is valid in all Member States.
– The EMA's Committee for Advanced Therapies (CAT) assesses the quality, safety and efficacy of the ATMPs and issues a draft opinion. The draft is sent to the Committee for Medicinal Products for Human Use which also adopts an opinion on the ATMP.
– The final decision on the application is made by the Commission.
– Transitional periods for any necessary retrospective authorisation have been established for ATMPs which are already on the market. The requirements of the ATMP Regulation had to be met
  - by 30 December 2011 in the case of gene therapy and somatic cell therapy and
  - by 30 December 2012 in the case of tissue engineered products.

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– Ten authorisation applications had been made by 30 June 2013, of which five related to ATMPs already on the market. Of the ten applications made by 30 June 2013
  - four were successful,
  - four, including one for an ATMP already on the market, were refused and
  - two were still under assessment.

Certification procedure

– The certification procedure enables the ATMP developer to receive confirmation that the quality and preclinical aspects of the development conform to the regulatory requirements.
– The certification procedure is only available to small and medium-sized enterprises (SMEs). It is intended to help them obtain the necessary funds to carry out clinical trials.
– By 30 June 2013, three applications for certification had been made. The EMA issued certificates to all three manufacturers.
– SMEs currently receive a 90% fee reduction.

Classification procedure

– The classification procedure allows the ATMP developers to have their product assessed by the EMA in order to determine whether it must be classified as an ATMP under the Regulation.
– The classification recommendation is binding EU-wide.
– By 30 June 2013, 87 classification requests had been received and 81 classification recommendations issued.
– Of the classification requests
  - almost 50% came from SMEs
  - 15% from non-profit organisations and
  - 5% from large pharmaceutical companies.
– The classification procedure is free of charge.

Scientific advice

– The ATMP developer can obtain scientific advice from the European Medicines Agency (EMA) as early as the development phase so that the authorisation procedure has the greatest possible chance of success.
– By 30 June 2013, the EMA had provided scientific advice on 93 occasions relating to 65 different products.
– The advice applied,
  - in 60% of cases, to ATMPs from SMEs
  - in 6% of cases, to ATMPs from academia and
  - in fewer than 10% of cases, to ATMPs from large pharmaceutical companies.
– Scientific advice had been previously requested in seven out of ten authorisation procedures.
– There is a 90% fee reduction for SMEs.

Additional proposals

– The Commission may adopt requirements relating to authorisation applications, good manufacturing practices, good clinical practice and the traceability of ATMPs (Art. 4, 5, 14 and 15).
– It has issued rules on authorisation requests (Directive 2009/120/EC) and guidelines for good manufacturing practice (SANCO/AM/sl/ddg1.d.6(2012)860362).
– The Commission believes that additional experience is necessary for specific requirements regarding good clinical practice and the traceability of ATMPs.

Experience gained from the application of the ATMP Regulation

– According to the Commission, it is not possible to ascertain whether the ATMP Regulation has given rise to a larger number of ATMPs in the EU because the Member States have insufficient data about the ATMPs which were already available before the Regulation came into force.
– The Commission is very sceptical of hospital exemptions. On the one hand, they allow patients fast access to ATMPs. On the other hand, they may result in a failure to apply for EU-wide authorisation for ATMPs so that they fall under the exemption. They then do not come onto the internal market and can only be used within the framework of the exemption, i.e. only for other domestic patients.
– The fact that there have only been authorisation applications for five ATMPs already on the market is, according to the Commission, due to the fact that the Member States have approved hospital exemptions for other ATMPs.
– The authorisation procedure is, according to the Commission, too complex and should be "streamlined". It makes no concrete proposals although it does want to look at the specific characteristics of autologous products.
  - In the case of autologous products, the patient's own cells are taken, treated or expanded and finally reintroduced.
  - Because the starting material is different for each patient, the manufacturing process has specific characteristics not applicable to other medicinal products.
– The Commission finds it "disappointing" that the certification procedure has hardly been used. It believes there are two reasons for this:
  - The fee reductions do not apply to non-profit organisations and
  - the value of certification is too low because the procedure only applies to the preclinical sector and is not linked to the authorisation procedure.

– The Commission gives the classification procedure a positive assessment but sees room for improvement.
  - The positive elements are that the procedure is carried out centrally for the whole EU and is free of charge.
  - The weakness is that the national authorities cannot use it when they are confronted with difficulties of classification.
– The Commission regards the scientific advice in a predominantly positive light. It could, however, be improved by including non-profit organisations in the fee reduction.

Commission's conclusions

– Burdensome requirements for the ATMP developers must be limited to what is necessary as they obstruct development. This must not, however, undermine patient safety.
– Regulation must be "adapted to rapid scientific progress".
– The Commission sets out the following concrete criteria:
  - "fine-tuning the current definitions of ATMPs" to cover all ATMPs and to prevent disparities in national classifications,
  - revision of the hospital exemption to avoid negative incentives,
  - adapting the authorisation requirements for special products, particularly autologous ATMPs,
  - extending the certification procedure to cover non-commercial organisations and ensuring "better linkage" with the authorisation procedure,
  - improvement of the conditions for non-profit organisations.

Policy Context

In 2013, the Commission held a public consultation on the experience obtained in relation to the ATMP Regulation whose results have been taken into account in the report.

Options for Influencing the Political Process

Directorates General:	DG Employment and Social Affairs (leading)
Committees of the European Parliament:	Employment (leading), Rapporteur Alejandro Cercas (S&D Group, E);
Federal Ministries:	Family (leading)
Committees of the German Bundestag:	Labour (leading); Economic Affairs; Family

ASSESSMENT

Economic Impact Assessment

Ordoliberal Assessment

This report on the current implementation of the ATMP Regulation indicates the weak points of the legislation - not least due to the dynamic nature of the sector - which is a precondition for remedying them. In particular, a more precise definition of ATMPs is necessary in order to keep pace with scientific development and provide the ATMP manufacturers with planning certainty. The classification procedure at EU level should also be more closely linked to definition procedures at national level - such as by way of reporting obligations for Member States where there are problems of classification. This would ensure that all ATMPs are treated equally EU-wide.

Impact on Efficiency and Individual Freedom of Choice

Revision of the hospital exemption, which allows ATMPs to be used without a marketing authorisation in domestic hospitals, is not necessary for the purpose of reducing negative incentives. Admittedly, it gives rise to an incentive to refrain from applying for an EU-wide ATMP authorisation - at least in the short term - since the authorisation is more time-consuming and costly than the hospital exemption. Nevertheless, the Commission is exaggerating the problem. It arises only where the manufacturer wants to provide its ATMP exclusively in domestic hospitals and only in individual cases because the hospital exemption only applies in the Member State where the manufacturer is established. As a rule, the manufacturer will be aiming to market its product EU-wide because ATMPs are generally only appropriate for a small number of patients. This requires EU-wide authorisation.

The - still valid - hospital exemptions for older ATMPs, for which no EU-wide authorisation has been applied in the transition phase, are unproblematic. They simply show that there may certainly be manufacturers for whom the restriction to domestic hospitals is sufficient and who therefore do not apply for the costly authorisation. To take the hospital exemption away from these manufacturers in the hope that they then apply for an authorisation for their ATMP, is risky. It is possible that, if the hospital exemption is removed, they will prefer to take their ATMPs off the market altogether rather than apply for the authorisation. These medicinal products would then no longer be available even to domestic patients. In addition, the national authorities already have the possibility of withdrawing the hospital exemption. This exists, inter alia, where the treatment ceases to be non-routine in nature as, in fact, a large number of patients are being treated. Nor would it be productive for the EMA to issue EU-wide hospital exemptions, applicable to hospitals in all Member States because this would take away any incentive for any of the ATMP developers to apply for authorisation as long as the non-routine nature of the product was recognised.

The certification procedure serves as a quality label and signals the promising nature of an ATMP to potential lenders and equity providers thereby making it easier for developers to obtain finance. **Extending the certification procedure to cover universities** and other non-commercial bodies **is appropriate because these organisations** are greatly involved in ATMP research and r**equire better access to finance in order to** fund the establishment of new companies and **convert their ATMPs into marketable products.** It would also be conceivable to have additional certification for when the development reaches the point where the success of the ATMP has been verified in initial clinical trials and the end of the authorisation procedure is foreseeable.
Although the advice procedure does not guarantee that the authorisation will be issued it does significantly improve the chances of success because sensitive points already become apparent during the development phase which will be relevant subsequently in the authorisation procedure. The fee reduction for SMEs should also apply to non-commercial institutions such as universities because they are generally short of funds.

Impact on Growth and Employment

Negligible.

Impact on Europe as a Business Location

Creating innovation-friendly legislation on ATMPs helps to strengthen Europe as a location for research.

Legal Assessment

Legislative Competency

The Commission is obliged to submit this report (Art. 25 ATMP Regulation). The proposals to which it gives rise for amending the ATMP Regulation will essentially be aimed at improving the internal market for which the Commission is competent (Art. 114 TFEU).

Subsidiarity

Insofar as it can be determined, the objective of possible amendments to the ATMP Regulation is to provide better availability of ATMPs in the whole of the EU. This objective can be better achieved by EU action, in particular by way of a uniform authorisation procedure, than by national measures.

Proportionality with Respect to Member States

Not yet assessable.

Compatibility with EU Law in other Respects

Not yet assessable.

Impact on German Law

Insofar as the hospital exemption is amended, changes to the German Medicines Act (AMG) will be necessary, in particular to Section 4 b AMG which contains special provisions for advanced therapy medicinal products.

Alternative Approach

In the interests of clarity, the provisions on ATMPs should be assimilated into a separate chapter of the Code relating to medicinal products for human use (Directive 2001/83/EC) and into the Rules of Procedure (Regulation (EC) No. 726/2004).

Conclusion

Revision of the hospital exemption, which allows ATMPs to be used without a marketing authorisation in domestic hospitals, is not necessary for the purpose of reducing negative incentives. Extending the certification procedure to cover universities and other non-commercial bodies is appropriate because they require better access to funding in order to convert their ATMPs into marketable products.