Regulation 1394/2007: the "hospital exemption" – Art. 28

- ✓ Excluded from the scope of the regulation
  - ATMP prepared in a non-routine basis (Art. 28(2))
    - Used within the same member state, in a hospital, for an individual patient
    - In that case : manufacturing is authorized by the MS. Traceability, pharmacovigilance requirements, specific quality standards at national level should be equivalent to the regulation
- ✓ "Hospital exempted products"
  - are still considered as medicinal products
  - Still considered as ATMP
  - Should be authorised by the National Competent authority
  - Following the same standards and criteria as for a marketing authorisation: *"Member States shall ensure that national traceability and pharmacovigilance requirements as well as the specific quality standards are equivalent to those provided for at Community level in respect of advanced therapy medicinal products*" (art. 28, Regulation)

Committee for Advanced Therapies (CAT)

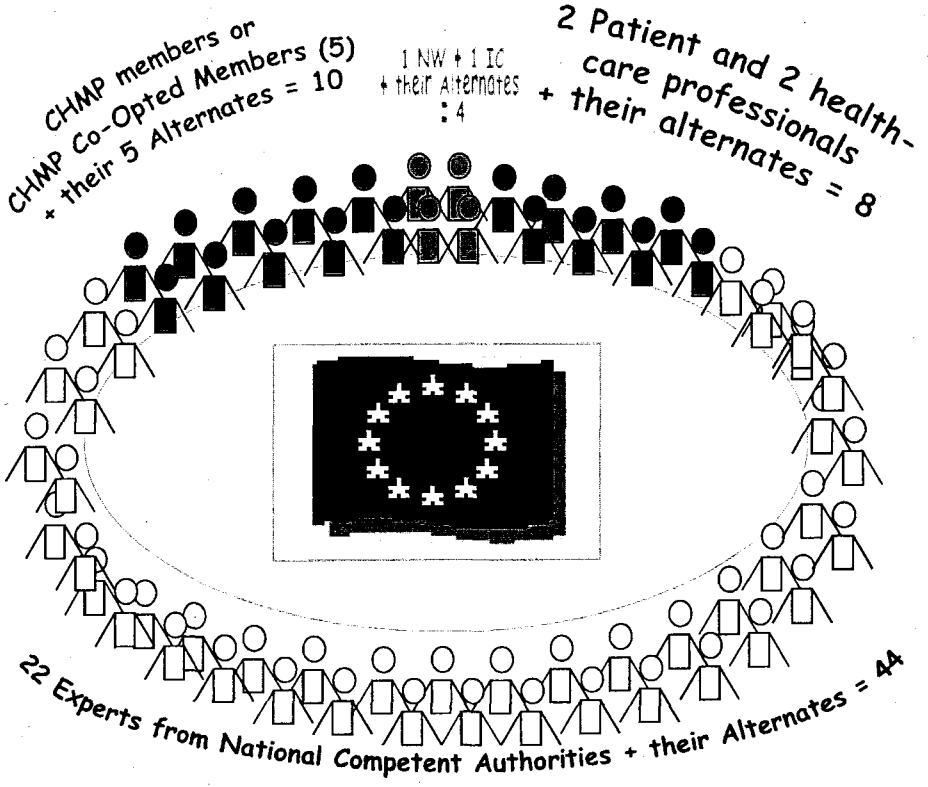
- ✓ New Committee within the EMEA
  - pooling of Community expertise
  - multidisciplinary nature:
    - biotechnology
    - medical devices
    - risk management
    - ethics
    - …
  - representation of Civil Society and Research Community

CAT COMPOSITION

CAT should covers the scientific areas relevant to advanced therapies, including:

- Medical devices [2+2 at least],
- Tissue engineering,
- Gene therapy,
- Cell therapy,
- Biotechnology,
- Surgery,
- Pharmacovigilance,
- Risk management and
- Ethics.

[Recital 9 & Art.21 of ATM Reg]



Presentation outlook

✓ CAT activities

- Dossier evaluation
- Classification
- Scientific advice
- Technical guidelines
- Certification

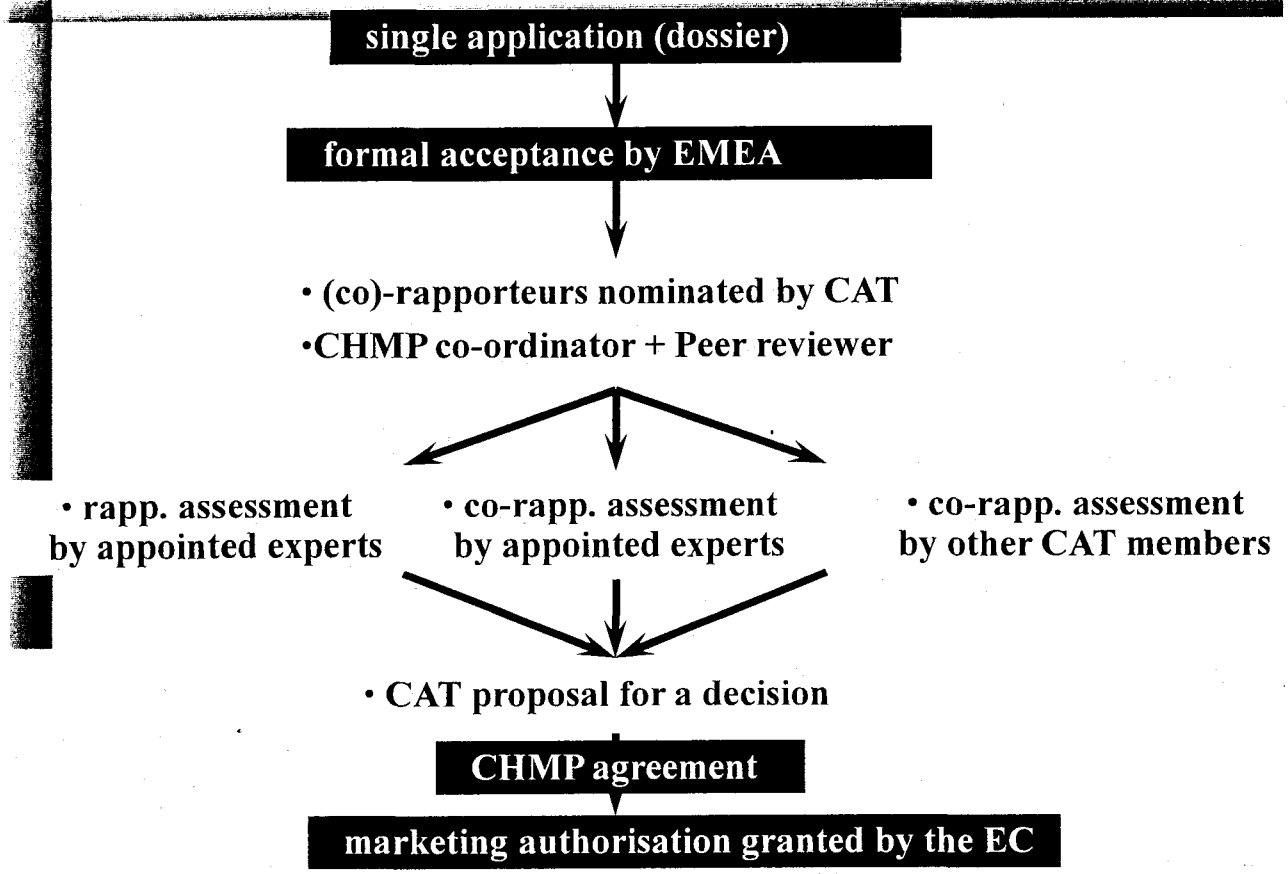
Tasks of the Committee for Advanced Therapies (art. 23)

- ✓ to formulate a draft opinion on the quality, safety and efficacy of an advanced therapy medicinal product for final approval by the CHMP → dossier evaluation
- ✓ to provide advice, on whether a product falls within the definition of an advanced therapy medicinal product → classification
- ✓ to advise on any medicinal product which may require, for the evaluation of its quality, safety or efficacy, expertise in one of the scientific areas → Scientific advice
- ✓ to assist scientifically in the elaboration of any documents related to the fulfilment of the objectives of this Regulation → criteria and guidelines

Tasks of the Committee for Advanced Therapies (art. 23)

- ✓ to formulate a draft opinion on the quality, safety and efficacy of an advanced therapy medicinal product for final approval by the CHMP → dossier evaluation

Assessment and draft opinion for authorisation



Tasks of the Committee for Advanced Therapies (art. 23)

- to provide advice, on whether a product falls within the definition of an advanced therapy medicinal product → classification

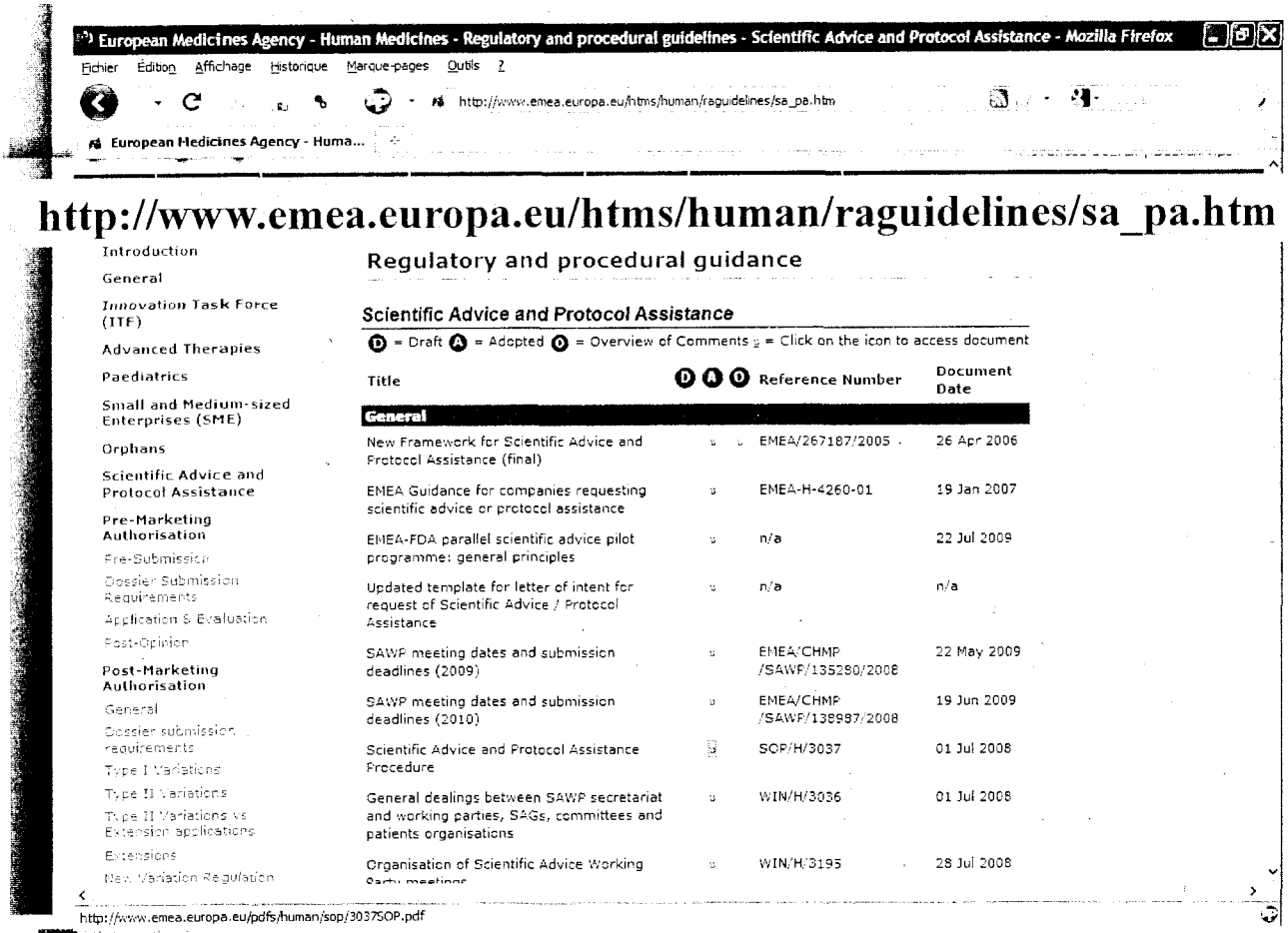
Scientific recommendation on advanced therapy classification (art. 17)

(b) to provide advice, pursuant to Article 17, on whether a product falls within the definition of an advanced therapy medicinal product;

- The CAT will answer the following questions for a given product submitted for classification:
  - Is it a biological ?
  - Is it a medicinal product
  - Is it an ATMP
  - What ATMP ?
- Within 60 calendar days following receipt of a valid request for scientific recommendation classification, the EMEA with involvement of the CAT, shall deliver its recommendation after consultation with the European Commission (EC).

Tasks of the Committee for Advanced Therapies (art. 23)

- to advise on any medicinal product which may require, for the evaluation of its quality, safety or efficacy, expertise in one of the scientific areas
  → Scientific advice



Tasks of the Committee for Advanced Therapies (art. 23)

to assist scientifically in the elaboration of any documents related to the fulfilment of the objectives of this Regulation → criteria and guidelines

New criteria and Guidelines

- Multidisciplinary approach
- Specific questions due to the nature of the products (Ethics, methodology, long term follow up, …)
- New concept and mechanisms to take onboard
- Adaptation of the current approaches both for the scientific criteria and production processes

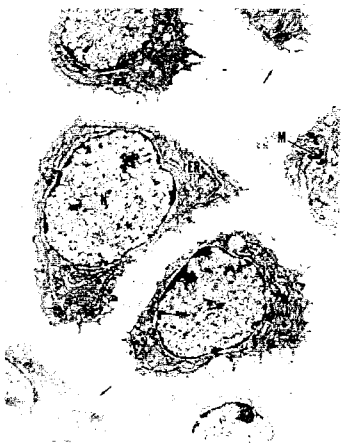
Examples of specific questions

- Quality
  - Impurities
  - Cells: Culture conditions and their impact on differentiation
  - Bioassay, characterisation and definition of the product
  - …..
- Safety
  - tissue cross-reactivity?
  - unwanted biodistribution?
  - toxicity studies: relevance of the experimental models (animal or in silico) ?
- Efficacy
  - Relevance of the clinical endpoints
  - additional safety measures required?
  - Immunogenicity
  - Long term follow-up
- Regulatory
  - How to find the correct regulatory routes for guidance documents (e.g. cell-based tumour vaccines)
  - How to deal with products that have already been used without evidence?
  - Regulation of long-term follow-up of efficacy
- Ethics
  - How to perform first-in-human trials?
  - How to deal e.g. with the risk of insertional mutagenesis?

Challenges with cell-based products

✓ Cells are complex systems

- Cells are dependent on their (micro-)environment
  - Species-specificity
  - Disease-specificity
- Cells are reactive to their environment
- Cell cultures can become heterogeneous
- Cells might de-differentiate (e.g. during longer cell culture)
- Cells might migrate („biodistribution")
- Cells are fragile and (sometimes) mortal



➢ **Regulatory consequences:**

√ Need for adequate characterization

√ but also necessity to accept limitations

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Need for a "risk-based" approach

✓ The following general risk criteria can be used in the estimation of the overall risk of the product:

- origin (autologous - allogeneic);
- ability to proliferate and differentiate;
- ability to initiate an immune response (as target or effector);
- level of cell manipulation (in vitro/ex vivo expansion / activation / genetic manipulation);
- mode of administration (ex vivo perfusion, local, systemic);
- duration of exposure (short to permanent);
- combination product (cells + bioactive molecules or structural materials)
- availability of clinical data on or experience with similar products.

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Tissues/cells [engineered] products – Tokyo – 25th August 2010

Technical Guidances available: Gene therapy

- Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products CPMP/BWP/3088/99 Apr 2001 Oct 2001
- Development and Manufacture of Lentiviral Vectors CHMP/BWP/2458/03
- Non-Clinical testing for Inadvertent Germline transmission of Gene Transfer EMEA/273974/05
- Development of a guideline on the quality, pre-clinical and clinical aspects of medicinal products containing genetically modified cells CHMP/GTWP/405681/06
- Non-clinical studies required before first clinical use of gene therapy medicinal products CHMP/GTWP/125459/06
- Scientific Requirements for the Environmental Risk Assessment of Gene Therapy Medicinal Products CHMP/GTWP/125491/06
- Environmental Risk Assessments for Medicinal Products containing, or consisting of, Genetically Modified Organisms (GMOs) (EMEA/CHMP/473191/06)
- Quality, non-clinical and clinical issues relating specifically to recombinat adeno-associated viral vectors CHMP/GTWP/587488/07
- Follow-up of patients administered with gene therapy medicinal products CHMP/GTWP/60436/07
- ICH Oncolytic Viruses CHMP/GTWP/607698/08
- ICH General Principles to Address Virus and Vector Shedding CHMP/ICH/449035/09

www.emea.europa.eu/htms/human/humanguidelines/biologicals.htm

Technical Guidances available: Cell therapy

- Human cell-based medicinal products CHMP/410869/06
- Points to Consider on Xenogeneic Cell Therapy CHMP/1199/02
- Potency testing of cell based immunotherapy medicinal products for the treatment of cancer CHMP/BWP/271475/06
- Revision of the Points to Consider on Xenogeneic Cell Therapy Medicinal Products CHMP/165085/07
- Xenogeneic Cell-based medicinal products CHMP/CPWP/83508/09
- Reflection paper on *In-Vitro* cultured chondrocyte containing products for cartilage repair of the knee CAT/CPWP/288934/09

www.emea.europa.eu/htms/human/humanguidelines/biologicals.htm

Certification of quality and non-clinical data (art. 18)

- ✓ Specific provision in the ATMP regulation (recital 25 and article 18)
- ✓ Incentive measure for small and medium-sized enterprises developing an advanced therapy medicinal product.
- ✓ submission to the Agency all relevant quality and, where available, non-clinical data required in accordance with modules 3 and 4 of Annex I to Directive 2001/83/EC, for scientific evaluation and certification.
- ✓ Speci

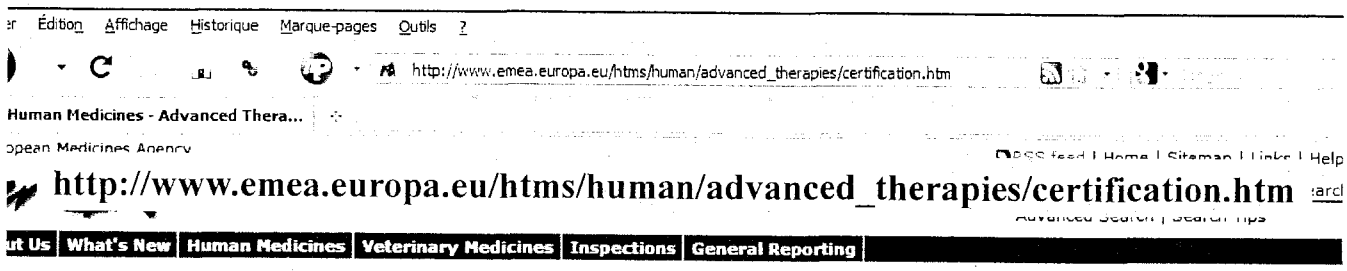
COMMISSION REGULATION (EC) No 668/2009

of 24 July 2009

implementing Regulation (EC) No 1394/2007 of the European Parliament and of the Council with regard to the evaluation and certification of quality and non-clinical data relating to advanced therapy medicinal products developed by micro, small and medium-sized enterprises

Objective of Certification Procedure

- ✓ Stand alone evaluation procedure
- ✓ Not directly binding for future MAA or Clinical trial application (CTA): Certificate will not replace any data to be submitted in MAA or CTA
- ✓ No Assessment of benefit/risk
- ✓ No Statements on appropriateness to enter into clinical trials
- ✓ No Prospective statements pertaining to the further development of the product: that is the role of Scientific Advice



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ommittee for Advanced herapies
AT Monthly Report

Certification procedure

The certification procedure is one of the new procedures provided for Advanced Therapy Medicinal Products (ATMPs) in the Regulation on Advanced Therapies (Article 18 of Regulation (EC) No 1394/2007). Commission Regulation (EC) No 668/2009 provides for implementing provisions for the certification procedure.

The certification procedure is the scientific evaluation by the CAT of quality and (where available) non-clinical data for ATMPs under development by Small and Medium-sized Enterprises (SMEs). Further to the scientific evaluation, EMEA will issue a certificate. A 90-day procedure has been developed for the evaluation and certification.

For more information on the procedure for certification and on the content of an application for ATMP certification, please consult following documents:

- Procedural advice on the Certification of quality and non-clinical data for small and medium-sized enterprises developing advanced therapy medicinal products (corr. 1 (23/09/09))
- Scientific Guideline on the minimum quality and non-clinical data for certification of advanced therapy medicinal products (corr. 1 (23/09/09))

Templates for the letter of intent to submit an application for ATMP certification and for the certification application form will be published shortly.

SMEs planning to submit an application for certification in the next months should contact

Contact Point

Questions relating specifically to the authorisation of advanced therapy medicinal products may be submitted to: AdvancedTherapies@emea.europa.eu

Conclusions

- ✓ Tissues and cells [engineered] products: two possible regulatory status in Europe, medicinal products or not
- ✓ New « advanced » products are now classified as medicinal products by EU regulation:
  - European centralised procedure for their authorisation prior marketing
  - European Scientific committee dedicated for their evaluation and proposal for authorisation
- ✓ For Tissues or Cells products, which are not classified as ATMP, considering their characteristics, not only in terms of benefit but also in terms of potential risk, it is important to regulate them, so that the patients, in the EU community, are offered reliable products and services.
  - EU Directive foresees the contribution of the National competent authorities at the various stages of the life cycle of those products

Acknowledgment

Afssaps

- Sandrine Jacob
- Dominique Labbé
- Sophie Lucas
- Pierrette Zorzi

EMEA

- Patrick Celis
- Lucia d'Apote
- Veronika Jekerle
- Elisa Pedone
- Marie-Hélène Pinheiro
- Christian Schneider (CAT Chair)
- Paula Salmikangas (CAT Vice Chair)