PUBLIC CONSULTATION PAPER
ON THE REGULATION ON ADVANCED THERAPY MEDICINAL PRODUCTS

Deadline for Public Consultation: 31 March 2013

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Contributor:
„ACADEMIC GMP" – an FP7-funded Research Consortium (grant agreement # 260773)
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Project full title:
The impact of Regulation (EC) No 1394/2007 on the development of Advanced Therapy Medicinal Products (ATMPs): an academic perspective

Concept and objectives:

Within call: FP7-HEALTH-2010.4.2-6, ACADEMIC GMP addresses the impact of the recent regulatory developments on Advanced Therapy Medicinal Products (ATMP) particularly on the academic and hospitals sector.
Academic GMP facilities are major contributors to the development of ATMPs[1]. They respond to clinical needs and foster therapeutic innovation in an environment which is not industrial by definition nor by intention. European investigator-initiated multicenter trials of ATMPs critically depend on academic GMP facilities as will the future delivery of many of these new medicines even after commercialisation.
We have assessed the impact of Regulation (EC) No 1394/2007 and related Directives on academic GMP facilities by: a) conducting a European survey in this sector; b) organising workshops for a targeted, collaborative discourse; c) establishing a web-based platform for information exchange; d) analysing publications and guidance from the perspective of better regulation principles; e) analysing innovation statistics in relation to ATMPs.

More details can be found at: www.academic-gmp.eu.

[1] Maciulaitis R, D'Apote L, Buchanan A, Pioppo L, Schneider CK. Clinical Development of Advanced Therapy Medicinal Products in Europe: Evidence That Regulators Must Be Proactive. *Mol Ther* 2012; **20:** 483-512.

2. CONSULTATION TOPICS

2.1. Marketing authorisation application requirements for advanced therapy medicinal products.

The Advanced Therapy Regulation provided for adapted requirements in terms of the dossier that applicants must prepare to demonstrate the quality, efficacy and safety of the medicinal products when applying for a marketing authorisation.
The amount of data that must be generated for the submission of a marketing authorisation application is critical to ensure a high level of public health protection. Proportionality of the requirements is also important to facilitate the marketing of advanced therapies.
Please provide your comments on the requirements for marketing authorisation applications set out in the Regulation.

Response:

Academia is usually not seen as being capable of pursuing the clinical development of a medicinal product, especially and ATMP, up to the stage of a marketing authorisation. However, the pathways in ATMP development are complex, and some of these can be served mainly by Academic institutions. Some ATMPs will be developed and attain marketing authorisation. Of these, some will be suitable for central manufacture and direct supply to clinicians whilst others will be manufactured centrally but will still require near-patient end-stage processing (thawing/dosing etc), necessitating a partnership between the central industrial manufacturer and a CMO or hospital/academic unit near to the patient (e.g. human embryonic stem cell derived retinal epithelial cells currently in UK and US trials). Finally, there will be many ATMPs which are definitely not suitable for commercialisation. These will never obtain a marketing authorisation, nor were they intended to. Yet, they address a critical unmet clinical need (e.g. tissue-engineered tracheas as implanted at UCL and Karolinska recently). Apart from the Hospital Exemption Clause discussed below, Academic Institutions are contributing substantial numbers of **investigational ATMPs** which shall be addressed here.

In the course of our survey, in public consultations and in the interviews, accumulating evidence showed that the **provision of pre-clinical data** for compilation of the medicinal product dossier to investigational ATMPs often leads to use of very contrived animal models. There is a significant risk of underestimating toxicity of human-specific biologic reagents when evaluated in animal models, even primates, as pharmacologic activity and unanticipated adverse side effects may be species-specific[2]. Standard animal models may also not be predictive of toxicity due to differences in lifespan, and because the equivalent human application cannot be adequately mimicked. The testing of an “equivalent” ATMP derived from tissues from the experimental host is flawed also as the starting materials (cytokines, culture media, supplements and even culture vessels) are likely to be substantially different to the human product.

[2] Suntharalingam G, Perry MR, Ward S et al. Cytokine storm in a phase I trial of the anti-CD28 monoclonal antibody TGN1412. New Eng J Med 2006; 355:1018-1028.

For the development of ATMPs, a paradigm shift in the approach to pre-clinical testing required for clinical trial authorisation (CTA) may be needed[3]. As exemplified in the UK, patients can be treated on the basis of clinical need outside of a trial, but pharmacovigilance is provided through the existing MHRA reporting structures. Clinical outcome and adverse event data are retained and used in place of or in addition to relevant preclinical animal data in subsequent dossiers for submission of the same product in a formal clinical trial.

Not withstanding the issues detailed above, there are already and will continue to be, ATMPs which require marketing authorisation for their continued provision to patients in the EU. It is likely, however, that the unique reliance of many ATMPs on patient or donor derived tissues as critical starting materials and the innate biological variation of human cells will require greater flexibility in product definition than is currently accepted for medicines obtaining marketing authorisation.

[3] Lowdell MW, Birchall, M, Thrasher AJ. Use of one-off, compassionate use, advanced therapy medicinal products (ATMP) as a safe and valid alternative to animal models for pre-clinical data for clinical trial submissions? Lancet 2012; 379:2341.

2.2. Requirements for combined advanced therapy medicinal products.

The existence of advanced therapy medicinal products that incorporate one or more medical devices has been recognised and regulated in the Advanced Therapy Regulation. In particular, combined advanced therapy medicinal products are to be authorised by the Commission following the scientific assessment of the European Medicines Agency. The applicant must demonstrate that the essential requirements of the specific legislation on medical devices have been complied with and there is a possibility for the Agency to consult the relevant notified bodies.
No application for a combined advanced therapy medicinal product has been submitted to the European Medicines Agency yet.
Please provide your views on the authorisation procedure foreseen in the Advanced Therapy Regulation for combined advanced therapy medicinal products.

Response:

A critical issue, and a potential explanation for the lack of combined ATMPs en route to marketing authorization, might be seen in the **heterogeneity of classification of ATMPs**. The interviews provided information regarding the heterogeneous implementation of the Directives and the Regulation across the EU and the impact this heterogeneity has on development. The definition of a cell therapy or tissue engineered product as an ATMP, despite Regulation 1394/2007/EC, is not harmonised. Even if one requests a classification from EMA it is not legally binding and each member state may classify the same product differently. One such example was a case of three similar products consisting of cultured human natural killer cells as an anti-cancer immunotherapy. In two states and in Switzerland these expanded products were classified as an ATMP, in a third they were deemed “not substantially modified” and thus not regulated as a medicine whilst in a fourth Member State a similar NK product which was not even expanded was classified as an ATMP. All products have been taken to clinical trial successfully but, from the perspective of drug development it is difficult to obtain industrial uptake with such regulatory confusion and hard to predict what will happen when a product is submitted to EMA for centralised marketing authorisation and yet is not even a medicine in one or more Member State.

2.3. Hospital exemption.
The Advanced Therapy Regulation empowers Member States to authorise the use of advanced therapy medicinal products in hospitals for individual patients in the absence of a marketing authorisation. The so-called hospital exemption provides for flexibility to address the situation of individual patients; however, a too large application of this exemption may discourage the application for marketing authorisations.
Please provide your views on the application of the hospital exemption.

Response:

In the interviews performed with experts from academic institutions in most EU member states and associated European countries, a consistent and most contentious issue was the **lack of harmonisation of implementation of the Hospital Exemption Clause (HEC)** in Regulation 1394/2007/EC across the Member States. Several Member States have not yet implemented a structure to assign HEC production licenses yet, and in those who have done so there are wide differences in how it may be used. Most Member States have annual applied limits to the numbers of a specific product type which can be manufactured under an HEC license, presumably in response to the stated requirement for "non routine" production in Regulation 1394, whilst others apply no limits. The limit on numbers of individual ATMPs under the HEC is seen as nonsensical by most respondents. It is another potential cause of patient migration from their own Member States to and adjacent Member States or non-EU country to receive a treatment simply because an arbitrary maximum number of patients have been treated in a single centre in one year. Clarification of the definition of "non routine" from the Commission to the CAs in each Member States would be valuable.
The use of the HEC for clinical trial product manufacture is forbidden in all MS as required in the Regulation. However, several CA are encouraging the use of HEC to produce ATMPs for first-in-man cases and allowing the data arising from these to be used as part of the investigational medicinal product dossier for subsequent clinical trial applications. This is in line with a recommendation by EMA /CAT regarding the use of clinical data from first-in-man studies to replace pre-clinical animal studies where appropriate[4]. Indeed, some CA are referring to these first-in-man compassionate use cases as a new "phase 0" type of clinical study. The continued availability of the HEC for this type of application and for the provision of ATMPs which will never be suitable for a marketing authorisation was regarded as **essential** by all respondents.

Apart from the "Hospital Exemption Clause", another path of ATMP development discussed in the interviews forms **Article 5.1 of the Medicines Directive (2001/83/EC**). This "Specials Clause" Legislation allows for the manufacture of ATMPs as "unlicensed" medicines formulated in accordance with the specifications of an authorised health-care professional. In many ways this route is similar to the HEC above but, critically, it can only be used to provide a medicine "**in the absence of a licensed alternative"**. This prevents it being used to undermine the supply of ATMPs with a marketing authorisation. These medicines are intended for use by an individual patient under his/her direct personal responsibility, they can be exported. Only the UK is applying this legislation for the manufacture of ATMPs, but most interview partners greeted such an approach as most helpful, and national regulatory bodies from other EU member states have expressed their interest in having this chapter of legislation available.

[4] "Clinical data may, in part, compensate for non-clinical studies; inappropriate animal studies are worse than reliance upon in vitro data only". Dr Christian Schneider, Chair of EMA Committee for Advanced Therapies at ATMP Stakeholders' Workshop, EMA, London, January 2012. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2011/11/event_detail_000545.jsp&mid=WC0b01ac058004d5c3

Proposals:

The HEC is **appreciated and understood as a route of ATMP development and manufacture in small populations**, small batches and for the treatment of exremely rare diseases in specialized, mostly academic centers and in the absence of an interest from industry. BUT:

- The conditions and terms for application of the HEC urgently need a unified definition.
- A trajectory for a use of the HEC in conjunction with clinical trials needs to be developed.
- The lack of industry in this field of development makes this a political issue, with the need to support Academia that is filling a gap in an attempt to provide complex therapies to EU citizens.
- The adoption of Article 5.1 of 2001/83/EC for ATMP should be encouraged in ALL Member States.
- The HEC should be restricted to provision of ATMPs ONLY where there is no licensed alternative

2.4. Incentives for the development of advanced therapy medicinal products.
Advanced therapies are at the cutting edge of innovation. The full development of the potential of this sector is closely linked to the evolution of scientific knowledge. The Advanced Therapy Regulation provides for a number of incentives to support the development of these products, such as certification for quality and non-clinical data, reduced fees, scientific advice.
Please provide your views on the incentives provided for under the Advanced Therapy Regulation.

Response:

In the development, manufacture and clinical testing of ATMPs, the Rules of Good Manufacturing Practice (GMP) and related regulations require in-depth discussions between manufacturers and regulators. Traditionally, only large pharmaceutical companies are equipped to shoulder the burden of maintaining GMP manufacturing facilities, of coordinating complex trials to the requisite standard and to meet the considerable bureaucratic requirements.

The ATMP regulation established special provisions and cost benefits for SMEs. However, it is sometimes overlooked that a great proportion of ATMP are not pioneered by industry but as individual ventures of a single (university) hospital, often on the initiative of clinicians collaborating with local academic groups. The transition from Academia to Industry has not been defined sufficiently in the ATMP regulation:

- Academia is not allowed to apply for an ATMP certification for pre-clinical and quality data, thus being deprived from a tool that might very well help to define the transition to industry,
- Industry is reluctant to embark on high-risk early phase clinical trials, leaving a gap to be filled again by Academia,
- No distinction is made between products that are commercially viable and, one day, might reach marketing authorisation, and products that have never been intended to receive marketing authorisation, and never will do so simply because they are not considered commercially viable. Only with the Hospital Exemption clause, the latter pathway of development has been sketched, but in an insufficient way to help Academia fill the gap in fulfilling a duty for patients in need that are not helped sufficiently otherwise and, as shown in many saddening examples, succumb to medical tourism, scientifically unsound concepts of therapy, or death.

2.5. Scope and adaptation to technical progress.
The Advanced Therapy Regulation applies to gene therapy medicinal products, somatic cell therapy medicinal products and tissue engineered products.
Please provide your views on the scope of the Regulation and in particular as to whether the scope should be modified to take account of technical progress.

Response:

Regulation (EC) No 1394/2007 has been designed to ensure the free movement of ATMPs within the European Union (EU), to facilitate their access to the EU market and to foster the competitiveness of European pharmaceutical companies in the field, while guaranteeing the highest level of health protection for patients[5].

We have found **evidence of poor harmonisation of implementation** at the level of delivery across the Member States and uncertainty about the regulatory process; stifling development and commercialisation of these therapies. Most disturbing is is he detrimental effect on translation to early phase trials which remain largely academic investigator-led. Academic GMP practitioners should strengthen their political visibility and contribute to the development of functional and effective EU legislation in this field.

On the level of legislation, the performance of phase I/II trials needs facilitation. Here, the European Medicines Agency has a growing sense for the specific characteristics of ATMPs and a strong interest in the interaction with stakeholders, including Academia, as interested parties in a constant dialogue. As a result of the opinons received in the interviews as well as during the workshops performed by "Academic GMP" from stakeholders in the field, the following points merit further attention:

- A more precise definition of the quality requirements for an IMPD,
- An acceptance that animal models may be inappropriate for some developments (a view shared by the EMA)
- The recognition of the fact that this field is important for EU GDP but is currently >90% academic led
- Support for small academic GMP facilities, moving to a more risk-based approach as fostered by the FDA
- An increased availability of EDQM reagents for manufacturing
- Increased availability of funding to universities to invest in translational research beyond F-I-M, and a provision of GMP & GCP resources needed for academics
- An EU funded mechanism for the **Open** exchange of SOPs and reagent qualifications between academic GMP groups
- Frank and honest reporting of non-trial F-I-M results (data registry?)

So, Regulation of cell therapies as medicines is essential, and Regulation 1394/2007/EC has improved the EU situation but more needs to be done.

[5] 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. *Official Journal of the European Union* 2007; **L 324:** 121-131.

Proposals:

1) In current legislation, the recognition of Academia as a major contributor and partner is essential for better ATMP development

2) First-in man proof of principle studies in small patient groups should be facilitated (within the "Hospital Exemption" Clause? Is this what the HEC was meant for? "Preceding" phase I/II trials?), for instance by omitting a high workload required for documents such as a full-length IMPD (Investigational Medicinal Product Dossier) or a Common Technical Document (CTD) at this stage, and adopting the pharmacovigilance requirements to the small-scale scenario. A simplified procedure for ethical approval and GMP requirements should at least be considered.

3) The adoption of Article 5.1 of 2001/83/EC for ATMP should be encouraged in ALL MS

4) The interaction between Academia and Industry needs support (as provided by the FP7 programme, especially with SMEs), but also requires a better definition within the manufacturing trajectory.

5) ATMP development in the EU MUST address both pathways of development:

- commercially viable products and

- non-commercial products

6) It should be noted that a network of GMP-compliant academic/hospital units is being established across EU which work to same standards as "industry"

7) Legislators, regulators, funding bodies, universities and commercial sector must work together to develop this field, in collaboration with patients[6].

Munich, February 7, 2013

Martin Hildebrandt, M.D., and Dr Mark Lowdell, PhD FRCPath, on behalf of the

Academic GMP Research Consortium

[6] Bignami F, Kent AJ, Lipucci di Paola M, Meade N. Participation of patients in the development of advanced therapy medicinal products. *Bundesgesundheitsbl* 2011; 54: 839–842.