Advanced Therapy Medicinal Products:

recent experience with
- classification,
- scientific advice
- certification

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CAT Member

Disclaimer

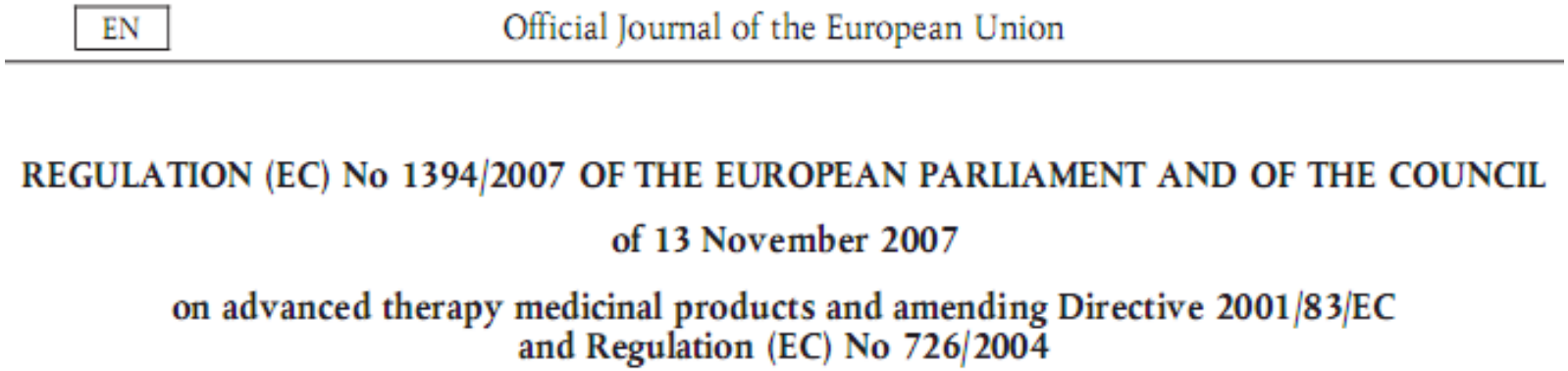
- ✓ Although being a member of EMA committees and working parties, my presentation might not be the view of the CHMP and the EMA, nor that of the French Medicines Agency (Afssaps).
- ✓ This presentation reflects only personal views and binds in no way the organisations mentioned above.

ATMPs

- ✓ Regulation 1394/2007
  - Definition of Advanced Therapy medicinal products
  - The Committee for Advanced Therapy Medicinal product (CAT)
- ✓ Focus on
  - Classification
  - Contribution to the Scientific Advice
  - Certification

Advanced Therapy Medicinal Products (ATMP)

- ✓ Regulation 1394/2007



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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

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(a) 'Advanced therapy medicinal product' means any of the following medicinal products for human use:

— a gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,

— a somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,

— a tissue engineered product as defined in point (b).

(b) 'Tissue engineered product' means a product that:

— contains or consists of engineered cells or tissues, and

— is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue.

Regulation 1394/2007

Article 1

Subject matter

This Regulation lays down specific rules concerning the authorisation, supervision and pharmacovigilance of advanced therapy medicinal products.

Article 2

Definitions

1. In addition to the definitions laid down in Article 1 of Directive 2001/83/EC and in Article 3, points (a) to (l) and (o) to (q) of Directive 2004/23/EC, the following definitions shall apply for the purposes of this Regulation:

(a) 'Advanced therapy medicinal product' means any of the following medicinal products for human use:

— a gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,

— a somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,

— a tissue engineered product as defined in point (b).

- ✓ Classifying tissue-based or cell-based products as medicinal products → pharmaceutical legislation applies in all aspects of the product life cycle:
  - Development and Clinical trials
  - GMP for the production/quality control
  - Pharmacovigilance
  - With additional requirements (long term follow up –art.14)
- ✓ EMA responsible for the regulatory framework
- ✓ One centralised Marketing Authorisation
- ✓ One scientific Committee to deal with the submission : CAT

Consequence of the regulation -1-

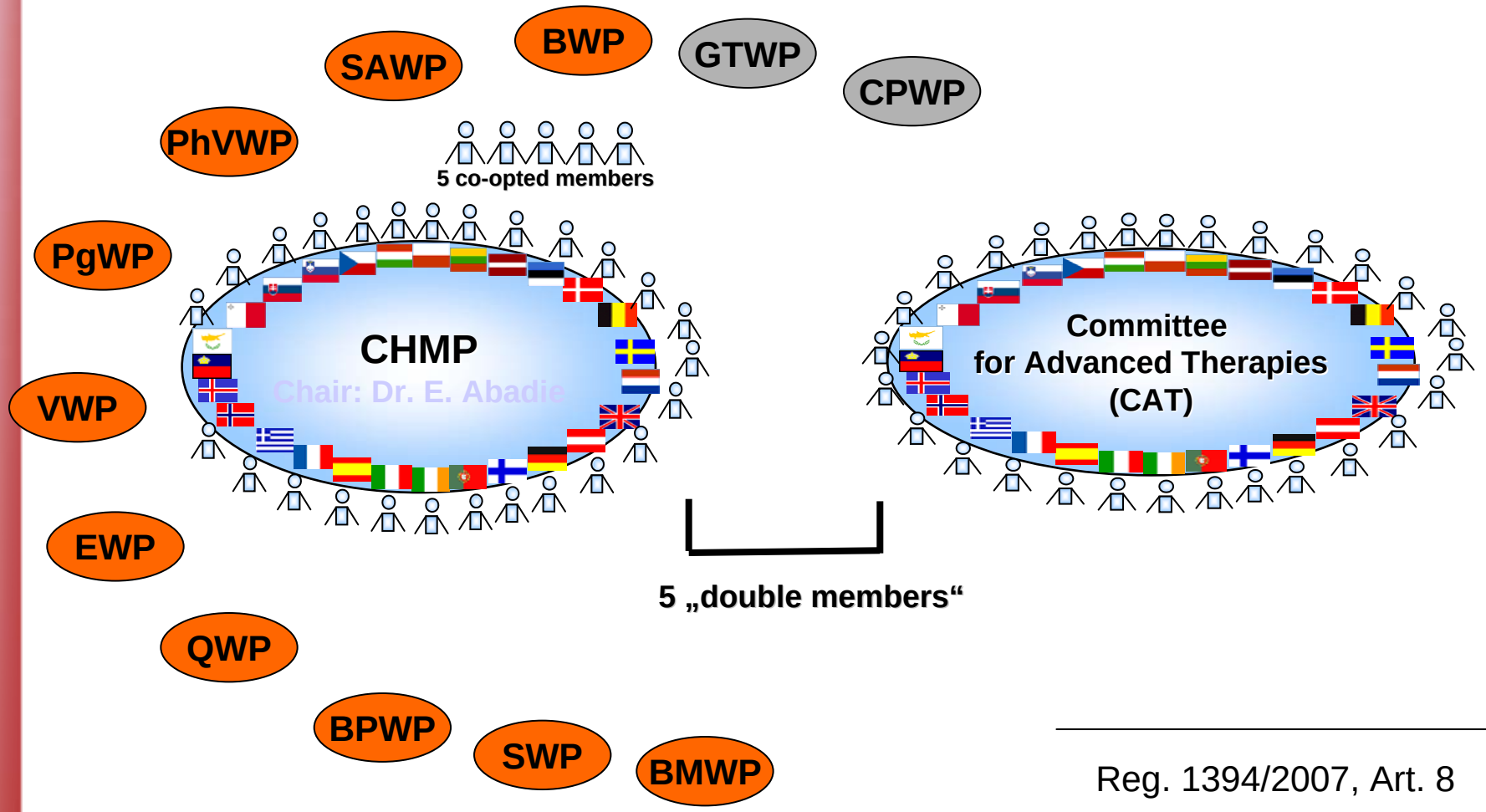
- ✓ For products within the scope:
  - No marketing without prior authorisation
  - Assessment of the Quality, Safety & Efficacy
  - Post-authorisation vigilance; specific obligation for safety and for efficacy
- ✓ Authorisation via the centralised procedure mandatory
- ✓ Same dossier as for a medicinal product (CTD) with technical adaptations)
- ✓ Combined products:
  - Assessment for both the MD and MP
  - If NB assessment exist=> obligation to submit it
  - If not=>EMEA seeks opinion, unless CAT decides it is not required.

Ref.: Articles 27-28 of the proposal

Consequence of the regulation -2-

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

CAT COMPOSITION
Interaction with other working parties



Reg. 1394/2007, Art. 8

Consequence of the regulation -3- Competitiveness Aspects

- ✓ SMEs: Certification of quality and non-clinical data
- ✓ Additional Fee reduction if applicant is SME or hospital and can prove there is a particular public health interest in the Community
  - 50% fee reduction on MA fee
  - 50% post-authorisation activities during one year
  - Applies only during transitional period

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

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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).

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Scientific Recommendation on classification of Advanced Therapy Medicinal Products Request Form and Briefing Information Article 17 - Regulation (EC) No 1394/2007

The letter of intent (at least one month prior to the start of the procedure) and the request for scientific recommendation should be sent to AdvancedTherapies@ema.europa.eu (no fee required).

Submission of scientific recommendation should follow the submission dates listing (link).

Please send this form in Word format as it is. Do not convert it to PDF.

Note that all the fields followed by a red asterisk (*) are mandatory. If any of the mandatory fields is missing, the request will not be processed.

Information on the Request*

Classification procedure

✓ The following **scientific information** are deemed as minimal, in order for the CAT to classify a product:

- Active substance: description of active substance including
  - starting materials,
  - any additional substances such as scaffolds, matrices, biomaterials, biomolecules
  - medical device or active implantable medical device).
- Finished Product:
  - qualitative & quantitative composition, pharmaceutical form
  - mode of administration,.
- Mechanism of Action / Proposed use:
  - claimed mechanism of action,
  - properties (including pharmacological, immunological or metabolic,
  - indication (including therapeutic, prophylactic, diagnostic).
- Summary of the status of the development
  - key elements of manufacturing, level of manipulations on cells and tissues
  - Outline of Non-Clinical development and Clinical development relevant for the ATMP classifification.

Classification procedure

- ✓ The CAT express itself on whether a product is an ATMP
  - Fulfilment of one of the definitions of gene therapy medicinal product, somatic cell medicinal product, tissue engineering or combined ATMP;
  - The CAT is not a classification body; hence, it cannot express opinions on whether a product is or is not a medicinal product.
  - The ATMP classification is a non-mandatory procedure that can be used by developers to clarify the applicable regulatory framework
- ✓ The ATMP classification helps
  - to position the product in the ATMP category,
  - To clarity on the development path and scientific-regulatory guidance to be followed
  - to clarify questions of borderline with other areas,
  - to open the door to other incentives designed for Advanced Therapies
- ✓ ATMP classification, in many cases has facilitated further dialogue with the Agency and the provision of guidance early in the development process and throughout the lifecycle of the product

Classification results

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Summaries of CAT scientific recommendations on ATMPs classification

Product Description	Therapeutic Area	Classification	Date
Allogeneic human fibroblasts cultured onto a biodegradable Matrix	Dermatology	Tissue engineered product - combined	04/04/2011
Medicinal product composed of living, genetically modified Lactococcus lactis bacteria, containing the human Trefoil Factor 1 (hTFF1) gene	Intended for prevention and treatment of Chemotherapy-Induced and/or Radiotherapy-Induced Oral Mucositis in patients with cancer of the head and the neck	Gene therapy medicinal product	08/02/2011
Lentiviral vector expressing the naturally occurring human anti-angiogenic proteins endostatin and angiostatin	Intended for treatment of age-related macular degeneration	Gene therapy medicinal product	30/11/2010

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000301.jsp&murl=menus/regulation

Classification results
From Jan. 2009 to May 2011

✓ 41 classification requests

- 11 classified as Gene therapy
- 15 classified as Cell based medicinal product including 1 combined
- 12 classified as Tissue engineered medicinal product including 3 combined

✓ 3 products have been considered as not an ATMP

1. product consisting of naturally occurring antigen-specific CD8+ donor lymphocytes isolated with streptamers → Intended for the treatment of infectious diseases
2. Mesenchymal stem cell-derived microvesicles → intended for the treatment of renal disease
3. Fresh and freeze-dried thrombocytes isolated from autologous or allogeneic blood → intended for wound healing in orthopedic or dental surgery

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Scientific advice

- ✓ At any time of the development of a medicinal product, the sponsor can seek, from EMA and its scientific committees, advice on technical/scientific questions
- ✓ Specific procedure, via the Scientific Advice Working party (SAWP)
- ✓ For ATMPs,
  - CAT will appoint coordinators to contribute to the responses
  - Discussion will take place at the CAT meeting,
  - Meeting with company when appropriate (CAT members attendance)
  - SAWP prepares the final report and response to the sponsor

Scientific advice

- ✓ Questions can be put on
  - Quality/biology → Discussion at the BWP and preparation of a report
  - Preclinical
  - Clinical
- ✓ The process is under management and supervision of SAWP
- ✓ CAT (and BWP) provide their input

Some examples: Quality questions -1-

- ✓ Does the Agency agree with the proposed definition of Drug Substance and Drug Product?
- ✓ Quality for an excipient of biological origin
  - Important in selecting, declaring and qualifying the supplier as any change in the quality profile of the excipient may impact the quality of the drug product
  - Regulatory aspects to be considered when using as excipient a plasma-derived medicinal product
    - Dossier to be submitted ?
    - Only batches subjected to official batch release may be used

Some examples: Quality questions -2-

- ✓ Are the proposed routine control tests relevant?
  - recommended to identify critical tests based on critical quality attributes.
  - proposed IPC and release tests should be based on the final commercial manufacturing process
- ✓ Use of non irradiated bovine serum
- ✓ Viral safety of the various reagents and raw materials used in the process

Some examples: Quality questions -3-

- ✓ Impurity profile
  - Does the Agency agree that the strategy for evaluation of impurities is adequate to support a marketing authorization application?
    - Product impurities (cells, cell debris, ..
    - Process related impurities
- ✓ Stability
  - Does the Agency agree that the proposed release and shelf-life testing strategy is appropriate to support a marketing authorization application

Some examples: Quality questions -4-

- ✓ Comparability issues:
  - Change introduced in the manufacturing process between phase II and Phase III clinical trial
  - Relevance of the “comparability protocol” : are the characterisation tests satisfactory and suitable to establish the comparability of the pre & post change products

Some examples: Quality questions -5-

- ✓ Biossay(s), potency assays
  - Need to correlate the acceptance criteria with clinical data
  - Need to establish a strong correlation between phenotypic markers and expected bioactivity (in vitro-in vivo correlation)
  - Demonstrate that potency characteristics remain unchanged in-between testing and administration
  - Investigate the possibility for inclusion of other phenotypic markers
- ✓ Use of “model cells” (from healthy donors) to validate some steps or characteristics when cells from patient are rare and cannot be wasted

Some examples: Quality questions Summary

- ✓ Quality
  - Characterisation of the product, quality attributes
  - Definition of the process, critical steps,
  - Comparability after a change is introduced between CTs
  - Selections of the release parameters
    - Case of the final products with a very short shelf life
  - Potency assay
  - Phenotypic markers
  - Cell bank strategy
  - Viral safety
- ✓ Complex products → efficacy/safety profile is also dependent on their quality attributes

Some examples: Safety, non clinical

- ✓ Need for an animal model
  - What studies to be performed for
    - An autologous situation
    - An allogeneic situation
    - Nb of “batches” to be tested in preclinical tests, to cover the patient variability
    - Relevance of using « model cells » when cells from the patients are not available for preclinical testing
- ✓ Need for a biodistribution study, what species?
- ✓ Questions are posed about :
    - Choice of most appropriate animal species – mice and minipigs?
    - Relevance of a given model for PoC
    - The acceptability to use only male animals,
    - The appropriateness of the proposed model to study germline transmission in the mini-pig

Some examples: Clinical -1-

- ✓ Issues to be clarified on Clinical development
  - The dose chosen for pivotal trials need further justification.
  - Primary outcome measure and clinical relevance and suitability to measure the success of treatment.
  - Pros and cons on various clinical trial designs
    - comparison against best supportive care
    - Superiority study versus treatment of reference
    - the patient as the own control.
  - choice of endpoint:
    - need for absolute response
    - need for greater emphasis on secondary outcomes
    - accept uncontrolled prospective study
  - Infeasibility of blinding
  - Adequacy of the proposed duration of follow-up

Some examples: Clinical -2-

✓Use of historical controls:

- The use of historical controls may be acceptable but would complicate the evaluation of the proposed primary efficacy variable
- Clinical endpoints would be preferred.
- Considering the clinical heterogeneity of some conditions, variability in the prognosis and the time course of disease it is recommended to focus on a limited spectrum disorders.

Some examples: Clinical -3-

- ✓ Does the agency agree that the safety data provided from the company's Phase I trial is adequate preliminary data to support a pivotal clinical study as part of a marketing-authorization application ?
- ✓ Does the agency agree that the proposed population is appropriate to support a pivotal clinical study as part of a marketing-authorization application (MAA)?
- ✓ Does the agency agree that the proposed primary and secondary endpoints are appropriate for to support a pivotal clinical study as part of a marketing-authorization application (MAA)?

Scientific advice
Summary

- ✓ Despite the broad spectrum of products under development, the questions are very common to all products, essentially on the main principles and criteria
  - Quality
  - Safety
  - Efficacy
- ✓ For the quality questions, they may be more « product related », whereas for clinical they are more « indication » orientated

Scientific advice Recommendations

- ✓ The Sc Ad procedure is NOT :
  - a pre-evaluation of the dossier to be submitted
  - a consultation with a consultant to get further input or suggestions on the development of the product → developer responsibilities
  - For getting an approval or assessment on a product for clinical trials → National competences
- ✓ The Sc Ad procedure is aimed at
  - Providing advice and recommendations on difficult technical issues where guidelines may be differently interpreted
  - Providing an opportunity to raise questions which are not covered in the existing guidelines
- ✓ Quality of the responses provided is largely dependent upon
  - the relevance and quality of the question(s) put
  - and the documentation provided to support the Company position

Scientific advice experience

- ✓ Since Jan. 2009
  - 48 sc advice procedures
    - 11 for Gene therapy
    - 24 for Cell-based products
    - 13 for tissue engineering
- ✓ Repartition of questions for Quality, Safety and Efficacy

Question On	Total	Gene therapy	Cell therapy	Tissue Eng. p
Q	3	1	2	
Q + S	6	2	3	1
Q + E	3	2	1	
Q + S + E	15	3	8	4
S	5	1	3	1
S + E	3	2	1	
E	12		5	7

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.
- ✓ Specific regulation adopted in July 2009

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

Scope of the certification evaluation

- ✓ to certify that the submitted data and relative testing methodologies followed by the applicant comply with the relevant scientific and technical requirement set out in the Annex I to Directive 2001/83/EC and adequately follows state-of-the-art scientific standards and guidelines.

  =>scientific evaluation of experimental data

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 on benefit/risk
- ✓ No Statements on appropriateness to enter into clinical trials
- ✓ No Prospective statements regarding further development of the product: role of Scientific Advice
- ✓ Aim at facilitating the dialogue with the regulatory authorities early in drug development.
- ✓ The assurance provided by the certification may help SMEs to attract investors and to raise more capital for the development (EMA press release).


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http://www.emea.europa.eu/htms/human/advanced_therapies/certification.htm
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Inspections
General Reporting
Introduction
Advanced Therapies Regulation
Regulatory and Procedural Guidance
Special procedures designed for ATMPs
ATMP Classificaton
Certification Procedure
Scientific guidelines
How to get support from the EMEA
Interested parties
See also:
Committee for Advanced Therapies
CAT 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

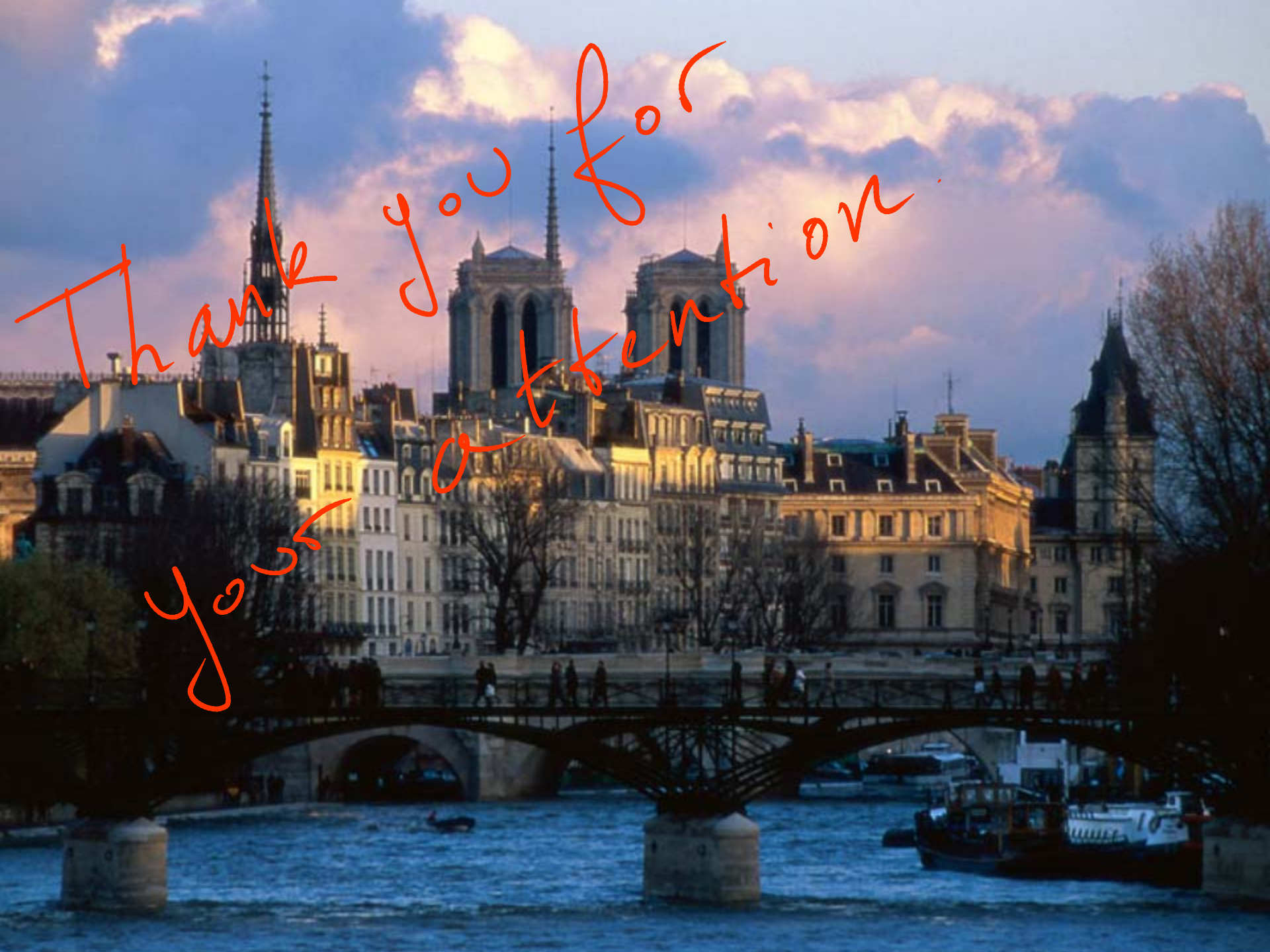
CAT experience with certification procedure

- ✓ Since Jan. 2009, one certification procedure has been achieved (EMA press release, May 2010)
  - The ATMP concerned
    - a suspension of mononuclear cells
    - proposed therapeutic use: acute myocardial infarction and chronic ischaemic heart disease

Conclusions

- ✓ New « advanced » products are now classified as medicinal products
- ✓ European centralised procedure for their authorisation prior marketing
- ✓ Scientific committee (CAT) dedicated for
  - assistance during development
  - evaluation and proposal for authorisation
- ✓ Take advantage of the various opportunities offered through
  - Classification
  - Scientific advice
  - Certification

to keep in contact with CAT, so as to facilitate mutual better understanding of the products under development.


Thank you for
your attention