ALLIANCE for Advanced Therapies

Consultation Paper

European Commission Public Consultation on Regulation (EC) No 1394/2007 on Advanced Therapy Medicinal Products

29 March 2013

ALLIANCE for Advanced Therapies

1. Alliance for Advanced Therapies (AAT)

The Alliance for Advanced Therapies' mission is to improve the legislative, business and science climate for advanced therapies innovation in Europe. In order to do so, AAT promotes the interests of its members and the advanced therapies sector in Europe.
The Alliance represents the innovation interests of over 35 larger companies, SMEs, academic institutes, regional organisations and other stakeholders within Europe. For more information, see the AAT website.

This document is prepared by the AAT Regulatory Committee with input from the Alliance's membership.

2. Background

Regulation (EC) No 1394/2007 was published on December 2007 to address new scientific progress in cellular and molecular biotechnology leading to the development of Advanced Therapy Medicinal Products (ATMPs). It came into effect on 30 December 2008. Its scope includes gene therapies, somatic cell therapies and tissue engineered products and clarifies the regulatory path for such products, which were previously classified inconsistently across Member States.
The Regulation aims to facilitate the widening of the European market to innovative new ATMPs and therefore has been a major step to stimulate the development and approval of ATMPs in Europe.

To date, only two ATMP Marketing Authorisations have been approved since the ATMP Regulation has come into effect. Three applications are currently under evaluation. Only two of the recent applications are thought to come from the 40 or so ATMPs that were on national markets prior to December 2008, one of which (Hyalograft C) was withdrawn in January this year. Another application was withdrawn in March 2013 (OraNera). A large number of products are in early clinical development, with a significant pipeline in late stage development (Molecular Therapy, vol. 20, March 2012, 479-482).[1]

Currently, EMA has classified 63 products as ATMPs through the new optional classification procedure. It has been estimated that approximately 5 percent of orphan designated products and approximately 5 percent of scientific advice/protocol assistance procedures are for ATMPs.[2]

While the Regulation has not resulted in a sudden increase of approved products, it has brought much needed clarity and significant harmonisation among Member States. Understandably, many stakeholders are anxious to see more rapid progress, but opinions are divided as to what the most important barriers to innovation are. It therefore remains important to continue the dialogue between regulators and developers to ensure expectations are met on both sides. In this context, AAT welcomes the efforts of EMA and national competent authorities to organise workshops with interested parties.

Since the Regulation was implemented, a further key Directive was issued (2009/120/EC of 14 September 2009) amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use with regard to ATMPs. This Directive adapts Part IV of Annex 1 of 2001/83/EC with regard to the data requirements for ATMPs (including combination ATMPs), against which the quality, safety

[1] Romaldas Maciulaitis, Lucia D'Apote, Andrew Buchanan, Laura Pioppo and Christian K Schneider; Molecular Therapy; 2012; volume 20: 479-48
[2] CAB Ltd, upublished analysis of data from the EMA website.

and efficacy of the product should be assessed. The definitions and detailed scientific and technical requirements for gene therapy medicinal products and somatic cell therapy medicinal products were also updated.

Although this Directive is not specifically part of the scope of the consultation, it is referred to below, as some aspects impacting regulatory development of ATMPs, such as the risk based approach, are introduced within it.

A second Directive which underpins development and authorisation of cell and tissue based medicinal products is Directive 2004/23/EC [3] on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. Basic principles regarding donation, procurement and testing of the cell or tissue starting material are laid down in this Directive and are supplemented by additional requirements in Regulation (EC) No 1394/2007.

[3] Implemented by Commission Directive 2006/17/EC of 8 February 2006 as regards certain technical requirements for the donation, procurement and testing of human tissues and cells and Directive 2006/86/EC of 24 October 2006 as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells.

3. General Comments on Regulation 1394/2007/EC, Related Directives and Guidelines

The Alliance for Advanced Therapies (AAT) thanks the European Commission for the opportunity to submit comments on the implementation of Regulation 1394/2007/EC on Advanced Therapy Medicinal Products (ATMPs).

AAT recognizes that the Regulation aims to facilitate the widening of the European market to innovative new ATMPs and provides more certainty on the marketing requirements for those products. AAT is convinced that it has been a major step to stimulate the development and approval of ATMPs in Europe.

While we do not identify any major issues with the Regulation itself, other than article 28 on the so-called "Hospital Exemption", there are significant issues with the interface between the Regulation and other Directives (in particular the Tissue and Cell Directive 2004/23/EC) which need attention. These are discussed in detail in section 3.6 below.

AAT suggests that the Commission improve the communication regarding the process of developing EMA opinion on the evaluation of ATMPs, including the roles of the individual committees. AAT also proposes improvements to the communication of the final opinion. AAT believes it is necessary to develop a communication process that results in clear messages while ensuring the necessary transparency as described in section 4.7 below.

It is AAT's opinion that there is a further need for adapted and reinforced guidelines to clarify technical requirements and ensure proportionality of the requirements for data to be generated for marketing authorisations. We believe it is important to take into account the limited marketing authorisation experience so far, the diversity of ATMPs and the rapid state-of-the art developments.

In particular, the risk-based approach (RBA), as introduced by the legislation, could positively help bring proportionality to the amount of data to be generated, if this approach is further clarified and does not remain a concept only (see section 3.1 below).

Finally, we would welcome more detailed and balanced technical guidelines on:

- Characterization of Cell Based Medicinal Products (CBMP)
  - In particular, guidelines specifying to which extent a mixed population of cells needs to be characterised (cells participating in mode of action and cells considered impurities),while considering the scarcity of testing materials, and taking into account the intrinsic biological variability, especially for autologous products.
- How to assess equipment used in ATMP manufacture
  - In particular, guidelines on how to position/evaluate specific equipment or materials when they have a direct impact of modifying the quality of an ATMP and whether and/or when they need to be CE marked and/or included in the MAA dossier and when they can be handled at a GMP level.

- Non-clinical requirements
  - Guidelines on the requirements for non-clinical data and acceptable alternatives that should be considered based on a risk based approach, in particular when suitable preclinical models are lacking and clinical data are available.
  - Clarifications on some non-clinical aspects are desirable, for example.
    - In which cases tumorogenicity studies are required for ATMPs intended to be used in oncology
    - Acceptability of GMP-like material for non-clinical studies, to enable manufacturers to gain a readout before having to invest in manufacture at GMP quality and
    - Good Laboratory Practice (GLP) requirements for toxicity studies for studies employing specialized test systems that may not comply fully with GLP.
- CMC requirements for 3-D Tissue Engineered Products (TEPs)
  - The requirements should convey the complexity of these products, where the cells may develop into functional, organised tissue either inside or outside of the body. Sometimes cells are seeded within a scaffold or matrix, which may degrade or dissolve as the new tissue is formed. In other cases, a synthetic scaffold can provide the basis for tissue regeneration in an *ex vivo* bioreactor. On the whole, 3-D tissue-engineered products, while having characteristics in common with cell-based medicinal products, also have additional intricacies that make them unique.
  - AAT believes that is imperative to assist developers by providing specific guidance on quality and safety aspects, particularly with respect to characterisation and application of analytical processes specifically developed (over many years) for the study of anatomical structure and function, as well as how to assess structural properties of these 3D tissue engineered products. An initial step may be to have a dedicated group within the CAT such as the FDA Tissue Reference Group (TRG), with experts who understand the characteristics and the potential risks of these products.
- A proportionate approach to comparability of autologous products manufactured at multiple manufacturing sites
  - If autologous therapies are to succeed as commercial medicinal products, recognition of the complexity of manufacturing strategies needs to be more fully accounted for in regulatory requirements. These products need to be made in multiple sites across the EU to support the necessary short supply chain timeframe. Autologous products such as cultured bone marrow-derived MSCs are manufactured in very simple processes with limited opportunity for phenotypic change in culture (a huge amount of research has been published on MSC identity). It is AAT's view that it would be appropriate to expect manufacturers to confirm identity and purity of their cell population when manufactured at multiple sites. However, requiring very detailed in vitro and in vivo characterisation would be excessive. If requirement would be taken to the extreme, manufacturers could be expected to provide new clinical data each time a new manufacturing site is introduced (principles of ICH Q5E), and for a

relatively simple product this is unreasonable. For many tissue engineering products with structural or tissue regeneration endpoints, demonstration of efficacy can take months or even years, which would represent a completely disproportionate burden especially for very small companies.

- A practical approach on how to work with products necessitating a last manufacturing step in a hospital, when a very short shelf life prohibits product shipment after this last step
  - Examples for this issue could be the thawing and re-suspension of cryopreserved cells, the ex-vivo gene transduction of cells or the IL-2 activation of lymphocytes. As the finished product is considered to be the cell suspension, the ex-vivo genetically modified cells or the IL2 activated lymphocytes, all these steps are considered manufacturing steps and therefore should be done according to GMP-standard and the finished product should be released by a Qualified Person (QP). AAT believes it should be clarified under which conditions the hospital pharmacies could take the responsibility of these steps and how comparability between the different finished products at each implantation site needs to be assessed and established.

4. Specific Comments on Consultation Topics as Defined by the EU Commission

The following headings reflect the topics identified by the European Commission for further consideration during the consultation on the Regulation 1394/2007/EC on Advanced Therapy Medicinal Products (ATMPs). The most important topics are discussed in more detail in the appropriate section.

Since the Regulation in part amends the core medicines Directive (Directive 2001/83/EC), some comments are also provided on the technical Directive (Directive 2009/120/EC) that amended Annex I, Part IV of Directive 2001/83/EC.

4.1 Marketing Authorisation Application Requirements for Advanced Therapy Medicinal Products

The Regulation provides for specific requirements in terms of the marketing authorisation application dossier that applicants must prepare to demonstrate the quality, safety and efficacy of ATMPs. The type and amount of data that must be generated for the submission of a Marketing Authorisation Application (MAA) is critical to ensure a high level of public health protection. However, AAT would like to stress that the proportionality of the requirements for a MAA is important to stimulate the introduction of new advanced therapies.

Therefore, even though AAT recognizes regulation 1394/2007on ATMPs as a good basis for the development of new therapies, we welcome clearer and balanced guidelines to specify regulators' expectations on evidence to be generated in support of an MAA.

4.1.1 Risk-Based Approach and Assessment

Background

The concept of using a risk-based approach (RBA) was first introduced in the Guideline on Human Cell-Based Medicinal Products, CHMP/410869/2006, and later included in Directive 2009/120/EC. Neither the Guideline nor the Directive explained what was meant by a risk-based approach, nor what the implications might be for the development of ATMPs.

The draft Guideline on the RBA (Annex I, part IV of Directive 2001/83/EC applied to Advanced Therapy Medicinal Products) identifies that a risk analysis approach can be used by applicants to justify the product development and evaluation plans. In particular, due to the specific nature of ATMPs, an RBA may now be applied to justify the extent of quality, non-clinical and clinical data to be included in the MAA, in accordance with the scientific guidelines relating to the quality, safety and efficacy of medicinal products.

An RBA can further serve as input for the preparation of a post-marketing risk management plan (Risk Management System (RMS) - to be put in place for ATMPs where necessary on Public Health Grounds; Article 14 of the Regulation).

Key Regulatory Documentation

- Draft Guideline on the risk-based approach according to Annex I, part IV of Directive 2001/83/EC applied to Advanced Therapy Medicinal Products
- Guideline on Human Cell-Based Medicinal Products (CHMP/410869/2006)
- Guideline on risk management systems for medicinal products for human use (EMEA/CHMP/96268/2005)

Current Obstacles

In 2012, EMA issued a draft Guideline on the risk-based approach according to Annex I, part IV of Directive 2001/83/EC applied to Advanced Therapy Medicinal Products, which was adopted on February 11, 2013. This guideline is useful but remains vague on the methodology to apply for the identification of risks and risk mitigation.

Indeed, this guideline states that "*The risk-based approach should be distinguished from Risk Management Systems as defined in Regulation (EU) No 1235/2010, Environmental Risk Assessment according Article 8(3) of Directive 2001/83/EC and the Benefit / Risk Assessment in the context of a marketing authorisation evaluation. It should also be differentiated from risk analysis such as it is used for medical devices or as part of quality management of ATMP production as described in ICHQ9/Annex 20 GMP guideline*[1]*. The risk-based approach should also not be used to address risk-based quality management and risk factors, which are subject to principles of GMP, GLP and GCP*". There is concern that different stakeholders may have different interpretations of the RBA. It may be useful to provide further clarification of what the RBA is, and what it is not. Please note as well that in order to compile the marketing authorisation application in a consistent and effective manner, it will be necessary to specify clearly the location, format and content of the RBA document. So far, Module 2 has been specified, although according to ICH's web site; "Module 1 is region specific and Modules 2, 3, 4 and 5 are intended to be common for all regions" [http://www.ich.org/products/ctd.html] while the request for an RBA for ATMPs is still EU-specific.

AAT Position

AAT believes that advanced therapies innovation needs a flexible approach (for developers and regulators) to ensure the proportionality of the amount of data to be generated in relation to the patients' needs. AAT believes that the RBA could be an effective tool to ensure clarity between developers and regulators on the roadmap towards a reasonable risk-benefit ratio relative to the product's specifics.

However, it would be helpful to have clearer guidelines on the RBA to provide consistency and practical directions on how this RBA could efficiently help justify the product development from early stages onwards. AAT believes that misunderstanding may come from different interpretations of the term "risk-based approach" and the fact that the Guideline and Directive are not clear enough on what RBA is and is not (for example product risk classification or QbD approach). This point is of interest because a developer may submit an insufficient dossier if the intent of the RBA is misunderstood.
In order to build confidence in the approach and assist both the developer and EMA, it would be beneficial for EMA to actively encourage those seeking scientific advice for ATMPs to include their RBA. It would also be important for the SAWP/CAT/CHMP to comment on the RBAs as a matter of course (without the need to ask specific questions). It would also be advisable for the CAT to hold one or two workshops to discuss how the RBA should be used in development and at MAA.
Further advice is needed from EMA on where this information should be inserted in the MAA-documents.

4.1.2 Quality Requirements for Raw Materials

Background

Since most ATMPs are parenteral products, and since most are composed of living cells or viral-derived vectors, the manufacturing normally cannot incorporate viral clearance steps or steps to sterilise the final product. Consequently, microbial and adventitious agent safety must be achieved through more stringent control of starting and raw materials. However, compared to other sterile biotech products, many ATMPs use more complex raw materials such as cytokines and growth factors. Some products use a large array or complex raw materials. This leads to considerable problems identifying suitable quality materials, preferably manufactured under a suitable quality system such as GMP. In some cases there are no such sources in existence, those raw materials being provided "for research use only".

During R&D, raw materials used in the preparation of ATMPs are very often selected on their performance rather than on their quality grade. Raw materials for Cell-Based Medicinal Products (CBMPs) are for example usually selected based on their cellular growth-effect, and may contain growth factors, cytokines or enzymes as part of a growth medium. This is why innovative products developed in a research laboratory often use materials that are "for research use only". These research laboratories often cannot afford using GMP grade materials.

The requirements for raw materials are being scrutinized in order to improve the safety and quality of ATMPs. A working group between EMA and EDQM (the RCG working party) has been established to agree on the level of quality to be applied (i.e. GMP manufacturing, compliance with specific Ph. Eur. monograph or other). This working group includes producers of raw materials, product developers and assessors.

Section (17) of the ATMP Regulation emphasises that the manufacture of ATMPs should be in compliance with the principles of Good Manufacturing Practice (GMP)[1]. Recently, the revised Annex 2 of GMP which covers Manufacture of Biological active substances and Medicinal Products for Human Use demands that the quality of raw materials is brought under GMP.

In addition to the quality of raw materials, Directive 2009/120/EC also specifies stringent requirements for the qualification of growth media insofar that it must be shown that they are be suitable for use, for example regarding their growth promoting properties. The ATMP Regulation (Annex IV section 3.3.2.3) also indicates that when biologically active molecules are present as components of the product (such as growth factors, cytokines), their impact and interaction with other components of the active substance has to be characterized.

Key Regulatory Documentation

- Annex 2 of Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use
- Directive 2009/120/EC
- RCG working group survey to identify needs of stakeholders

Current Obstacles

At early stages of development, many developers with limited funding cannot afford using high quality/GMP grade raw materials. In these cases, the quality of the raw materials becomes an issue during technology transfer or later stages of development. The ATMP legislation and the new Annex II of GMP cause a large burden on producers of cell media and other raw materials to manufacture materials to GMP quality, with two possible consequences:

1. Some key raw materials remain available only at laboratory grade and therefore cannot be used anymore in ATMP processes
2. The cost of ATMPs using GMP grade raw materials increase significantly.

In later phases of development, a developer may need to

- Change the source of a raw material,
- Characterise himself the raw material, or
- Remove it from the manufacturing process.

Since these raw materials were originally selected for their performance (example: cell growth), it may not be straightforward to substitute them, and re-qualification of the

[1] As set out in Commission Directive 2003/94/EC of 8 October 2003 specifying the principles and guidelines of good manufacturing practice with respect to medicinal products for human use and investigational medicinal products for human use.

alternative source in the manufacturing process may not be trivial. Furthermore, the costs of characterising and re-qualifying new raw materials are very high.

Developers also tend to use cocktails of growth factors in early manufacturing process development that may not be fully qualified. This may have a major impact on later developments, when the process is fixed and GMP grade raw materials have to be sought.

Currently, it is unclear to developers which quality levels and performance test must be used in the selection of raw materials. In response, suppliers have been producing raw materials under GMP condition. However, it is unlikely that this will be sufficient. It is therefore unclear which materials developers have to select for ATMP manufacturing processes.

AAT Position

AAT believes it is necessary to develop a balanced and proportionate approach for GMP requirement for early stages of ATMP development. We recommend aligning EU requirements with the current U.S. approach which allows further development of GMP during Phase I/II clinical trials.

It is also important to clarify what is meant by clinical / GMP grade. For example, are CE marked cell media (manufactured according to the ISO 13485 standard) considered GMP compliant?

We look forward to hearing the outcomes of the survey initiated by the RCG working group on the quality requirements for raw materials[2] used in the manufacture of cell based and gene therapy products.

AAT believes that the necessary clarity cannot be accomplished by providing a few general chapters or even elaborate monographs for key raw materials. The reason is that one needs to consider the use of complex raw materials such as cytokines when deciding on the quality that is required. AAT therefore suggests that EDQM provide a certification service for quality of complex raw materials, similar to the EDQM certification of suitability for TSE risk.

4.2 Requirements for Combined Advanced Therapy Medicinal Products

Relatively few products under development are a combination of an ATMP and a device, although many use novel delivery devices. The resulting lack of experience with these combinations means that it remains unclear whether the provisions of the regulation are proportionate or fit-for-purpose for these types of combination ATMPs (cATMPs).
A specific question is whether the exchange between the CAT and the Notified Bodies will be effective. There is also uncertainty about the potential impact on cATMPs of the current proposals to amend the medical devices Directives.

[2] This review will cover antibodies, basal media (for cell culture), serum/serum replacements, growth factors and cytokines but exclude feeder cells, a-cellular matrices, etc.

AAT believes that too much emphasis is currently placed on the CE mark assessment by a Notified Body, which according to us, is not always adequate for a proper assessment of the intended use of the device in the combined ATMP. Directive 2001/83/EC Annex Part IV requires:

> *"evidence of conformity of the medical device part with the essential requirements laid down in Annex I to Council Directive 93/42/EEC (1), or of conformity of the active implantable device part with the essential requirements laid down in Annex 1 to Council Directive 90/385/EEC.*
> *Where available, the results of any assessment of the medical device part or the active implantable medical device part by a notified body in accordance with Directive 93/42/EEC or Directive 90/385/EEC.*
> *The notified body which has carried out the assessment referred to in point (d) of this section shall make available on request of the competent authority assessing the application, any information related to the results of the assessment in accordance with Directive 93/42/EEC or Directive 90/385/EEC."*

In this context, AAT identified the following issues:

- The development and CE marking of the medical device may not address all elements relevant to the use of the device in a combined ATMP. For example, a collagen scaffold CE marked as a haemostatic dressing will not have been assessed for safety upon implantation, or for its degradation in different parts of a body.
- It is entirely likely that an ATMP manufacturer is not the manufacturer of the CE-marked device being used in the combined ATMP. The ATMP manufacturer only has the presence of a CE mark on the device packaging as evidence of conformity with the medical device Directive. The device manufacturer has no obligation to provide any documentation, such as an EC design examination certificate, to the ATMP manufacturer.
- Depending on device classification and conformity assessment route, the CE mark process may not involve any assessment by a Notified Body.
- The requirement for a Notified Body (NB) to supply information relating to the assessment, if it exists, may make it difficult for ATMP manufacturers to source openly a medical device and negotiate the kind of contract necessary to meet MAH responsibilities for control of starting materials. Device manufacturers may not wish to allow this level of scrutiny of their documentation. Therefore, the NB will provide information directly to the Competent Authority (CA) assessing the application. The CA would then have access to information about the device that the ATMP manufacturer would not be party to. This is a situation explicitly prohibited in the context of drug master files, which may not be used for biological medicinal products.

AAT Position

We believe that the CE mark dossier should be made available to the ATMP developer before the Notified Body assessment of the device part of a combined ATMP is provided to EMA (similar to devices incorporating an ancillary human blood derivative).
Moreover, AAT believes that relying on the existing CE Marking of a device is sometimes not necessary, because the CE Marking might be completely irrelevant to the use of the cATMP as the device is very often not being used within its manufacturer's originally intended use. The device part should be compliant with the device Essential Requirements laid down in Annex I to Council Directive 93/42/EEC (1), or with the Essential Requirements laid down in Annex 1 to Council Directive 90/385/EEC (if active implantable device) but its intended use in the cATMP should always be considered. The text of Regulation (EC) No 1394/2007 and Directive 2001/83/EC use language such as "where available" but guidance should be introduced to ensure clarity. In the case of a combined ATMP where the device is an integral part of the product, such as a scaffold or matrix, multiple or not fully described mechanisms of action may apply, which may not be easily differentiated or defined. The device component may be used only as a temporary delivery device, may be permanently implanted, or may be metabolized or resorbed after implantation. The device data requirements should be proportionate to the role of the device in the combined ATMP; the role, form and function of the device within the cATMP may be different to the ones in the initial CE mark.

In particular, this guidance should clarify

- If and when it is considered necessary to involve a NB in the application assessment.
- Whether it would be possible to have a representative of a Notified Body as a medical device expert present at a scientific advice meeting with EMA (at the request of the Applicant).

4.3 AAT Position on the Hospital Exemption

The Alliance for Advanced Therapies appreciates and supports the Hospital Exemption (HE) as a means to offer individual patients a treatment with a customized, innovative and safe product, particularly when a disease occurs so rarely that the regular development and validation of the required therapy is not feasible. However, AAT would like to emphasize that the inconsistent implementation of the Hospital Exemption in the Member States and routine preparations of treatments under an exemption impede the development of new, safe and effective treatments. Furthermore, safety or efficacy issues resulting from Hospital Exemptions could seriously impact public confidence in advanced therapies and further impede their progress, as happened in the past with gene therapies.

Therefore, the Alliance believes that a harmonized and transparent European approach is crucial to bring more innovative, effective and safe therapies to all European patients. It is in

the best interest of patients to limit Hospital Exemptions to non-routine preparations of treatments based on article 28 of European Regulation 1394/2007 under all applicable safety and quality rules. The term "non-routine basis" needs to be clearly defined.
In addition, the supply of ATMPs under the hospital exemption should be periodically reported to, and reviewed by, the Commission. Safety reporting, including collection of information on Adverse Events, should be required from products supplied under the Hospital Exemption in the same manner as for other ATMPs. A safety database should be established for ATMPs subject to the Hospital Exemption; Commission Directive 2006/86/EC requires SAE reporting, but the equivalent of "black triangle" reporting would provide further safety support for Hospital Exempted ATMPs.

AAT considers it important that Hospital Exemptions will no longer be allowed when a fully validated, centrally approved Advanced Therapy Medicinal Product is available. At this moment, there is no European-wide legal certainty on this point.

We refer you to our white paper on the hospital for additional information.

4.4 Incentives for the Development of Advanced Therapy Medicinal Products

The Regulation provides several incentives in the pre-authorisation phase for the development of ATMPs by SMEs. These incentives are important for a poorly funded industry dominated by SMEs.

Currently, some interesting incentives are envisioned for the development phase of a product and the period around the MAA.

However, the first years after an authorisation are often financially very difficult, especially for small scale companies with a limited product portfolio. SMEs with highly innovative products will often not be able to cover the entire territory immediately. Following marketing authorisation, companies are also confronted with new and often very high expenses. These expenses include variations, translations, and post authorisation pharmacovigilance commitments.
Furthermore, these companies face challenging pricing and reimbursement negotiations, because their first in class products do not (fully) fit within the classical Health Technology Assessment rules. As a result, sales volumes only gradually increase over time. Finally, the investment climate for a company in this phase is very different from a typical early stage R&D company.

AAT Position

AAT encourages the Commission to continue the above-mentioned incentives in the immediate future, at least until the industry becomes more established. Our Alliance also calls for SME incentives for the post-MAA phase, including realistic pharmacovigilance fees.

Our not-for-profit members typically do not qualify for the incentives mentioned above. However, the long-term success of these stakeholders is likely to rely on their ability to partner with, or outlicense their technologies to companies that can commercialise them. Ensuring not-for-profit organisations have facilitated access to these regulatory procedures is paramount if they are to be attractive to the commercial sector.
In the current financial climate, it is increasingly difficult to outlicense promising products in the early development phase. The industry is extremely reluctant to consider any deal before at least phase II data are available. Consequently, there is a greater burden-of-proof on non-commercial developers to undertake all the ground work that would be expected for a product at that stage, and to consider commercial needs. Failure by such non-commercial developers to understand the regulatory requirements will jeopardise their chances to realise their potential. AAT therefore believes that especially the scientific advice and the Certification procedure incentives should be opened up to organisations that rely on public money or charitable donations.

AAT also emphasises that funding of advanced therapies research through Horizon 2020 should foster the development of all areas with high potential for bringing advanced therapies to patients.

4.5 AAT Position on Scope and Adaptation to Technical Progress

AAT underscores that the advanced therapies constitute a relatively new field of medical innovation with rapid developments. The European regulatory framework should be flexible enough to incorporate adaptions to relevant new developments.

4.6 Interface with other Directives

4.6.1 AAT Position on Tissues and Cells (Directive 2004/23/EC)

Need for a Regulation Rather Than a Directive

Differences in the implementations of Tissues and Cells Directive 2004/23/EC throughout Europe have led to variation and additional complexity in operating processes for collecting and handling human cells and tissue starting materials in the different Member States. In countries like Germany the process is even more complex because of the lack of national harmonization and differences in requirements among the “lander”. Another example refers to Belgium, where allogeneic ATMPs cannot be processed without involvement of a tissue bank, while this is not required by the ATMP Regulation.

AAT believes it is important to facilitate harmonisation of the routine methods for obtaining starting material for ATMPs, for example the methods for donation, procurement and testing. In our view, the best way to ensure harmonisation is to convert Directive 2004/23/EC into a Regulation.

Need to Clarify Acceptance of ATMPs Sourced in Compliance with Directive 2004/23/EC Itself Rather than National Transpositions thereof

Compliance with 2004/23/EC is required for donation, procurement and testing of human tissues and cells used in ATMPs. However, Member States have used the legal opportunity of this directive to introduce additional requirements; for example, virus testing of donors, and, for the extent to which donors may be compensated for their time, travelling expenses, etc.

The interface with the ATMP Regulation is not clear on this topic, because there seems to be an option for Member States to refuse acceptance of a centrally authorised ATMP on the grounds that the tissue donation did not meet the national requirements. This possibility needs to be clarified, because ATMP developers, especially of allogeneic products, need to be aware of an implied obligation to work according to the highest common denominator in respect of donor testing. Ideally, it should be sufficient to demonstrate compliance with either the baseline requirements of 2004/23/EC, or the national requirements in the Member State where the tissue was sourced.

Need to Clarify under Which Regulatory Umbrella (ATMP Regulation or Directive 2004/23/EC) the First Step of an ATMP Manufacturing Process, Involving Non Substantial Manipulations of Cells Or Tissues Should Be Governed

As said in Article 3 of the ATMP Regulation[3] on donation, procurement and testing,
Where an advanced therapy medicinal product contains human cells or tissues, the donation, procurement and testing of those cells or tissues shall be made in accordance with Directive 2004/23/EC.

It is not clear and subject to different interpretations by Member States whether the first step of an ATMP manufacturing process, involving non-substantial manipulations of cells or tissues could be governed by Directive 2004/23/EC or not, and therefore whether – for example – a selected cell population could be provided as starting material from a Tissue Establishment to an ATMP developer. This should be clarified to ensure a harmonised interpretation by the Member States.

[3] And in Article 2 of the Cell and Tissue Directive 2004/23/EC (Scope)
This Directive shall apply to the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells intended for human applications and of manufactured products derived from human tissues and cells intended for human applications. Where such manufactured products are covered by other directives, this Directive shall apply only to donation, procurement and testing.

4.6.2 AAT Position on Point Of Care Manufacturing Devices Used Within a Same Surgical Procedure

As said in Article 2 of the Directive 2001/83/EC on medicinal products,
This Directive shall apply to medicinal products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process.

As said in Article 2 of the Cell and Tissue Directive 2004/23/EC,
This Directive shall not apply to tissues and cells used as an autologous graft[4] within the same surgical procedure[5];

A number of companies have developed closed-system, stand-alone medical devices that can be used at the patient's bed to process tissues and cells for an autologous re-injection into the patient within the same surgical procedure.
These devices are currently CE marked but the regulatory status of the manufactured cell suspension is not clear. Most current devices are considered to only minimally manipulate the cells. However, when these cells are not used for the 'same essential function' in the donor as the recipient[6], the cells meet the definition of an ATMP. Nevertheless, the fact that these *cells can be used as an autologous graft within the same surgical procedure* raises the question whether they can fall in certain cases within the scope of Directive 2001/83/EC (and therefore of the ATMP Regulation) and of Directive 2004/23/EC.

An automated closed device could perform all manufacturing steps for relatively simple manufacturing processes. It is clear that this approach would solve many problems encountered by ATMP companies encountering logistical issues related to a short shelf life of their products.
This approach was not envisaged within the directives, so there is no clear path for its regulation. Some consideration should be given to the question of whether the device, or the cells it manufactures, is the product to be regulated. Another important question is how GMP compliance can be ascertained for the use of such closed system devices. This regulatory uncertainty is holding back the development of such devices, which are a smart solution to a complex problem.

AAT therefore solicits a clarification of the regulatory path of these types of technological solutions for autologous cell therapy manufacturing with the objective to stimulate their development.

[4] Tissues removed and transplanted back to the same individual.
[5] Without being subjected to any banking process.
[6] Same person for autologous products.

4.7 Improve Communication on EMA Opinions

As said in the introduction of the ATMP Regulation,
To ensure scientific consistency and the efficiency of the system, the Agency should ensure the coordination between the Committee for Advanced Therapies and its other Committees, advisory groups and working parties, notably the Committee for Medicinal Products for Human Use, the Committee on Orphan Medicinal Products, and the Scientific Advice Working Party.
The formation of an expert scientific committee to evaluate ATMPs is generally considered an important outcome of the Regulation. While it is accepted that healthy debate is an important part of science, it is essential that these debates between the CAT and the CHMP are acknowledged as such (article 8.4).
The recent review of Glybera has raised many questions and concerns about the relative roles of the CAT and the CHMP, and perhaps that of the Commission itself. It may not be widely understood that the roles of the CAT and CHMP are to provide scientific opinions to the Commission. The recent divergence of opinions have been seen by some stakeholders as a sign the regulators are divided, that they do not understand these products, or that the products should be regulated differently because they don't fit the current system. Perhaps more importantly, key stakeholders that have been informed only indirectly, such as investors, may perceive the discussion between the CAT and the CHMP as a sign of uncertainty, showing that the industry is not yet attractive enough for larger investments.

AAT Position

AAT suggests that the Commission improve the communication regarding the process of developing CHMP opinions on the evaluation of ATMPs, including the roles of the individual committees. AAT also suggests improvements to the communication of the individual CAT and CHMP opinions. In our view, it is necessary to develop a communication process that results in clear messages on the final opinions, while ensuring the necessary transparency of the discussion process between CAT and CHMP. This approach will support the development of advanced therapies as well as the credibility of the assessment process.

4.8 Additional Comments

- Pricing and reimbursement processes are very challenging for ATMPs, especially because of the lack of useful benchmarks and the need to manage expectations carefully. AAT would like to emphasize that certain parts of the current pricing and reimbursement processes for medicinal products will need to be adapted for ATMPs. A stronger interaction between regulators at EMA, national health technology assessors and developers is desirable, for example on joint scientific advice.
- AAT would like to stress that global harmonization between different regulatory jurisdictions would help stimulate the growth of advanced therapies. Harmonization

initiatives should cover at least EMA and FDA, but also include Health Canada, Asian authorities and, in the longer term, ICH.
AAT is interested to hear which advanced therapies topics are currently being discussed between EMA and FDA. Our Alliance believes it would be useful having the possibility to provide input for these discussions, for example through stakeholders meetings.

5. References

- Guideline on Human Cell-Based Medicinal Products (CHMP/410869/2006)
- Guideline on risk management systems for medicinal products for human use (EMEA/CHMP/96268/2005)
- Draft Guideline on the risk-based approach according to Annex I, part IV of the Directive 2001/83/EC applied to Advanced Therapy Medicinal Products
- Annex 2 of Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use
- Directive 2009/120/EC
- Directive 2004/23/EC
- RCG working group survey to identify needs of stakeholders
- Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells EMA/CAT/GTWP/671639/2008, which came into effect in November 2012.
- Draft reflection paper Clinical aspects related to tissue engineered products (CAT/CPWP/573420/2009)
- Committee For Advanced Therapies Reflection paper on in-vitro cultured chondrocyte containing products for cartilage repair of the knee (EMA/CAT/CPWP/568181/2009)
- Volume 2B, Notice to Applicants, Medicinal products for human use, Presentation and format of the dossier, Common Technical Document (CTD).

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