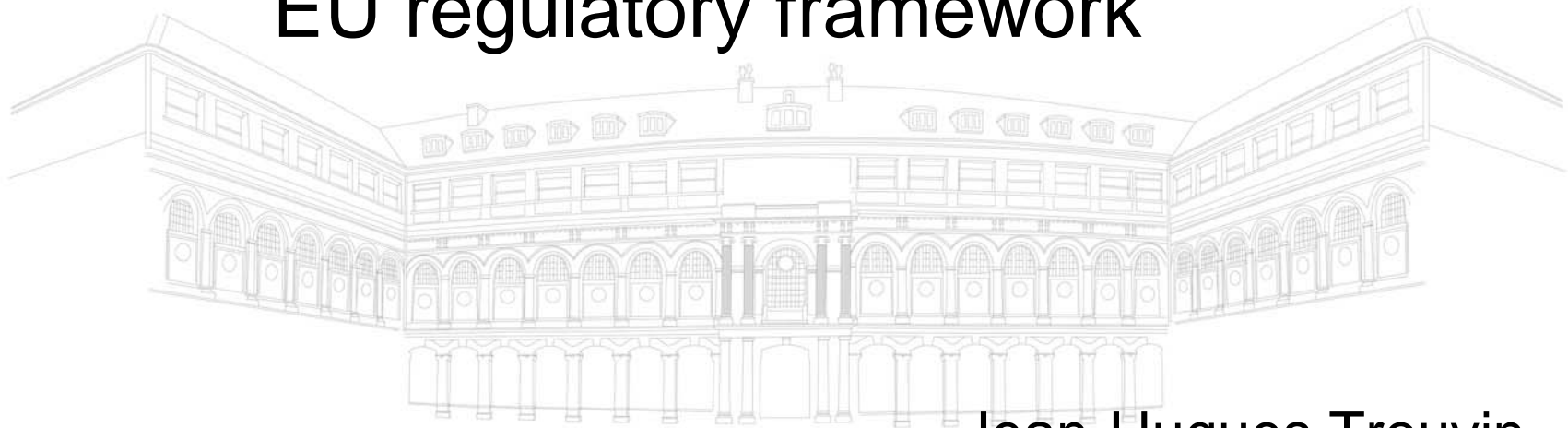


Advanced therapy medicinal products

EU regulatory framework



Jean-Hugues Trouvin

Faculté de Pharmacie- Université Paris Descartes
BWP Chairman, CAT member – EMEA, Londres

Outlook of the presentation

- ✓ Brief history
- ✓ Proposal and adoption of Regulation 1394/2007
- ✓ Consequences of the regulation
- ✓ The Committee for advanced therapy medicinal products CAT. Main tasks and missions

Brief history -1-

- ✓ New «products» emerged in the mid 90s:
 - Cell therapy products
 - Gene therapy products
- ✓ Not considered by the EU commission until 2003 → National regulations have developed, independently with various regulatory status:
 - medicinal products, medical devices, medicinal practice, etc.
- ✓ In 2003, EU commission proposed
 - a definition to cell therapy and gene therapy products
 - To qualify them as medicinal products
 - To create a new class of « advanced therapy medicinal products »

(Annex IV of directive 2003/63, modifying Dir. 2001/83)

COMMISSION DIRECTIVE 2003/63/EC

of 25 June 2003

amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use

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PART IV

ADVANCED THERAPY MEDICINAL PRODUCTS

Advanced therapy medicinal products are based on manufacturing processes focussed on various gene transfer-produced bio-molecules, and/or biologically advanced therapeutic modified cells as active substances or part of active substances.

For those medicinal products the presentation of the Marketing Authorisation application dossier shall fulfil the format requirements as described in Part I of this Annex.

Brief history -2-

✓ Original (2003) definitions

1. GENE THERAPY MEDICINAL PRODUCTS (HUMAN AND XENOGENEIC)

For the purposes of this Annex, gene therapy medicinal product shall mean a product obtained through a set of manufacturing processes aimed at the transfer, to be performed either *in vivo* or *ex vivo*, of a prophylactic, diagnostic or therapeutic gene (i.e. a piece of nucleic acid), to human/animal cells and its subsequent expression *in vivo*. The gene transfer involves an expression system contained in a delivery system known as a vector, which can be of viral, as well as non-viral origin. The vector can also be included in a human or animal cell.

2. SOMATIC CELL THERAPY MEDICINAL PRODUCTS (HUMAN AND XENOGENEIC)

For the purposes of this Annex, somatic cell therapy medicinal products shall mean the use in humans of autologous (emanating from the patient himself), allogeneic (coming from another human being) or xenogeneic (coming from animals) somatic living cells, the biological characteristics of which have been substantially altered as a result of their manipulation to obtain a therapeutic, diagnostic or preventive effect through metabolic, pharmacological and immunological means. This manipulation includes the expansion or activation of autologous cell populations *ex vivo* (e.g., adoptive immuno-therapy), the use of allogeneic and xenogeneic cells associated with medical devices used *ex vivo* or *in vivo* (e.g., micro-capsules, intrinsic matrix scaffolds, bio-degradable or not).

Brief history -3-

- ✓ However, other new « products » continued to emerge and particularly « combined products » and « tissue engineered products »
- ✓ Products « borderline » with medicinal products, autologous products and transfusion practice, medical devices, ...
- ✓ Need to have a EU regulatory position
 - What status: medical device, medicinal product, new status
 - What scientific criteria to apply for authorisation and follow up after marketing
 - What regulatory body(ies) should be responsible

National regulations for ATMPs

Commission survey (2005)

Country		Austria	Belgium	Bulgaria	Cyprus	Finland	France	Germany	Ireland	Netherlands	Poland	Slovakia	Spain	Sweden	UK
framework	not at all			●●	●●				●●	●●	●●	●			
	as medicinal product (MP)	●●	●●			●●		●●							
	as medical device (MD)														
	as MP or MD, decided on case-by-case basis												●●	●●	●●
	specific national guidance						●●								●●
	other regulations	●●											●		
authorisation	by product authorisation (PA)		●					●							
	by manufacturing authorisation (MA)	●●	●					●●							
	by accreditation... of the tissue establishment		●●									●			
	by PA and MA						●●	●					●●		
import	from EU MS mandatory through accredited... tissue establishment in your country		●●				●●					●	●●		
	from non-EU country mandatory through accredited... tissue establishment in your country		●●				●●					●	●●		

● autologous products

● allogeneic products

ATMPs are heterogenous

- ✓ cell-base immunotherapy of cancer
- ✓ proliferating and differentiating cells (SC, MSC)
 - cells differentiating in vitro or in vivo
- ✓ cell-products containing genetically modified cells
 - tracing, enhancing, secreting
- ✓ Autologous, allogeneic, xenogeneic origin of the “donor”
- ✓ Gene transfer products
- ✓ bone, cartilage or skin repair
 - autologous or allogenic cells or tissue
 - combined with growth factors and
 - biocompatible scaffolds/lattices
- ✓ endocrine cells
- ✓ “artificial tissues” and “artificial organs”
 - biomaterials, biomolecules,
 - ex vivo, in vivo use
 - sophisticated devices

Advanced Therapies



Commission proposal

Principles of existing legislation on medicines apply
to advanced therapies

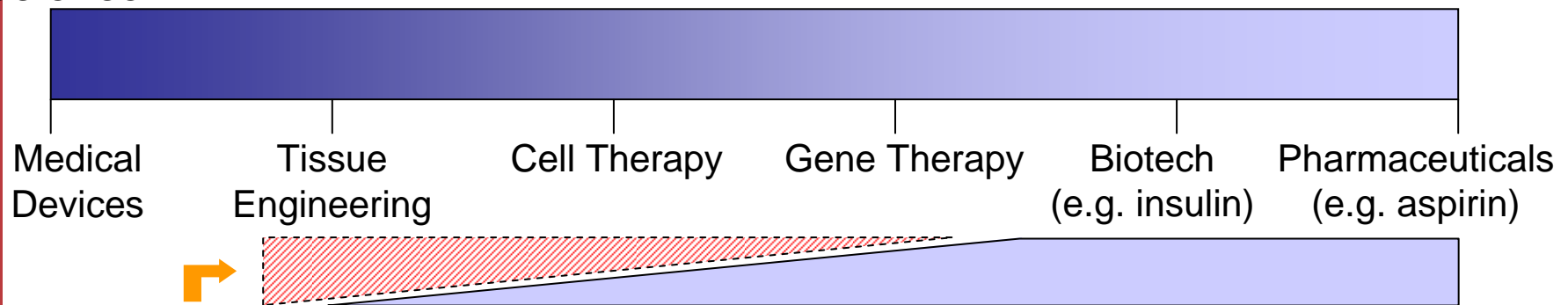
Legislation

Medical
Devices
93/42/EEC

Medicinal
Products
2001/83/EC

Advanced Therapies

Science



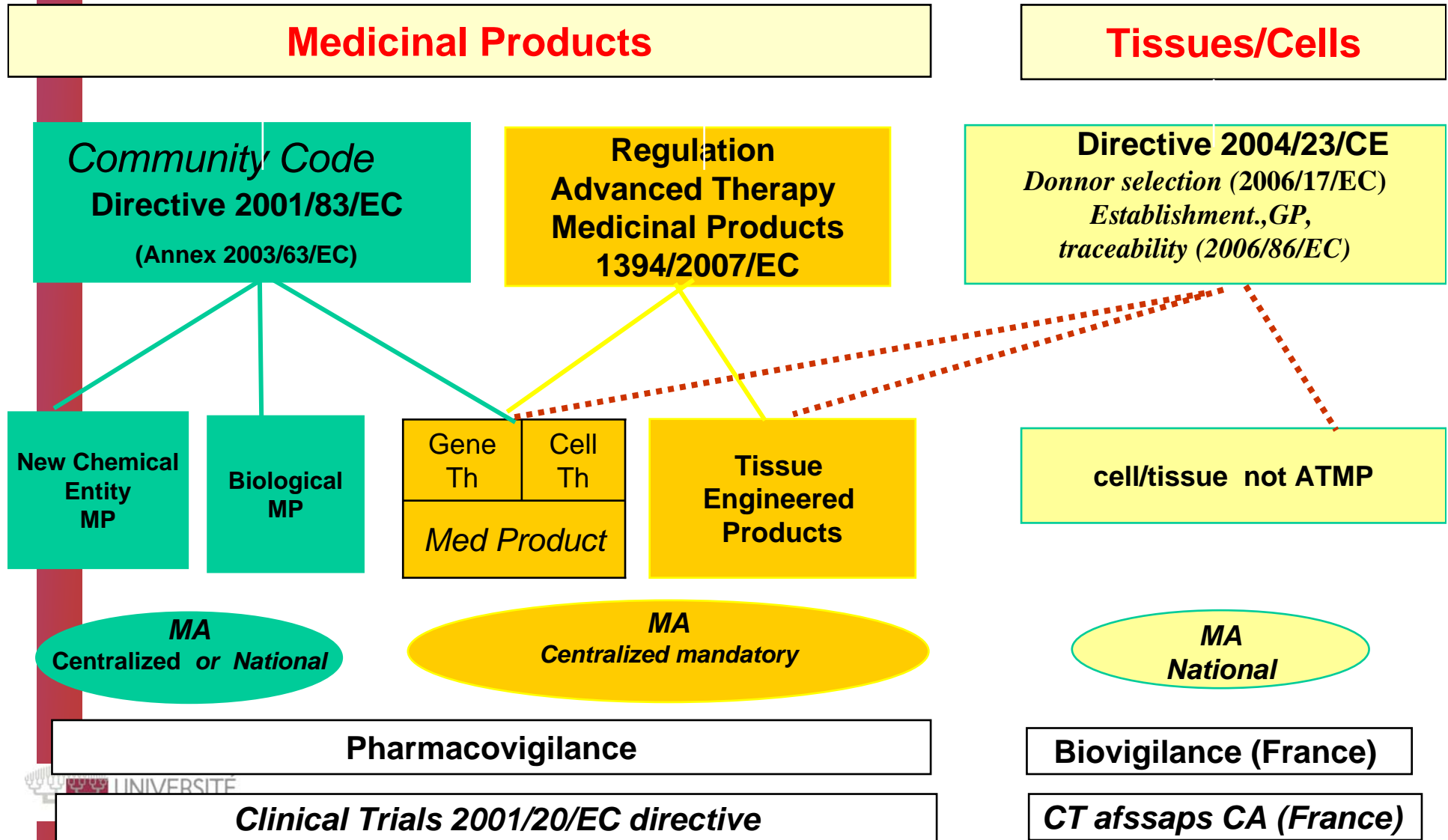
**NEW Committee for
Advanced Therapies
(CAT)**

Specific expertise

**CHMP
expertise**

N. Rossignol, by permission

Advanced Therapies Medicinal Products Regulatory Framework Overview



Commission regulation 1394/2007

Overarching principles and goals

- ✓ Bridge the regulatory gap: « lex specialis » regulation to complete regulation 726/2004 and directives (2001/83/CE + 2003/63/CE)
- ✓ Ensure coherence with existing frameworks
- ✓ Do not reinvent the wheel
- ✓ To provide legal certainty, while allowing for sufficient technical flexibility to keep the pace with science
- ✓ To harmonise and facilitate market access
- ✓ To foster the competitiveness of the Biotechnology industry
- ✓ While guaranteeing a high level of health protection

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****CHAPTER 1****SUBJECT MATTER AND DEFINITIONS***Article 1***Subject matter**

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

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**

(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.

Updated definition of Gene Therapy

Gene therapy medicinal product means a biological medicinal product which has the following characteristics:

- ✓ (a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;
- ✓ (b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

Gene therapy medicinal products shall not include vaccines against infectious diseases.

Updated definition of Cell Therapy

Somatic cell therapy medicinal product means a biological medicinal product which has the following characteristics:

- ✓ (a) contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, **or** of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor;
- ✓ (b) is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.

For the purposes of point (a), the manipulations listed in Annex I to Regulation (EC) No 1394/2007, in particular, shall not be considered as substantial manipulations.

Definition introduced for Tissue Engineered Product

(Reg. 1394/2007)

✓ 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.
- May contain cells or tissues of human or animal origin or both. May be viable or non-viable. May also contain additional substances (cellular products, bio-molecules, bio-materials, chemical scaffold or matrices).”
- Engineered cells or tissues fulfil at least one of the requirements :
 - subject to substantial manipulations so that their original biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved (the list of non substantial manipulations is appended)
 - are not intended to be used for the same essential functions in the recipient as in the donor”

Tissue engineered products (Reg. 1394/2007)

- ✓ Tissue Engineered Product
 - contains or consists of engineered cells or tissues (human or animal origin)
 - cells may be viable or non viable
 - may also contain additional substances :cellular products, biomolecules, biomaterials, chemical substances, scaffold, matrices
 - is presented as having properties for, or is used in, or administer to human being with a view to regenerating, repairing or replacing a human tissue
 - Products containing or consisting exclusively of non-viable human or animal cells and/or tissues, which do not contain any viable cells or tissues and which do not act principally by pharmacological, immunological or metabolic action, shall be excluded from this definition.

- ✓ Combined products : Combination product containing viable cells and medical devices : regulated under this new regulation

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.

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

Consequence of the regulation -3-

✓ Technical requirements:

- Pre-authorisation:
 - Compliance with 'Essential Requirements' for products incorporating medical devices
 - Specific guidelines on
 - GMP (Good Manufacturing Practice)
 - GCP (Good Clinical Practice) → EC consultation
 - Specific rules for labelling/packaging
- Post-authorisation requirements
 - Follow-up of efficacy and adverse reactions, and risk management: obligation for EMEA to inform relevant device/tissue national authorities
 - Traceability

GCP and Advanced therapy medicinal products



EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

IMPLEMENTATION OF THE 'ADVANCED THERAPIES' REGULATION
Regulation (EC) No 1394/2007

PUBLIC CONSULTATION PAPER

**DRAFT DETAILED GUIDELINE ON GOOD CLINICAL PRACTICE
SPECIFIC TO ADVANCED THERAPY MEDICINAL PRODUCTS**

Version: 2 July 2008

Deadline for Public Consultation: 15 October 2008

Consequence of the ATMP regulation on Clinical trial application forms



EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

IMPLEMENTATION OF THE 'ADVANCED THERAPIES' REGULATION
Regulation (EC) No 1394/2007

PUBLIC CONSULTATION PAPER

**DRAFT AMENDMENTS TO THE CLINICAL TRIAL APPLICATION FORM AS REGARDS
ADVANCED THERAPY MEDICINAL PRODUCTS**

Version: 22 July 2008

Deadline for Public Consultation: 15 October 2008

Consequence of the regulation -4-

- ✓ Article 14 (1) of Regulation (EC) No 1394/2007 requires the MAA to submit:
“the measures envisaged to ensure the follow-up of efficacy of advanced therapy medicinal products and of adverse reactions thereto.”
 - Pharmacovigilance plan
 - Efficacy follow-up plan

Pharmacovigilance and Long-term follow up



London, 20 November 2008
Doc. Ref. EMEA/149995/2008

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)

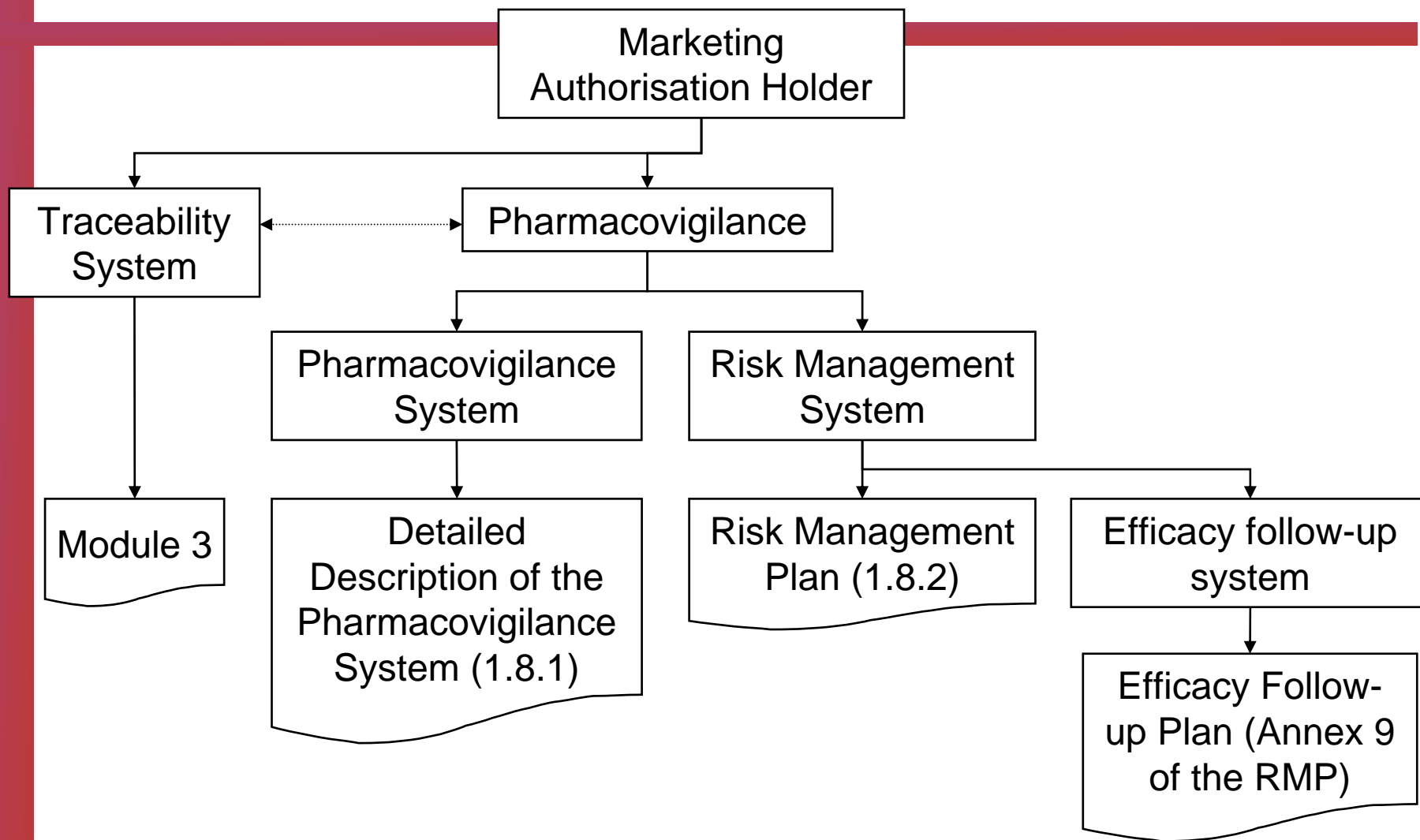
GUIDELINE ON SAFETY AND EFFICACY FOLLOW-UP - RISK MANAGEMENT OF ADVANCED THERAPY MEDICINAL PRODUCTS

DRAFTING GROUP DISCUSSION	December 2007 to February 2008
DISCUSSION IN GTWP, CPWP, PHWVP	February and March 2008
DISCUSSION AND ADOPTION OF THE DRAFT BY CHMP	March and April 2008
RELEASE FOR PUBLIC CONSULTATION	May 2008
END OF PUBLIC CONSULTATION (DEADLINE FOR COMMENTS)	15 August 2008
DRAFTING GROUP DISCUSSION ON COMMENTS	August and September 2008
DISCUSSION OF COMMENTS IN GTWP, CPWP, PHWVP, AND PRESENTATION TO BWP	September and October 2008
ADOPTION BY CHMP	November 2008
DATE FOR COMING INTO EFFECT	31 December 2008

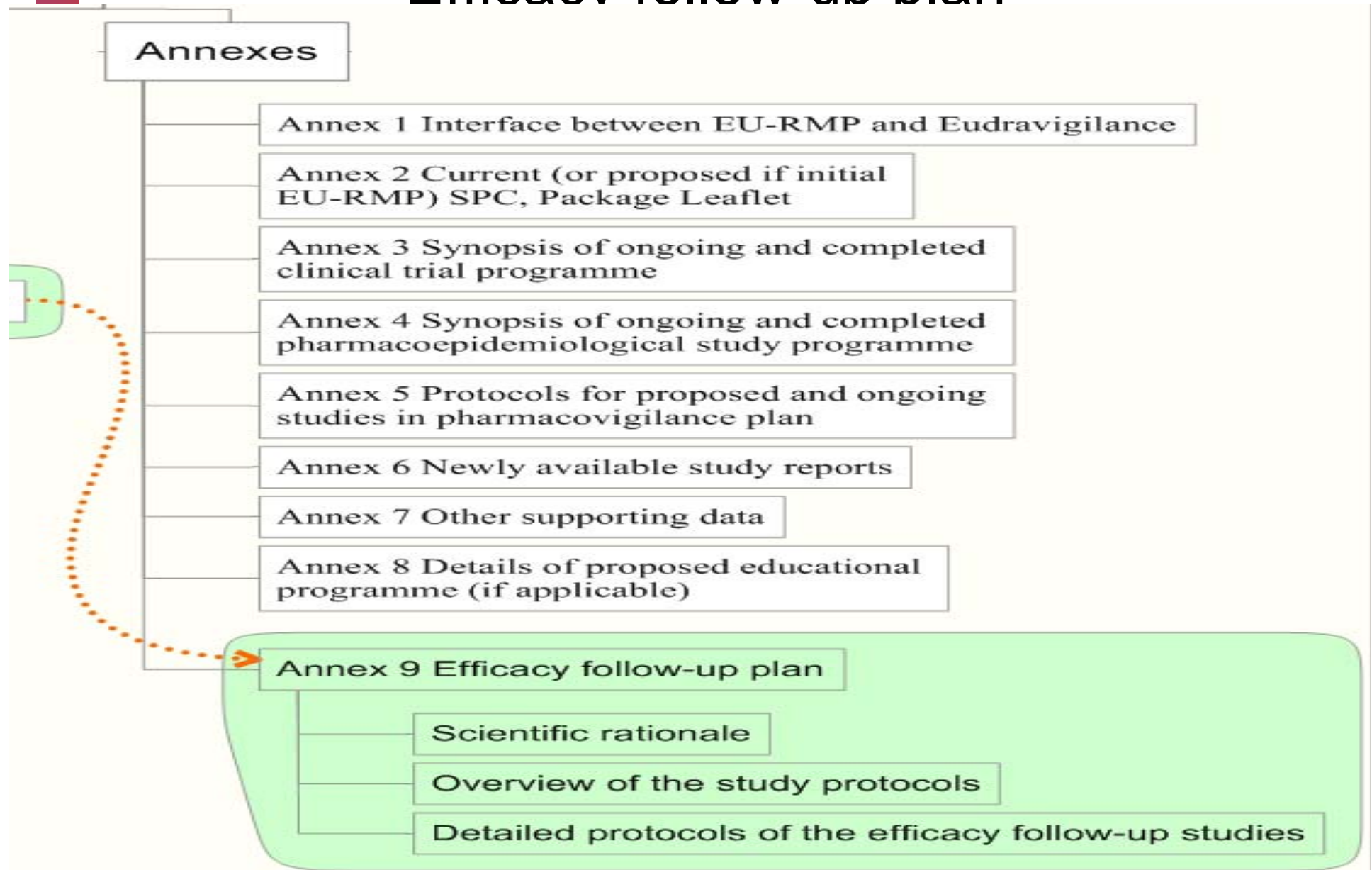
Elements of the guideline « follow-up »

- ✓ This guideline describes specific aspects of pharmacovigilance, risk management planning, safety and efficacy follow-up of authorised ATMPs, as well as some aspects of clinical follow-up of patients treated with such products.
- ✓ To detect early signals of delayed adverse reactions, to prevent clinical consequences of such reactions and to ensure timely treatment and to gain information on the long-term safety and efficacy of the intervention.
- ✓ The follow-up recommendations take into consideration the risk profile of the ATMP, the disease, co-morbidity and the patient target population and characteristics.

Place in the dossier



Efficacy follow-up plan



Regulation 1394/2007: the exclusions

- ✓ Excluded from the definition TEP
 - Product containing or consisting of non viable cells/tissues, which do not act principally by pharmacological, immunologically or metabolic actions

- ✓ 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
 - Exclusion if national legislation prohibits or restricts the use of any specific type of human or animal cells, or the sale, supply or use of medicinal products containing, consisting of or derived from these cells, on grounds not dealt with in the aforementioned Community legislation (Art. 28(3))

Transitional period

- ✓ Regulation shall enter into force 30 December 2008
- ✓ ATMPs other than tissue engineered products, which were legally on the Community market on 30 December 2008, shall comply with this Regulation no later than 30 December 2011.
- ✓ Tissue engineered products comply with this Regulation no later than 30 December 2012
- ✓ Any question (classification, certification, scientific advice) can be put to the EMEA which will coordinate the discussion with CAT (see below)

Competitiveness Aspects

Specific provisions (SMEs, hospitals)

- ✓ 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

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

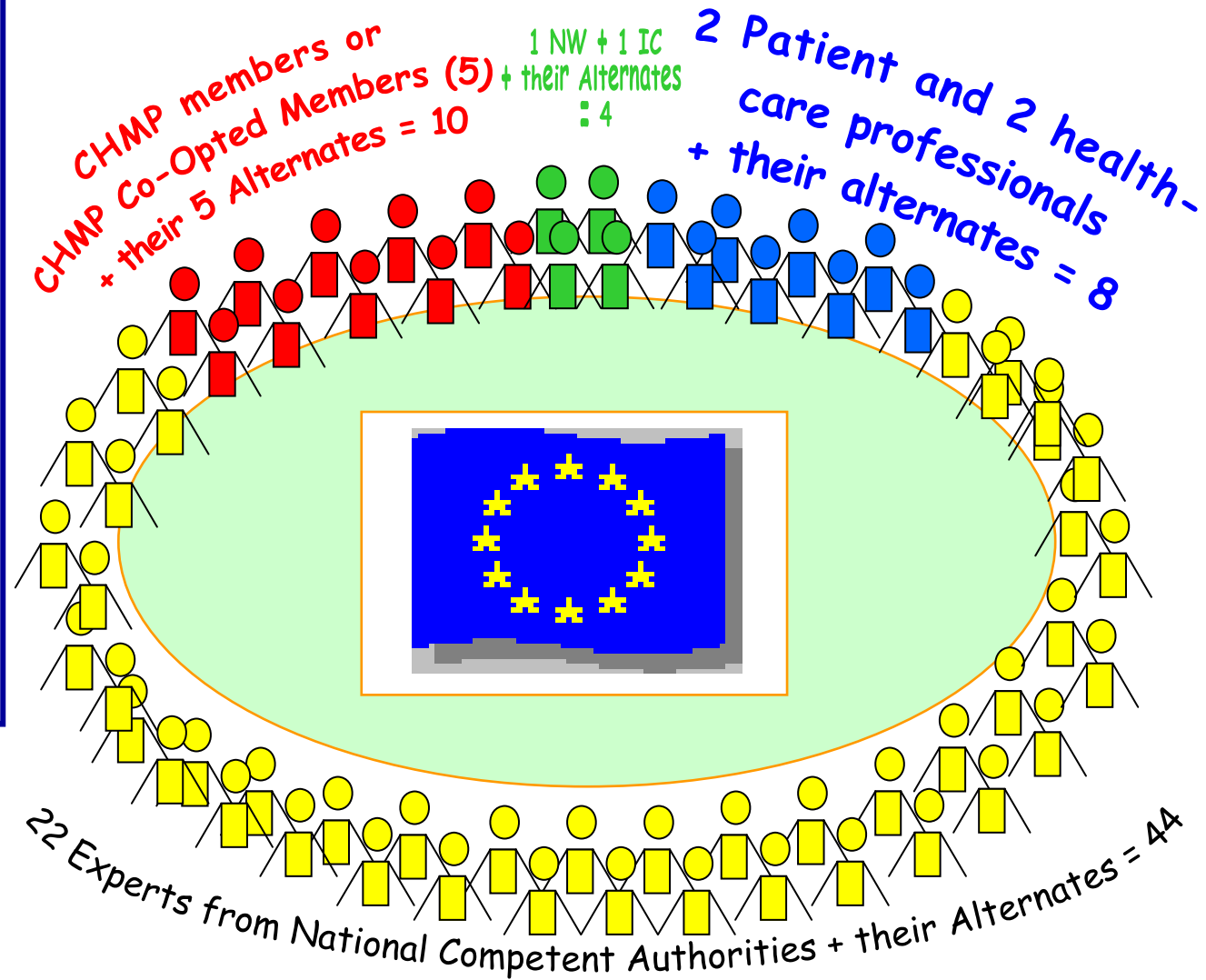
CAT COMPOSITION

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

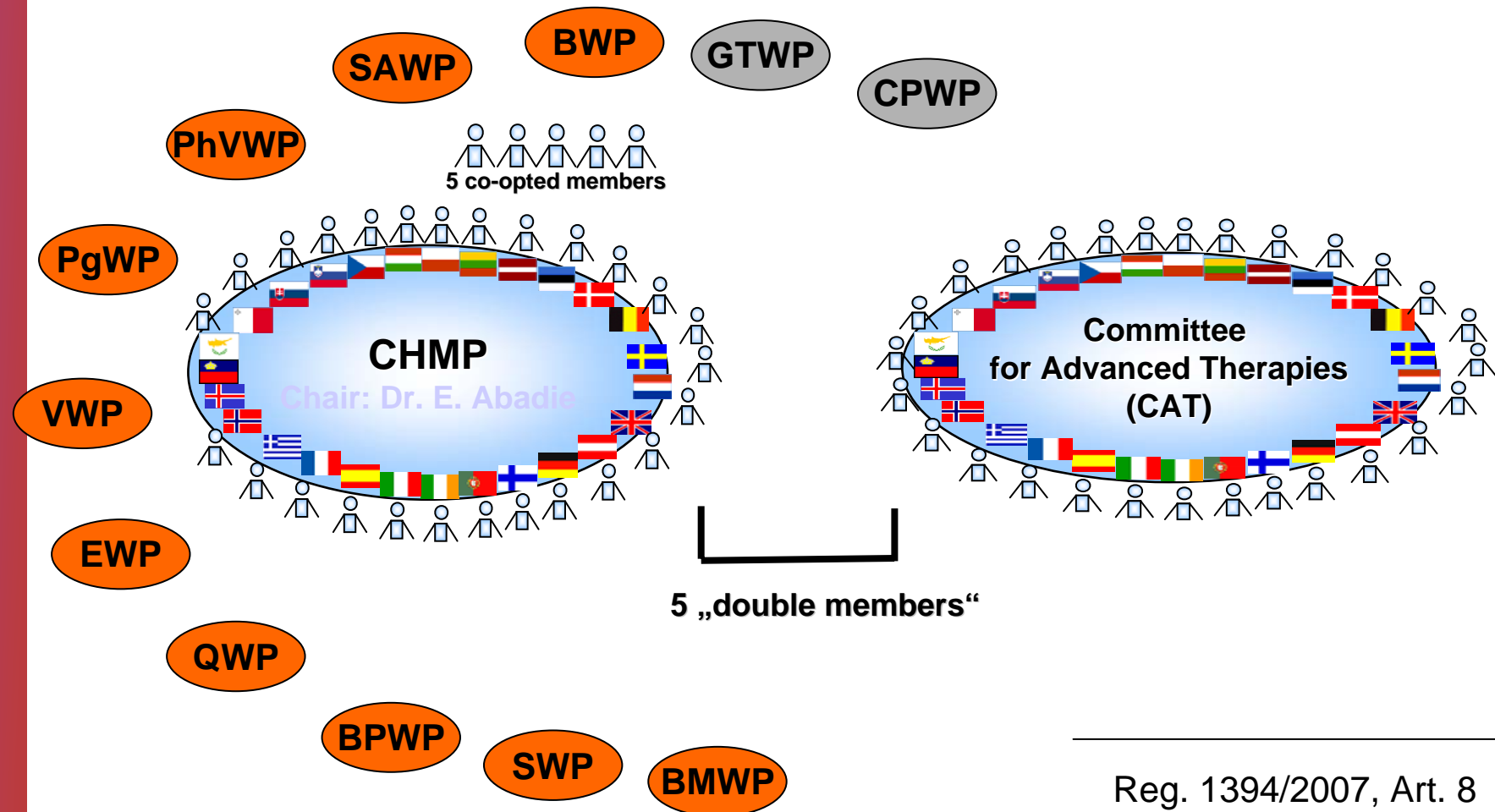
- Medical devices
 - Tissue engineering,
 - Gene therapy,
 - Cell therapy,
 - Biotechnology,
 - Surgery,
 - Pharmacovigilance,
 - Risk management
- and
- Ethics.

[2+2 at least],

[Recital 9 & Art.21 of ATM Reg]



CAT and other scientific committees and working parties at the EMEA



Reg. 1394/2007, Art. 8

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
- ✓ Miscellaneous:
 - to provide advice on any question related to advanced therapy medicinal products, at the request of the Executive Director of the Agency or the Commission;
 - to provide scientific expertise and advice for any Community initiative related to the development of innovative medicines and therapies which requires expertise in one of the scientific areas
 - to contribute to the scientific advice procedures referred to in Article 16 of this Regulation and in Article 57(1)(n) of Regulation (EC) No 726/2004.

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

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Assessment and draft opinion for authorisation

• **single application (dossier)**

• **formal acceptance by EMEA**

• **(co)-rapporteurs nominated by CAT**
• **CHMP co-ordinator + Peer reviewer**

• **rapp. assessment
by appointed experts**

• **co-rapp. assessment
by appointed experts**

• **co-rapp. assessment
by other CAT members**

• **CAT proposal for a decision**

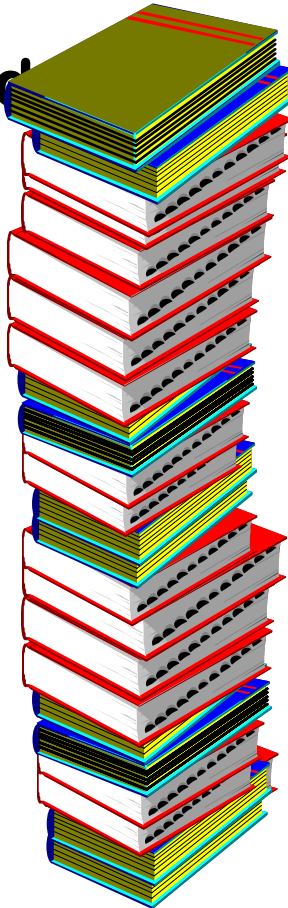
• **CHMP agreement**

• **marketing authorisation granted by the EC**

The centralised procedure (1)

Dossier submitted

CTD Modules 1 to 5



EMA meeting, if needed

**Rapporteur/
Co-Rapporteur
Evaluation
team**

**EMA
support**

**Initial Assessment reports
(by day 70)**

EMA/CHMP

Applicant

.../... contd

The centralised procedure (2)

Day 80: Assessment reports circulated

Overview of scientific data

+

Overall

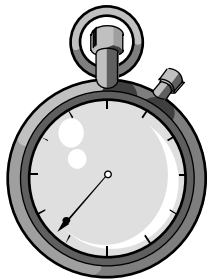
conclusions/recommendations

+

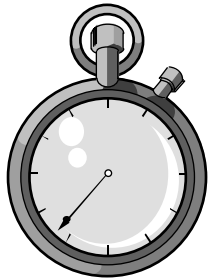
Consolidated list of questions

(Q, S, E, SPC, Labelling, PL)

Day 120



CLOCK OFF



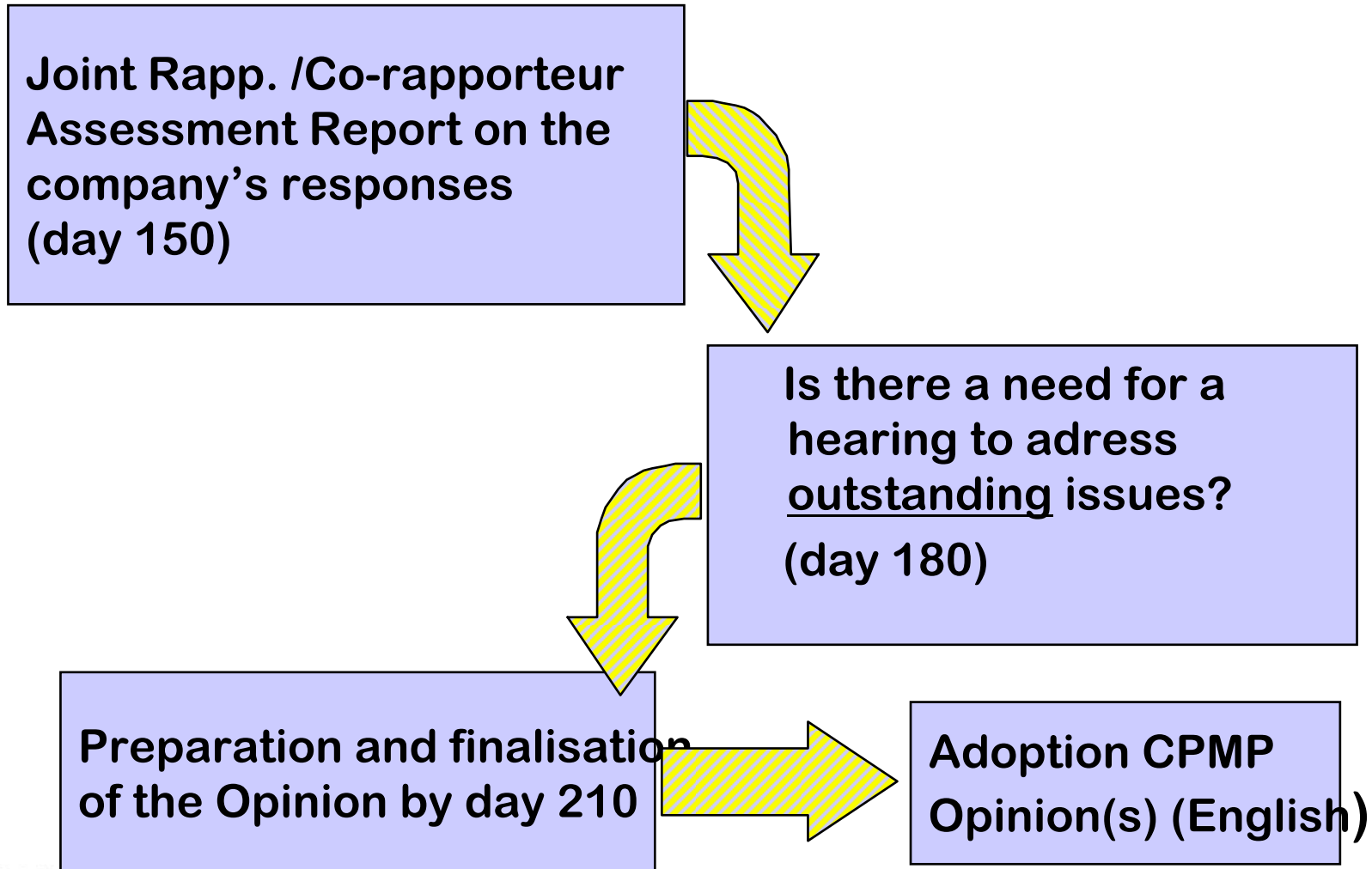
CLOCK ON

Day 121

Company's responses within 6 months:

- **revised SPC/Lab/PL**
- **“mock-ups”**

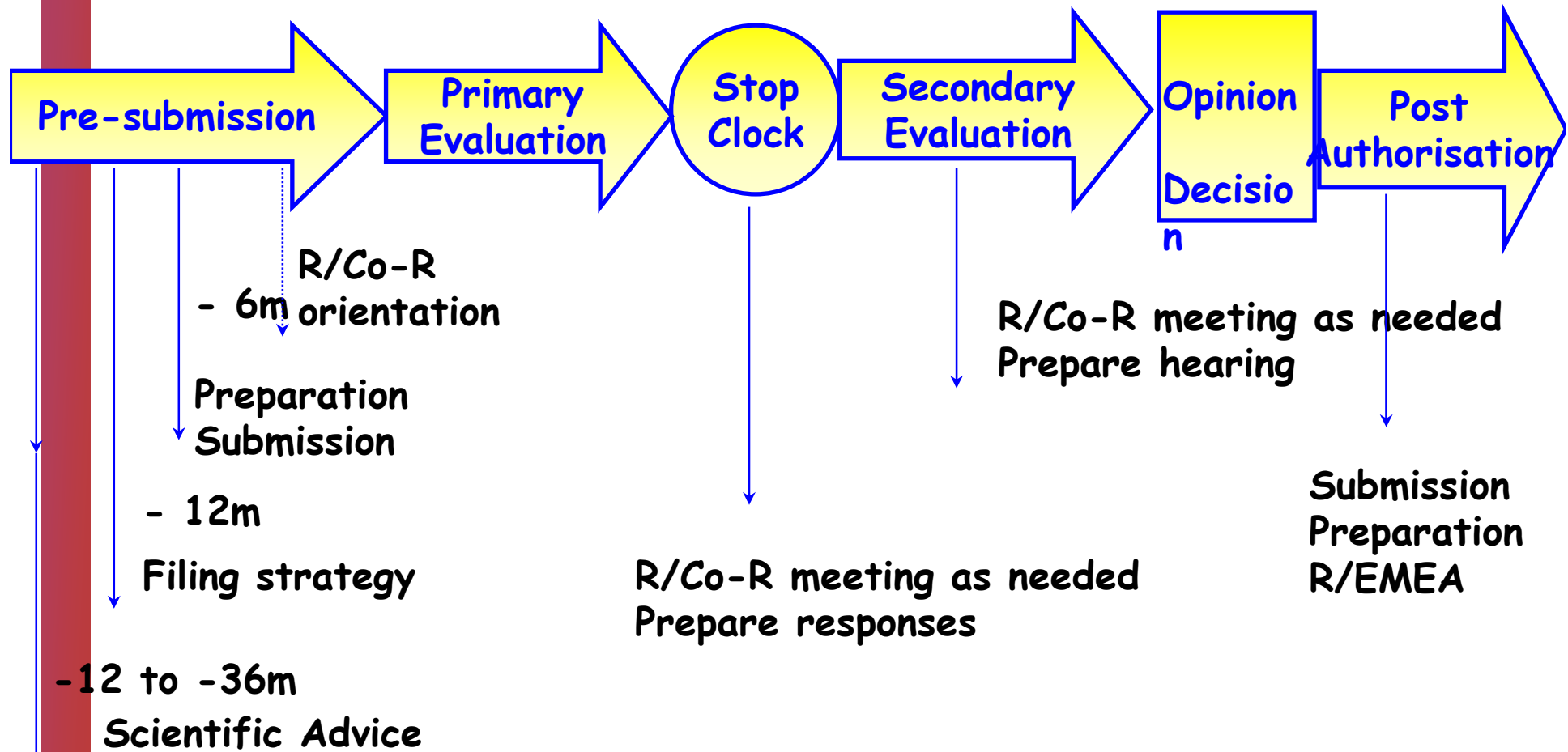
The centralised procedure (3)



Post Opinion - Decision making Phase

- ✓ EMEA / Company ~30 days to finalise translations final Opinion
- ✓ Commission ~30 days to prepare draft decision for circulation to Standing Committee(Member State representatives)
- ✓ Standing Committee ~30 days to review
- ✓ Commission ~30 days to implement changes and issue final Decision legally binding throughout the EU

The centralised procedure: an ongoing dialogue





European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

London, 31st March 2009
EMEA/630043/2008

**COMMITTEE FOR ADVANCED THERAPIES
(CAT)**

**PROCEDURAL ADVICE ON THE EVALUATION OF ADVANCED THERAPY
MEDICINAL PRODUCT IN ACCORDANCE WITH ARTICLE 8 OF REGULATION
(EC) NO 1394/2007**

DISCUSSION AT CAT	January 2009
DISCUSSION AT CHMP, CAT	February-March 2009
ADOPTION BY CAT	March 2009
ADOPTION BY CHMP	March 2009
RELEASE FOR EXTERNAL CONSULTATION	April 2009

http://www.emea.europa.eu/htms/human/raguidelines/advanced_therapies.htm

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 assessment
- ✓ 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
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 - to contribute to the scientific advice procedures referred to in Article 16 of this Regulation and in Article 57(1)(n) of Regulation (EC) No 726/2004.

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).

Classification procedure



European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

London, 16th April 2009
EMA/99623/2009

COMMITTEE FOR ADVANCED THERAPY MEDICINAL PRODUCTS (CAT)

PROCEDURAL ADVICE ON THE PROVISION OF SCIENTIFIC RECOMMENDATION ON CLASSIFICATION OF ADVANCED THERAPY MEDICINAL PRODUCTS IN ACCORDANCE WITH ARTICLE 17 OF REGULATION (EC) NO 1394/2007

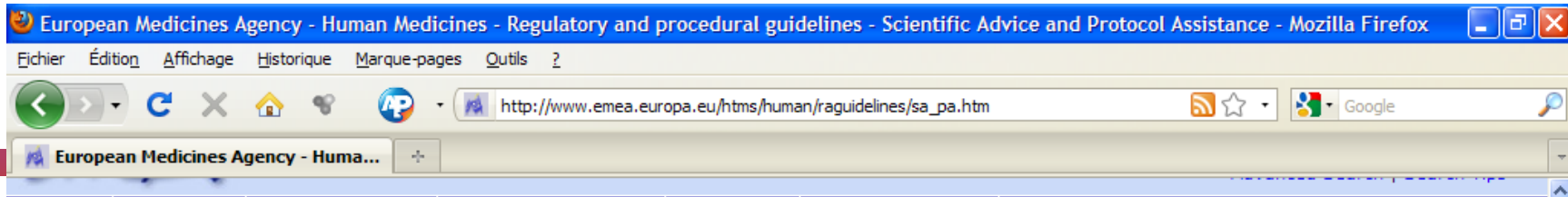
DISCUSSION AT CAT	January 2009
ADOPTION AT CAT	February 2009
RELEASE FOR EXTERNAL CONSULTATION	April 2009
ADOPTION BY CAT	

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Scientific advice

- ✓ At any time of the development of a medicinal product, the sponsor can seek, from EMEA and its scientific committees, advice on technical/scientific questions
- ✓ Specific procedure, via the Scientific advice working party
- ✓ For ATMPs, CAT will appoint coordinators to contribute to the responses prepared by the Scientific advice review group. Discussion and final report will be handled by CAT and transmitted to SAWP



http://www.emea.europa.eu/htms/human/raguidelines/sa_pa.htm

- Introduction
- General
- Innovation Task Force (ITF)
- Advanced Therapies
- Paediatrics
- Small and Medium-sized Enterprises (SME)
- Orphans
- Scientific Advice and Protocol Assistance
- Pre-Marketing Authorisation
 - Pre-Sub
 - Dossier Requirer
 - Applicant
 - Post-Op

Regulatory and procedural guidance

Scientific Advice and Protocol Assistance

D = Draft **A** = Adopted **O** = Overview of Comments **u** = Click on the icon to access document

Title	D	A	O	Reference Number	Document Date
General					
New Framework for Scientific Advice and Protocol Assistance (final)		u	u	EMA/267187/2005	26 Apr 2006
EMA Guidance for companies requesting scientific advice or protocol assistance		u		EMA-H-4260-01	19 Jan 2007



European Medicines Agency
Standard Operating Procedure

- Post-Marketing Authorisation
 - General
 - Dossier requirer
 - Type I \
 - Type II
 - Type II Extensic
 - Extensic
 - New Var

Title: Scientific Advice and Protocol Assistance procedure		
PUBLIC		Document no.: SOP/H/3037
Lead Author	Approver	Effective Date: 01-JUL-08
Name: Kristina Larsson	Name: Agnès Saint Raymond	Review Date: 01-JUL-11
Signature: On file	Signature: On file	Supersedes: SOP/H/3037 (15-JUN-02)
Date: 25-JUN-08	Date: 26-JUN-08	Track Wise record no.: 1826



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

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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

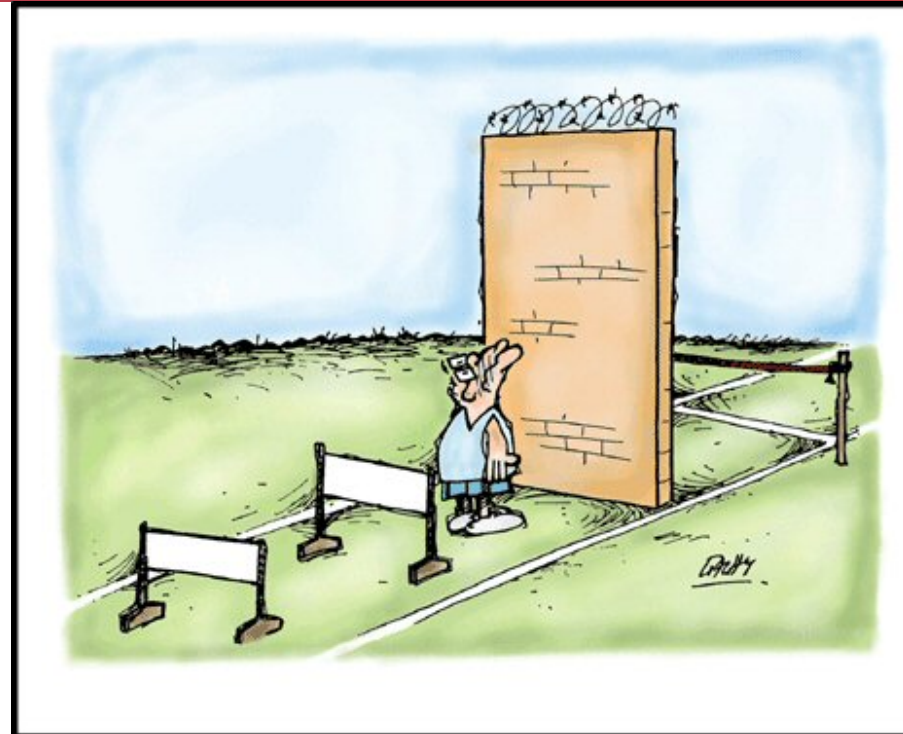
Examples of specific questions

- ✓ 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?

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.

Balanced view



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Hurdles should neither be too high... ..nor too low.

To develop an ATMP is not an excuse for an immature dossier or to neglect regulatory standards in the three criteria of Quality, Safety and Efficacy.

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 recombinant 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.
- ✓ Specific

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

Introduction

Advanced Therapies Regulation

Regulatory and Procedural Guidance

Special procedures designed for ATMPs

ATMP Classification

Certification Procedure

Scientific guidelines

How to get support from the EMA

Interested parties

See also:

Committee for Advanced Therapies

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, EMA 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](#)



European Medicines Agency

London, 17 April 2009

Doc. Ref. EMEA/CAT/418458/2008/corr.¹

COMMITTEE FOR ADVANCED THERAPIES (CAT)

DRAFT

PROCEDURAL ADVICE ON THE CERTIFICATION OF QUALITY AND NON-CLINICAL DATA FOR SMALL AND MEDIUM-SIZED ENTERPRISES DEVELOPING ADVANCED THERAPY MEDICINAL PRODUCTS

DRAFT DISCUSSED BY BWP, CPWP, GTWP, GMP/GDP AND GLP INSPECTORS WORKING GROUP	November/December 2008
ADOPTION BY COMMITTEE FOR ADVANCED THERAPIES	17 April 2009
RELEASE FOR CONSULTATION^{II}	4 August 2009
END OF CONSULTATION (DEADLINE FOR COMMENTS)	14 October 2009



European Medicines Agency

London, 19 June 2009

Doc. Ref. EMEA/CAT/486831/2008/corr¹

**COMMITTEE FOR ADVANCED THERAPIES
(CAT)**

DRAFT

**SCIENTIFIC GUIDELINE ON THE MINIMUM QUALITY AND NON-CLINICAL DATA
FOR CERTIFICATION OF ADVANCED THERAPY MEDICINAL PRODUCTS**

DRAFT AGREED BY CPWP, GTWP, BWP	March/April/June 2009
ADOPTION BY COMMITTEE FOR ADVANCED THERAPIES FOR RELEASE FOR CONSULTATION	19 June 2009
RELEASE FOR CONSULTATION^{II}	4 August 2009
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 October 2009

Conclusions

- ✓ New « innovative » products are now classified as medicinal products
- ✓ European centralised procedure for their authorisation prior marketing
- ✓ Scientific committee dedicated for their evaluation and proposal for authorisation
- ✓ Roles of the CAT :
 - Evaluation/assessment for the authorisation
 - Classification
 - Scientific advice during the development phase
 - Guidelines
 - Certification

Acknowledgment

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- Christian Schneider (CAT Chair)
- Paula Salmikangas (CAT Vice Chair)

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http://www.emea.europa.eu/htms/human/raguidelines/general.htm

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- Introduction
- General
- Innovation Task Force (ITF)
- Advanced Therapies
- Pediatrics
- Small and Medium-sized Enterprises (SME)
- Orphans
- Scientific Advice and Protocol Assistance
- Re-Marketing Authorisation
- Pre-Submission
- Dossier Submission Requirements
- Application & Evaluation
- Post-Opinion
- Post-Marketing Authorisation
- General
- Dossier submission requirements
- Type I Variations
- Type II Variations
- Type II Variations (v)

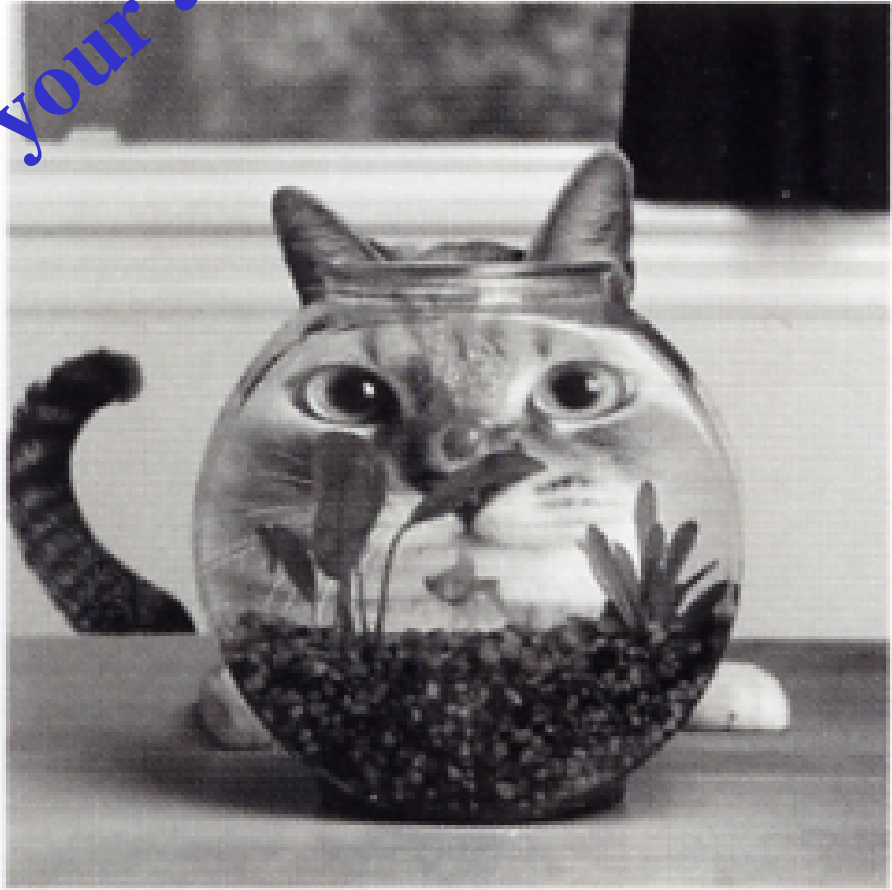
Regulatory and procedural guidance

General

D = Draft **A** = Adopted **O** = Overview of Comments **v** = Click on the icon to access document

Title	D	A	O	Reference Number	Document Date
Legislation					
Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.		v		Regulation EC 726/2004	31 Mar 2004
Consolidated Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use as amended by Directive 2002/98/EC, Directive 2003/63/EC, Directive 2004/24/EC, Directive 2004/27/EC and Directive 2008/29/EC		v		Consolidated Directive 2001/83/EC	06 Nov 2001
Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use		v		Directive 2003/63/EC	25 Jun 2003
'Marketing Authorisation', the Rules governing Medicinal Products in the European Community.		v		ENTR/F2/BL D(2002)	Nov 2005

Thank you for your attention



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