The Hospital Exemption for Advanced Therapies: the Regulator’s view

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Objectives of the ATMP Regulation

The overall policy objective is to improve patients’ safe access to advanced therapies by increasing the research, development and authorisation of gene therapy, somatic cell therapy, and tissue engineered products.

More specifically, the main objectives are:

- To guarantee a **high level of health protection** for European patients treated with advanced therapy products;
- To **harmonise market access** and to improve the functioning of the internal market by establishing a tailored and comprehensive regulatory framework for the authorisation, supervision and post-authorisation vigilance of advanced therapy products;
- To **foster the competitiveness** of European undertakings operating in this field;
- To provide overall legal certainty, while allowing for **sufficient flexibility at technical level**, in order to keep the pace with the evolution of science and technology.
Framework for ATMPs

Reg. 1394/2007/EC

Hospital exemption
Article 28, 1394/2007/EC: manufacturing licence for non-industrial (custom-made) ATMP products

New products

Products legally on national markets

> national MA?

Transitional period
ATMPs, other than TEP 30.12.2011

Marketing stopped

Centralised MAA

Courtesy of Dr. Ilona Reischl
Commission´s objectives for the HE

Advanced therapy medicinal products should be regulated in so far as they are intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process, within the meaning of Article 2(1) of Directive 2001/83/EC. Advanced therapy medicinal products which are both prepared in full and used in a hospital, in accordance with a medical prescription for an individual patient, should thus be excluded from the scope of the present Regulation.

- manufacturing licence for non-industrial (custom-made) ATMP production

→ for unmet medical needs / early product development

→ for rare conditions
"Hospital exemption" – products exempted from 2001/83/EC

Article 28, 1394/2007/EC:

• Any ATMP, ..., which is prepared
  - on a non-routine basis
  - according to specific quality standards, and
  - used within the same Member State
  - in a hospital
  - under the exclusive professional responsibility of a medical practitioner

• in order to comply with an individual medical prescription
  for a custom-made product for an individual patient

→ Manufacturing to be authorised by the MS competent authorities
→ National traceability and pharmacovigilance requirements
→ Specific quality standards ... as on the community level

• Currently under Commission evaluation (consultation and report Q1/2014)
National authorisation of ATMPs outside centralised MA

- Products nationally authorised under “hospital exemption” (art.28, Reg.1394/2007/EC)
- “Named patient” use (art.5 Dir.2001/83/EC)
- Compassionate use (art. 83 Reg. 726/2004/EC)
- Clinical trials (Dir. 2001/20/EC, under revision)
ATMP clinical trials in EU (EudraCT Database)

Maciulaitis, R. et al. (2012)
Molecular Therapy 20: 479-482
Manufacturing of ATMPs under hospital exemption requires:

- donation, procurement and testing of human cells and tissues according to FI Act on the Medical Use of Human Organs and Tissues
- if human blood or blood components are used, donation, procurement and testing according to FI Blood Service Act
- For genetically modified organisms, FI Act on gene technology to be followed
- production according to GMP (premises, equipment, personnel...)
- authorisation after assessment of the application with inspection of the manufacturing site (inspector + quality assessor, Fimea)
- pharmacovigilance follow-up
- traceability follow-up (registries)
- compliance with the quality requirements (any deviations to be reported), clarification on environmental aspects (gene therapy), clarification of the ethical aspects for the intended use

Finnish example - National Regulation 3/2009
Reporting

- Pharmacovigilance follow-up: serious adverse events must be reported to Fimea immediately, other AEs to be reported in an annual safety review.

- The manufacturer of the medicine is required to submit to Fimea an annual report concerning the advanced therapy medicinal products intended for the treatment of individual patients. The report is to be filed to Fimea by the end of March of the year following the year of manufacture. The report must provide the data identifying the medicine, the production volume, the number of patients treated with the preparation, the name of the physician prescribing the medicine and responsible for care, as well as any serious adverse incidents in the preparation of the medicine or any adverse reactions caused by it.
ATMP-KANSALLISEN VALMISTUSLUVAN HALTIJAT SUOMESSA

1. Regea Kudospelki ja Solukeskus, BioMediTech, Tampereen yliopisto
   www.regea.fi

2. Suomen Punaisen Ristin Veripalvelu Solutuotantokeskus, Helsinki
   www.veripalvelu.fi
First applications

- 4 Applicants (SME, University, Red Cross Blood Service)
- 2 applications for CBMPs, 2 for GTMPs
- First license was given for manufacture of an oncolytic virus preparation for treatment of solid tumours; the license was later withdrawn, as the Applicant proceeded to clinical trials. Second GTMP for ovarian cancer currently under evaluation
- The CBMP licenses are given for
  - allogeneic MSC-based product for treatment of GvHD
  - combinations of autologous MSCs with various biomaterials for maxillo-facial bone repair (applicant preparing for first clinical trial)
- All sites operate under full GMP
- License is specified for each manufacturer and may contain several products. Existing licenses can be amended to include additional products. However, the information and data specified in 3/2009 have to be provided for each product
EU wide experiences and feedback

✓ Different interpretations, variable national approaches

✓ Some NCAs request nonclinical or clinical data, no harmonised view on “non-industrial”, level of quality requirements unclear, exemption from what?

✓ In some MS products previously “legally on national markets” are now under HE??

✓ Too liberal approach can create even ATMP tourism, which cannot be prohibited by the others
EC consultation

✓ The number of contributions received was 63

✓ HE no 1. topic debated in the consultation – views both for and against the HE

✓ consensus in that the hospital exemption is an important tool to facilitate access of patients to new treatments for unmet medical needs

✓ Lack of a harmonised approach seen as a problem, conflict with industry; HE not acceptable if a licensed product available!

✓ concepts such as "non routine preparation" or "custom-made" be explained in the legislation

✓ legislation should clearly define the quality requirements
Conclusions

✓ From a regulatory point of view article 28 should be revised to avoid misinterpretation and national disharmonisation

✓ HE should be restricted to the original intended use, i.e. for early clinical development with focus on safety, especially in areas of unmet medical needs and for rare conditions where commercial interest is low

✓ Available for all developers, but not for export

✓ If patient exposure under proper framework, the results could support future MAA

✓ Clear harmonised rules and definitions
Thank you for your attention!