

Implementing the New EU Legislation on Advanced Therapy Medicinal Products

A workshop in London gave an important insight into the implementation of the European regulation on ATMPs. *Anne Dupraz-Poiseau* and *Valérie Pimpaneau* report.

The large number of people who attended the European Medicines Agency's first workshop on advanced therapy medicinal products reflects the interest of stakeholders for this rapidly evolving field. Around 160 individuals from regulatory authorities, industry and academia attended the much anticipated meeting, which took place in London on 3 April, a month after having been postponed due to severe weather conditions. Delegates from the EMEA and representatives from the EMEA's new Committee for Advanced Therapies presented the key implementation aspects surrounding the relevant legislation, Regulation (EC) No 1394/2007 on Advanced Therapy Medicinal Products, which has been in force since 30 December 2008.

Marisa Papaluca Amati, chair of the EMEA Innovation Task Force, explained that the number of EMEA procedures relating to the development of ATMPs has been increasing – including marketing authorisation applications, scientific advice, orphan drug designation and briefing meetings – with a permanent growth in demands relating to tissue-engineered products and stem cell-based products. Considering the novelty of these medicines – for example, a nanostructure might be used as a gene transporter or a gene might be used to activate a chemotherapy drug – and developing trends, the EMEA has invested a lot of effort in adapting its operational structure and procedures to ensure it is able to conduct adequate evaluations of ATMPs in this highly challenging innovation environment.

Committee for Advanced Therapies

The role and composition of the new Committee for Advanced Therapies were described, with special emphasis on the multidisciplinary capabilities of the selected team, which includes expertise in pharmaceuticals, medical devices, ethics, vigilance, risk management and surgery.

The expertise of the CAT members is described in Figure 1. One-third of the CAT is composed of members who are already familiar with the centralised pharmaceutical product evaluation procedure (co-opted from the EMEA's scientific advisory committee (the CHMP) or from EMEA working committees); one-third of members have experience as national competent authority assessors; and one-third is from academia or the clinic. Approximately one-third of the members' primary expertise is in quality-related issues, while the remaining members are highly experienced in nonclinical and clinical issues. Both the chair and co-chair – Christian Schneider (Paul Ehrlich Institute, Germany) and Paula Salmikangas (National Agency of Medicines, Finland) respectively – were elected from among the CAT members for a three-year term at the second meeting of the committee on 12 February 2009.

The appropriate level of medical device-related expertise among CAT members was debated as this is an essential element required for competently assessing combined ATMPs. The EMEA reiterated that it will seek notified body opinions whenever necessary if the internal device-related CAT expertise is not deemed sufficient.

Marie-Hélène Pinheiro (senior scientific administrator, regulatory affairs, EMEA) indicated that discussions with notified bodies are ongoing and that a clear framework for collaboration should be set up by the middle of the year. Detailed information on the role and composition of the CAT is posted on the EMEA website¹.

CAT activities are publicised in a publicly available monthly report which includes statistics on procedures involving the CAT as well as scientific and organisational topics covered during the meetings. The EMEA confirmed that the CAT has been involved in classification and scientific advice procedures since March 2009 and will be able to start the evaluation and certification of quality and nonclinical data of ATMPs in development by small and medium-sized enterprises from May 2009.

Scientific recommendations on classification

In certain cases there may be some uncertainty as to whether a given medicinal product is to be classified as an ATMP. Such cases can involve borderline situations such as:

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The CAT's role and composition were described, particularly the team's multidisciplinary capabilities

The CAT has been involved in classification and scientific advice procedures since March...

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- medicinal product versus medical device;
- ATMP versus transplant;
- process versus product; or
- viral vector versus viral vaccine.

...including determining into which category of ATMPs a product falls

If such questions arise, it is now possible to apply to the CAT secretariat for a classification request. The CAT, in collaboration with the EMEA's Innovation Task Force, will determine (i) whether a product is a medicinal product or not; (ii) whether it is an ATMP or not. If it is an ATMP, the CAT will then determine into which subcategory it will fall – gene therapy medicinal product (GTMP); somatic cell therapy product (sCTP); or tissue-engineering product (TEP). In case of doubts between two subcategories, the following order will apply: GTMP>TEP>sCTP. This 60-day procedure is voluntary and cost-free.

If additional information is required, a formal meeting with the CAT may take place at Day 31. Summaries of the scientific recommendations are to be published without confidential information on the EMEA website and will contain the applicant's position on the regulatory classification and the EMEA's position. These summaries will be approved by the applicant before being posted on the EMEA website.

The determination of classification will be based on the updated definitions of GTMPs, sCTPs, as defined in the revised Annex I of the main medicinal products directive, Directive 2001/83/EC, and the definition of TEPs as stated in the ATMP Regulation. The demarcation of products potentially subject to the "hospital exemption"² remains a key question to address.

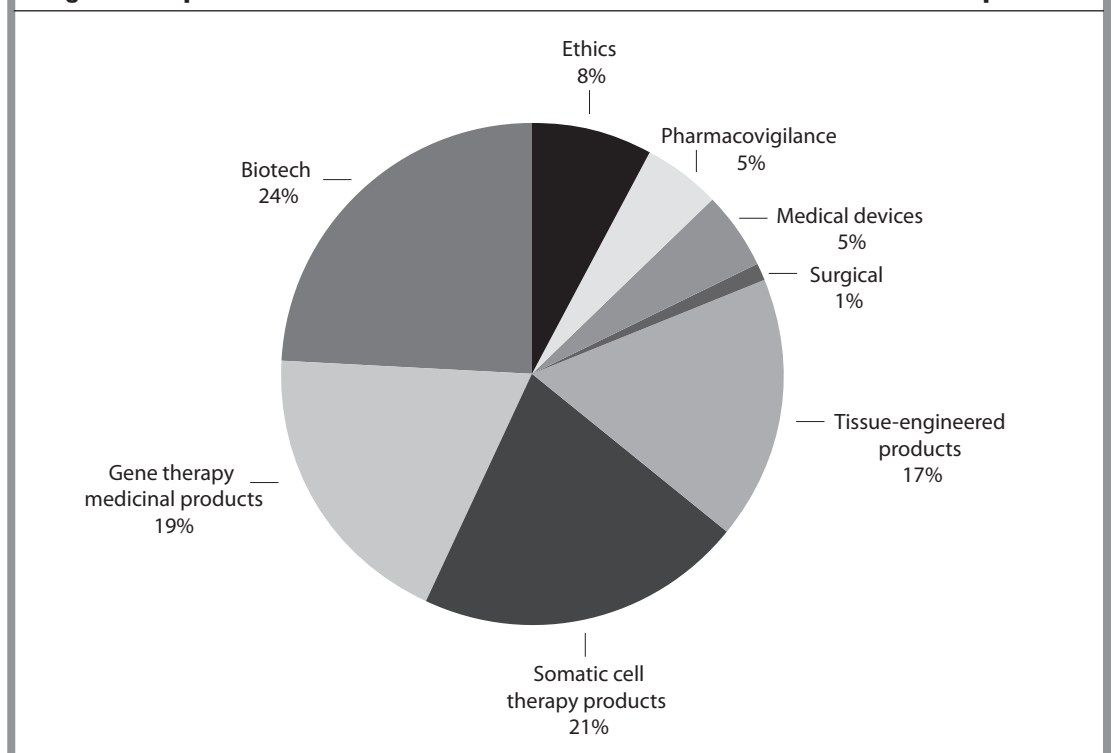
Indeed, even if the implementation of the relevant article of the regulation (Article 28(2)) is outside the remit of the EMEA but within the remit of member states, it is key to ensure consistent implementation among member states in order to adequately define the border between the products to be approved centrally and the products which may be assessed nationally through this hospital exemption.

The new definition of GTMP excludes synthetic nucleic acids and vaccines against infectious diseases as it now specifically refers to recombinant nucleic acid. The genetically modified organism nature of certain GTMPs was raised as an issue and there was concern about the lack of harmonisation amongst member states in this area.

GMO requirements will be driven by each member state

Dr Schneider acknowledged that this is indeed a matter the CAT needs to discuss further, as is the issue of when a CAT consultation will be required with a competent authority experienced with GMOs. Indeed, during clinical development, the GMO requirements will be driven by each member state while the CAT will be responsible for the evaluation of the marketing authorisation application, together with the environmental risk assessment³⁻⁵.

Figure 1. Expertise of the members of the EMEA Committee for Advanced Therapies



Certification of quality and nonclinical data by SMEs

The EMEA confirmed that it will be able to offer certification of quality and nonclinical data to SMEs (as per article 18 of the ATMP Regulation and implementing legislation) starting from May 2009. The 90-day procedure was explained as follows:

- a letter of intent will need to be issued by the applicant approximately four months before starting the procedure, in order for the EMEA to check the ATMP status of the product, the SME status of the applicant, the table of contents of the application and to appoint CAT co-ordinators;
- at Day 40, an initial assessment report will be issued by the lead co-ordinator;
- at Day 50, comments will be issued from the CAT peer reviewer and other CAT members;
- at Day 60 discussion will occur during a CAT meeting in order to define whether there is a need for inspection or for clarification. If so, the procedure will stop for one or two months maximum to allow an oral presentation by the SME on data requiring clarification. Therefore, it is envisaged that the entire procedure will not normally exceed 120 to 150 days. This might be longer when an inspection is involved, as the clock will remain stopped until it has been performed.

If the outcome is positive, the EMEA will give a certification of the data for the stage of product development concerned, ie that data provided are in compliance with the guidelines applicable to the stage of development of the product. The EMEA suggests that an optimal time to submit for certification may be just before the first-in-man studies. However, there were concerns regarding this stand-alone evaluation procedure – which is non-binding – with regard to both future marketing authorisation applications and clinical trial applications (ie there is no assessment of the risk:benefit ratio and no statement on the appropriateness of starting a clinical trial).

In addition, there were discussions about whether this procedure and the scientific advice fee reduction will be open to academia and hospitals in addition to SMEs. The EMEA advised academia and hospitals to contact the SME office and assured those concerned that the special fee will be granted if the product developed is of public health interest.

ATMP evaluation

Procedure

The ATMP's centralised evaluation procedure will follow the same key steps and time schedule as for conventional drugs (210 days evaluation time and clockstop). The main differences come from a dual evaluation by the CAT and the CHMP.

As defined in Regulation 726/2004/EC⁶ on the EMEA and centralised drug approval procedures, the CHMP will appoint the rapporteur and co-rapporteur. They will, however, be selected from the CAT, this being the committee with the relevant expertise for ATMPs. Therefore, for each application, there will be two evaluation teams, each comprising a CAT rapporteur or co-rapporteur and a CAT/CHMP co-ordinator. In addition, the assessment team will be composed of experts in quality, safety, efficacy, pharmacovigilance and environmental risk assessment. The CAT (co)-rapporteur will co-ordinate the assessment and the discussion at the CAT level while the CHMP co-ordinator will be responsible for the flow of information between the CAT and the CHMP as well as the discussion and adoption of the opinion at the CHMP level. This organisation will hopefully ensure a straightforward and efficient procedure with close communication between the two committees.

Replying to a question from the floor, CAT chair Christian Schneider stressed that the expert assessment team could be chosen from among the different member states and not only from the member states of the CHMP co-ordinators (ie the UK, Sweden, Luxembourg, Spain and Germany) in order to avoid an assessment concentrated on five countries.

The EMEA indicated that the re-examination procedure (ie the appeal) will follow the same concept as for the other drugs. A new assessment team will need to be appointed, however, and in the case of ATMPs, the application can be withdrawn before or after the draft opinion is adopted by the CAT, ie Day 200.

Key points to consider

Risk analysis and risk management plan

The adoption of the revised Annex I of Directive 2001/83/EC by the Standing Committee on Medicinal Products for Human Use on 2 March 2009 (and its foreseen approval by July after

The EMEA plans to offer certification of quality and nonclinical data to SMEs from May

An optimal time to submit for certification may be just before first-in-man studies

The ATMP centralised evaluation procedure will follow the same schedule as for conventional drugs

three months scrutiny by the European Parliament) introduces for the first time the concept of risk analysis in the premarketing development phase of all ATMPs. The revised annex further states that risk analysis can be used to justify the extent of quality, nonclinical and clinical testing required and can incorporate available experience with other ATMPs. The results of this risk analysis should be included in Module 2 of the marketing authorisation application. Although the concepts of this risk analysis are included in Annex I of Directive 2001/83/EC, the EMEA is preparing a detailed and much anticipated guideline on the matter. This guideline should in particular give more insight on the methodology to follow (and possible similarity/difference with the risk management methodology used for medical devices)⁷, and the link to the risk management plan as a postmarketing tool for medicinal products.

A specific guideline on RMP for ATMPs has already been issued⁸ and includes special emphasis on the need to put in place the appropriate infrastructure to cover long-term efficacy follow-up in addition to conventional safety follow-up. Jan Petracek (scientific administrator, pharmacovigilance and risk management, EMEA) emphasised that RMP will become a condition for marketing approval of ATMPs; he envisions an increase of conditional approval for these kinds of products.

Quality, nonclinical and clinical aspects

(i) Cell-based medicinal products (including sCTPs and TEPs)

The revised Annex I of Directive 2001/83/EC provides insight into the dossier requirements for cell-based medicinal products. An EMEA guideline⁹ also provides technical requirements for cell-based products.

At the workshop, CAT co-chair Paula Salmikangas underlined the key importance of quality aspects for these products, quality having a major impact on the safety. Considering that terminal sterilisation is not possible and that batch release controls on finished products might be difficult in particular for tissue type products, she insisted on the importance of integrating a risk-based approach to design the quality assessment of cell-based products and the amount of data needed for the marketing authorisation application. For example, the type of cells (stem cells, autologous or allogenic cells) and the nature of the process components (cytokines, chemicals, etc) will influence the final testing and quality evaluation scheme. Due to these constraints, a strong emphasis is to be made on risk mitigation by the selection of starting materials, process validation, aseptic manufacturing, in-process controls and thorough product characterisation including:

- identity (phenotypic and/or genotypic markers);
- purity (including analysis of contamination by other cell types and/or by non viable cells);
- impurities (including product related (eg cell fragments) and process related impurities (eg antibiotics, cell culture reagents);
- sterility (it is recommended to use alternative methods and test for the absence of bacteria, mycoplasma and fungi);
- potency (proof of functionality of the cells – potency assay should help in detecting clinically meaningful changes – can be *in vitro* or *in vivo* assays or based on surrogates markers);
- karyology/tumorigenicity; and
- components (eg cell/device) compatibility for combined ATMPs (quality needs to be assessed with the combined product as a whole).

Giovanni Migliaccio (CAT member, Agenzia Italiana del Farmaco, Italy), recognised that there is no sufficiently informative nonclinical model for ATMPs. However, nonclinical studies should be performed either on immunosuppressed animals, and/or in a homologous model, and/or *in vitro* assay in order to demonstrate proof of concept and define the pharmacological and toxicological effects predictive of the human responses.

Even if conventional absorption, distribution, metabolism and excretion (ADME) studies are not possible, biodistribution and cell differentiation studies should be performed. Ideally, a safe maximum dose should be determined, either per body weight or per volume/surface of missing tissue and should be linked with the product potency.

Considering the limits of the nonclinical assessment, Dr Migliaccio underlined the importance of the first-in-man study (Phase I/II) in order to assess the proof of concept in humans, the definition of appropriate markers, the validation of surrogate endpoints and adverse events. He insisted that at least one randomised clinical trial will be expected to support the product's clinical evidence for the marketing authorisation application. If comparative treatment is not possible, then a comparison to historical control is highly recommended.

The importance of quality aspects for cell-based medicinal products was emphasised...

...such as testing for impurities, sterility and potency

At least one randomised trial will be expected to support the product's clinical evidence for the marketing authorisation application

(ii) Gene therapy medicinal products

The revised Annex I of Directive 2001/83/EC also provides insight into the dossier requirements for GTMPs. Sol Ruiz (CAT member, Agencia Española de Medicamentos y Productos Sanitarios, Spain), referred to the note for guidance on the quality, preclinical and clinical aspects of GTMPs¹⁰. This guideline is to be revised but provides already a good foundation for quality assessment of GTMPs.

International Conference on Harmonisation guidelines are also to be referred to, in particular for the section on genetic development in order to describe the suitability of the vector, the construct, the control and stability of the gene expression, the selection of markers etc¹¹.

The section on process description should provide a detailed outline of the manufacturing process similar to those presented for other biological products, with flow charts and clear description of in-process controls particularly as it relates to impurity removal. As for cell-based therapy medicinal products, quality of the raw materials is critical and where possible reagents authorised as medicinal products or at least qualified reagents should be utilised. Where components of animal origin are to be used, a European Department Quality of Medicines (EDQM) Certificate of Conformity should be provided as it relates to Transmissible Spongiform Encephalopathy/Bovine Spongiform Encephalopathy (TSE/BSE).

Ideally, potency assays measuring the functionality of the product should be available but the EMEA understands that this is not always feasible and will very much depend on the product, its mode of action and the indication. Indeed, the potency assay should be based on the intended biological effect which should ideally be related to the clinical response. GTMP potency assays present the added challenge of implementing tools measuring multiple criteria related to biological activity: the efficiency of the gene transfer, and the level and stability of gene expression.

The critical quality issues for GTMP are related to establishment of viral or cell banks, viral and microbial removal, control of manufacturing process and reagents, identity, purity, potency and stability. These criteria will have to be taken into account during process changes and assessment of comparability.

It was noted that a general chapter of the European Pharmacopeia describes recommendations applicable for the production and control of GTMPs. In addition, the development of a new guideline for the quality, preclinical and clinical aspects of medicinal products containing genetically modified cells is being drafted¹² and should be presented as a stand-alone document describing all the specific requirements for medicinal products containing genetically modified cells.

Conclusion

This highly anticipated workshop gave an important insight into the implementation of the ATMP regulation and underlined the hard work performed by the EMEA. The implementation of the new regulation has taken place with a dynamic interaction between industry and agency. The EMEA has set up a framework providing opportunities for dialogue with stakeholders setting the path for the remaining questions to be addressed. As outlined by Patrick Celis (scientific administrator, EMEA), the CAT has already adopted systems and procedures to organise the information flow and collaboration between all parties, and is now fully operational to participate in procedural advice on the evaluation of ATMPs.

However, work remains to be done and the CAT is currently working on the preparation of various templates and standard operating procedures, guidelines on traceability, risk analysis, certification and good manufacturing practices specific to ATMPs.

Some questions – such as whether comparability testing is possible for ATMPs – remain unanswered and will need a multidisciplinary approach to be tackled adequately. The extreme complexity of using living complex organisms, cells, or tissues as medicines and the concept of permanent cure by repair or replacement of a defective function represent the hope of a new era of medicine. This comes, however, with a new set of challenges for which traditional drug development approaches are not likely to apply. A risk management approach and close collaboration between experts, industry and agencies are certainly needed to ensure a safe pathway for this new generation of medicine.

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The revised annex also provides insight into dossier requirements for GTMPs

A guideline for quality aspects of products containing genetically modified cells is being drafted

The CAT is preparing various templates and standard operating procedures specific to ATMPs

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