Advanced therapy medicinal products

Overview of the current approach to regulation of Advanced therapy medicinal products (ATMPs)

Chances and Challenges

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Drug Regulatory Affairs

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Overview

1. Introduction

2. Implementation and key features of the ATMP regulation

3. CAT composition and tasks

4. Summary and conclusion

Definition of ATMPs

The European definition of advanced therapy medicinal products is comprised of three subcategories:

- Gene Therapy Medicinal Products (GTMPs)
- Somatic cell therapy medicinal products (SCMPs)
- Tissue engineered products (TEP)

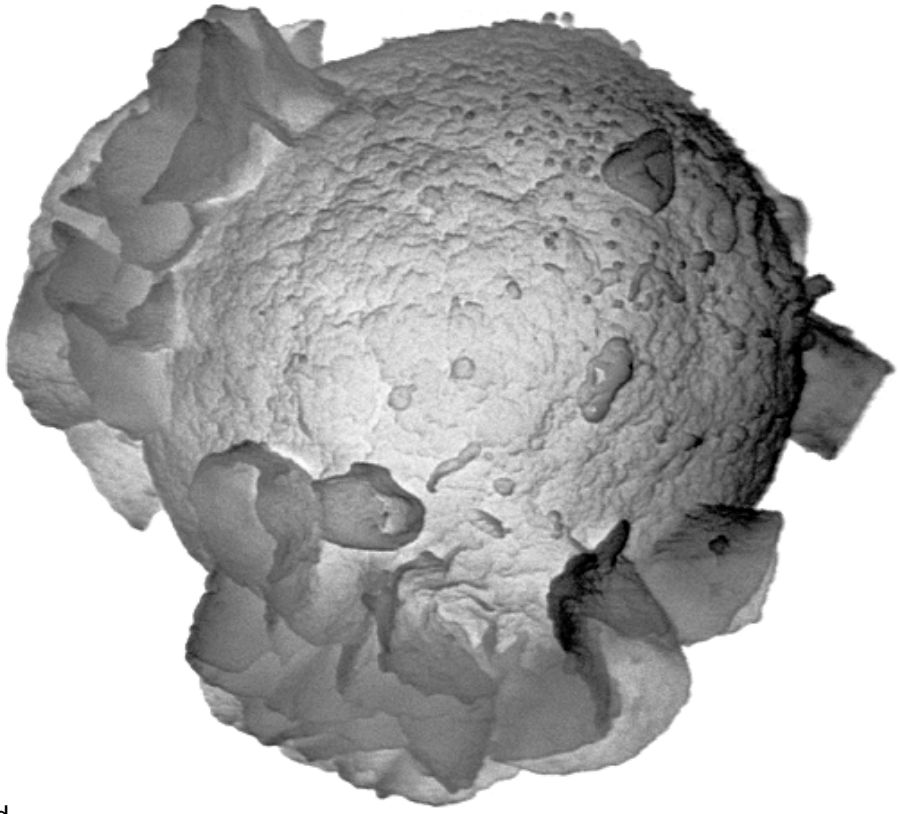
Complexity of ATMPs

IgG1 3D structure
http://www.pasteur.fr/recherche/unites/ImmStr/en/projects/recognition.html

Differences in quartenary structure and Post translational modifications (ie glycosylation profiles) were main factors which led to the biosimilar discussion =>

Impact of manufacturing process on efficacy/safety profile

Adopted from: Dr. Christian K Schneider, MD, Are regulators up to speed to address the challenges of biotechnological medicinal products? EMA, December 15th, 2010



B-cell budding virus
http://www.einstein.yu.edu/aif/gallery/sem/sem.htm

Scientific challenges and regulatory Consequences with ATMPs

Scientific challenges

- Non-uniform starting materials for autologous cell therapies
- Cells depend on their (micro) environment and react to it
- Cells may dedifferentiate and become heterogeneous during culturing processes or in-vivo after application
- Cells may migrate from their designated location
- ATMPs are often aimed at restoring physiological functions which last for a lifetime with a single or very few interventions
- Preclinical toxicity (animal) studies often are not applicable
- Current approaches for dose dependency / efficacy studies don't work for cell-based therapies

Regulatory consequences

Difficulties in demonstrating pharmaceutical quality

Need for adequate characterization
but also necessity to accept limitations

(e.g. karyotyping, expression patterns for various marker gens)

Difficulties to demonstrate Efficacy and Safety in initial MAA based on trial designs / endpoints for non-ATMPS Necessity to establish long term safety / efficacy follow-up protocols

Need to develop new tests, accept
surrogate models (use of immuno-deficient animals e.g. nude, SCID or Rag1 Mice models or use of a homologous model in an animal species)

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Regenerative medicine cell therapies currently on the market[1]

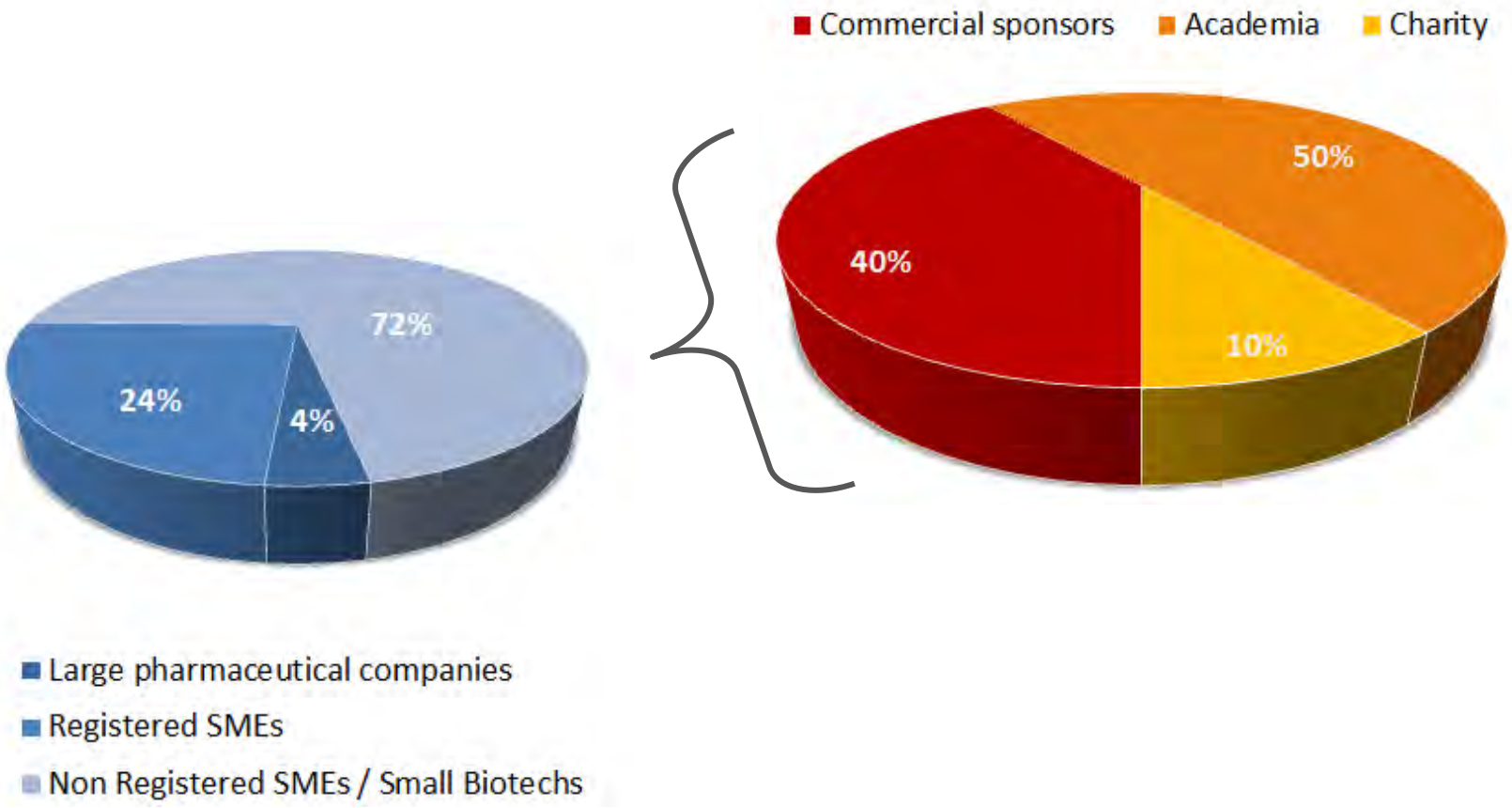
Product	Indication	Year of approval	Agency	Patients treated**
Carticel®	symtomatic cartilage defects of the femoral condyle	1997	FDA	17000
Apligraf®	venous leg ulcers	1998	FDA	250000
	diabetic foot ulcers	2001	FDA	
	chronic Ulcers and soft-tissue defects	2008	Reimbursement in Switzerland	
	diabetic foot ulcers and other chronic wounds	2010	SFDA*	
Dermagraft®	diabetic foot ulcers	2001	FDA	>50000
Orcel®	mitten-hand deformity	2001	FDA	>200
	donor site wounds burn patients	2001	FDA	
Epicel®	burn wounds	2007	FDA	1653
Chondrocelect®	symtomatic cartilage defects of the femoral condyle	2009	EMA	500

Total patients treated **>320000**

*Saudi Food and Drug Authority **cumulative number of patients until March 2010

[1]Regenerative medicine cell therapies: numbers of units manufactured and patients treated between 1988 and 2010, Regen. Med. (2010)5(3), 307-313

Unique composition of ATMP sponsors*



* Source: Clinical Development of Advanced Therapy Medicinal Products in Europe: Evidence That Regulators Must Be Proactive
R. Maciulaitis, L. D'Apote, A. Buchanan, L. Pioppo and C. K. Schneider, *Molecular Therapy,* vol. 20, no. 3, march 2012

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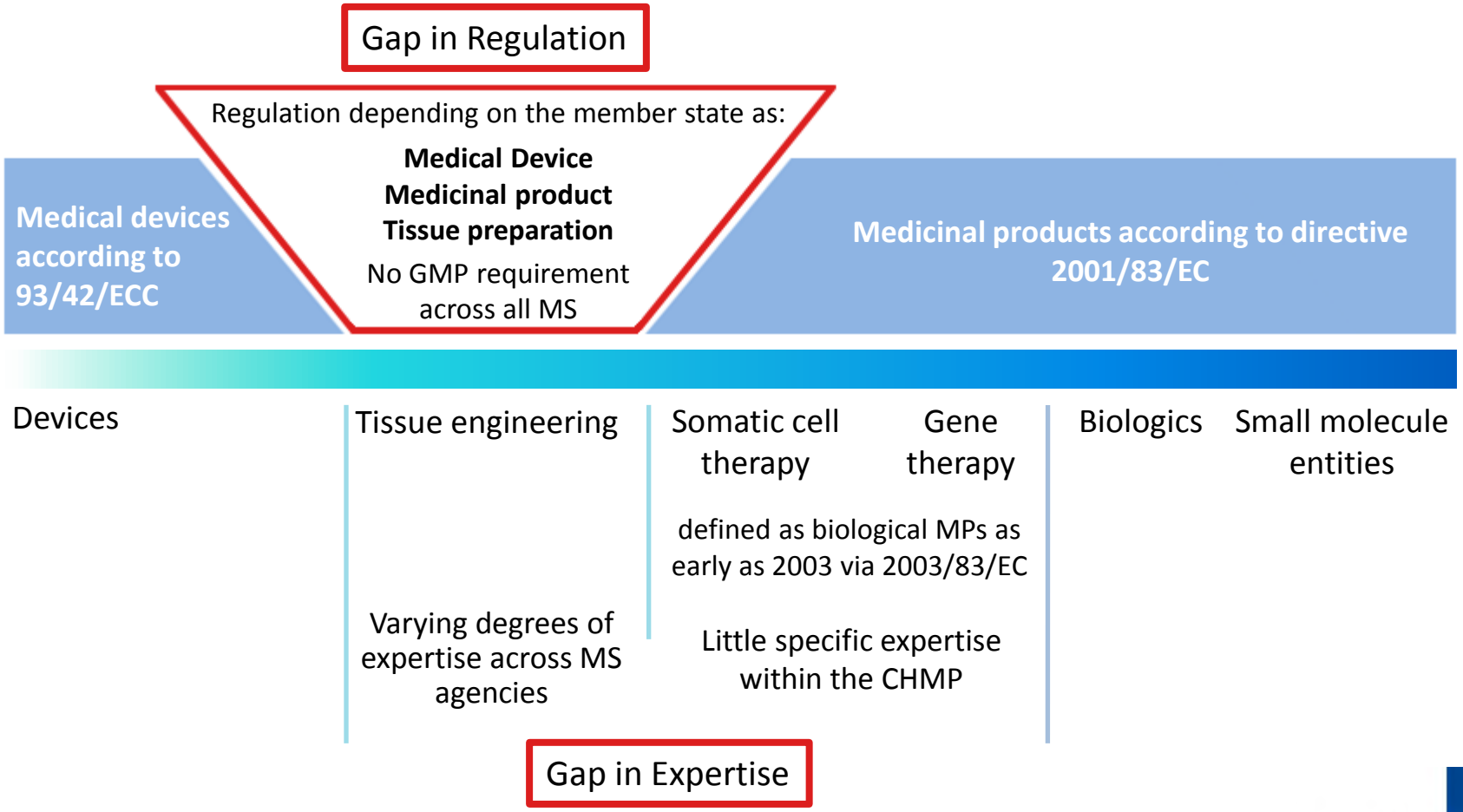
Definition of Gene Therapy Medicinal Products*

A Gene Therapy Medicinal Product is defined as:

- 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
- 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

* Directive 2001/83/EC, Annex 1, Part IV as amended by Directive 2009/120/EC

Regulation of cell based and gene therapy medicinal products before 2008:



Key features of the “ATMP” regulation 1394/2007

Harmonized rules are needed:

- ensure a high level of scientific evaluation of these medicinal products in the Community, preserve the confidence of patients and medical professions in the evaluation and facilitate Community market access for these innovative technologies

- Clear definition of ATMPs (in conjunction with Dir. 2009/120)
- Mandatory MA via centralized procedure for all ATMPs
- Establishment of a specialized Committee (CAT)
- Incentives for SMEs to foster innovation

Regulation of cell based and gene therapy medicinal products after introduction of the ATMP regulation

a single scientific evaluation of the quality, safety and efficacy of ATMPs carried out to the highest possible standard available

Reg. 1394/2007 introduced additional provisions to those laid down in Directive 2001/83/EC

Medical devices according to 93/42/ECC	ATMPs as defined in Regulation 1394/2007	Medicinal products according to directive 2001/83/EC

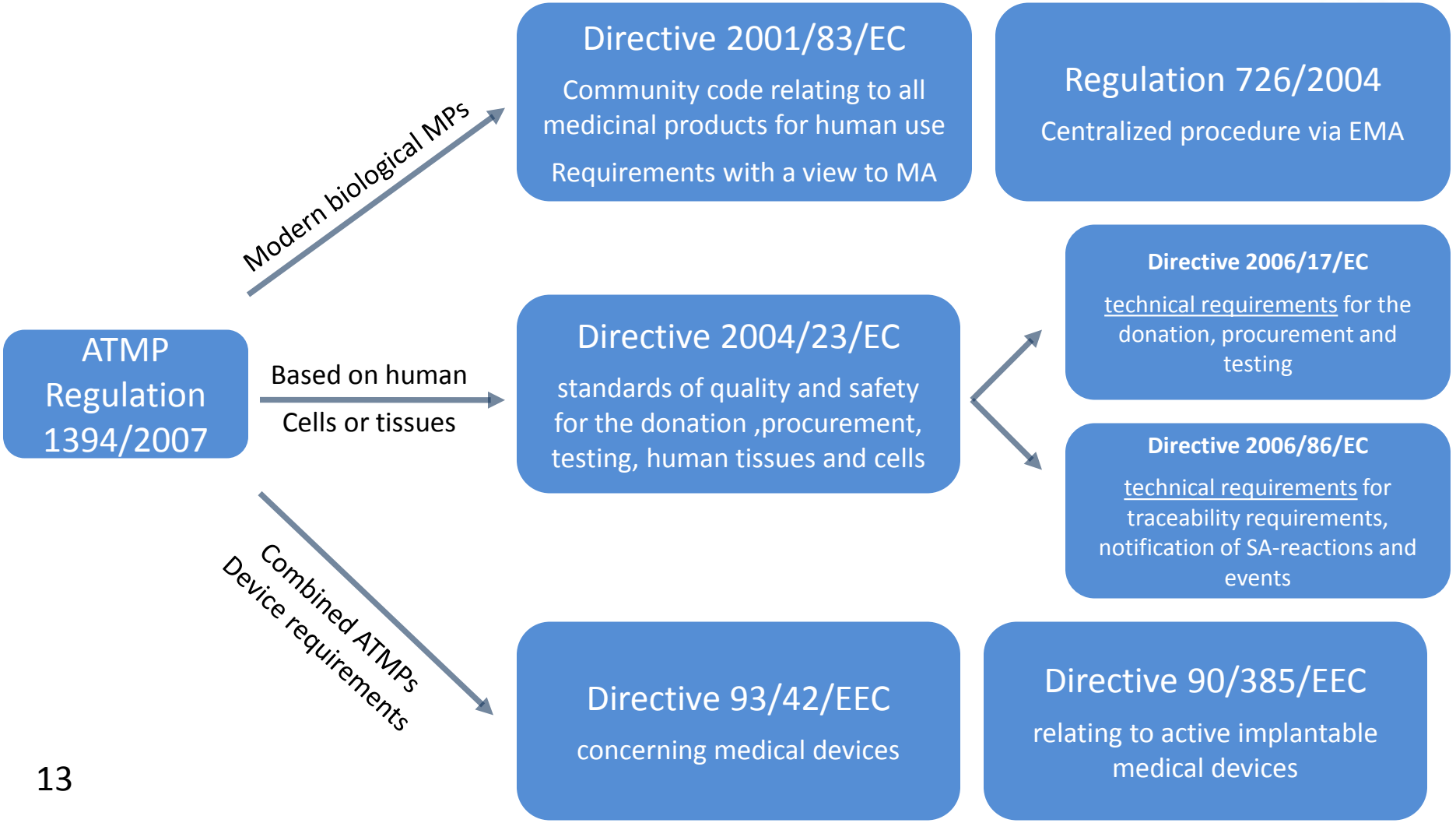
Devices

Tissue engineering | Somatic cell therapy | Gene therapy

Biologics | Small molecule entities

Regulatory / Scientific expertise is provided by the CAT

Regulation of cell based and gene therapy medicinal products after introduction of the ATMP regulation



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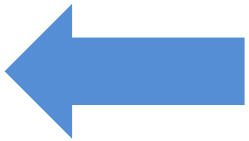

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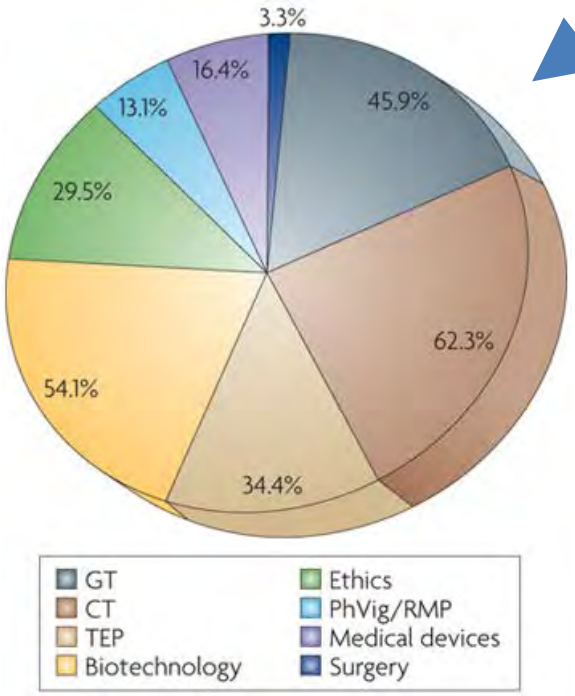
Composition of the Committee for advanced therapies (CAT)

CHMP

5 Members and alternates nominated from within the CHMP "CAT/CHMP Double members"

two members and alternates appointed by the European Commission to represent **patient associations**



61 CAT Members and their respective fields of expertise[1]

two members and alternates appointed by the European Commission to represent **clinicians**

1 Member and alternate appointed from national CA by each EU member state (27) except for those which are included in the CHMP nominees

[1]Source: Challenges with advanced therapy medicinal products and how to meet them, Nature Reviews Drug Discovery 9, 195-201 (March 2010)

Primary tasks of the Committee for advanced therapies (CAT)

- **Scientific evaluation of ATMP marketing authorization applications**

  Draft adopted by the CAT – Final opinion adopted by the CHMP

- **Classification procedure**

  Clarification whether your product falls within the scope of the ATMP regulation

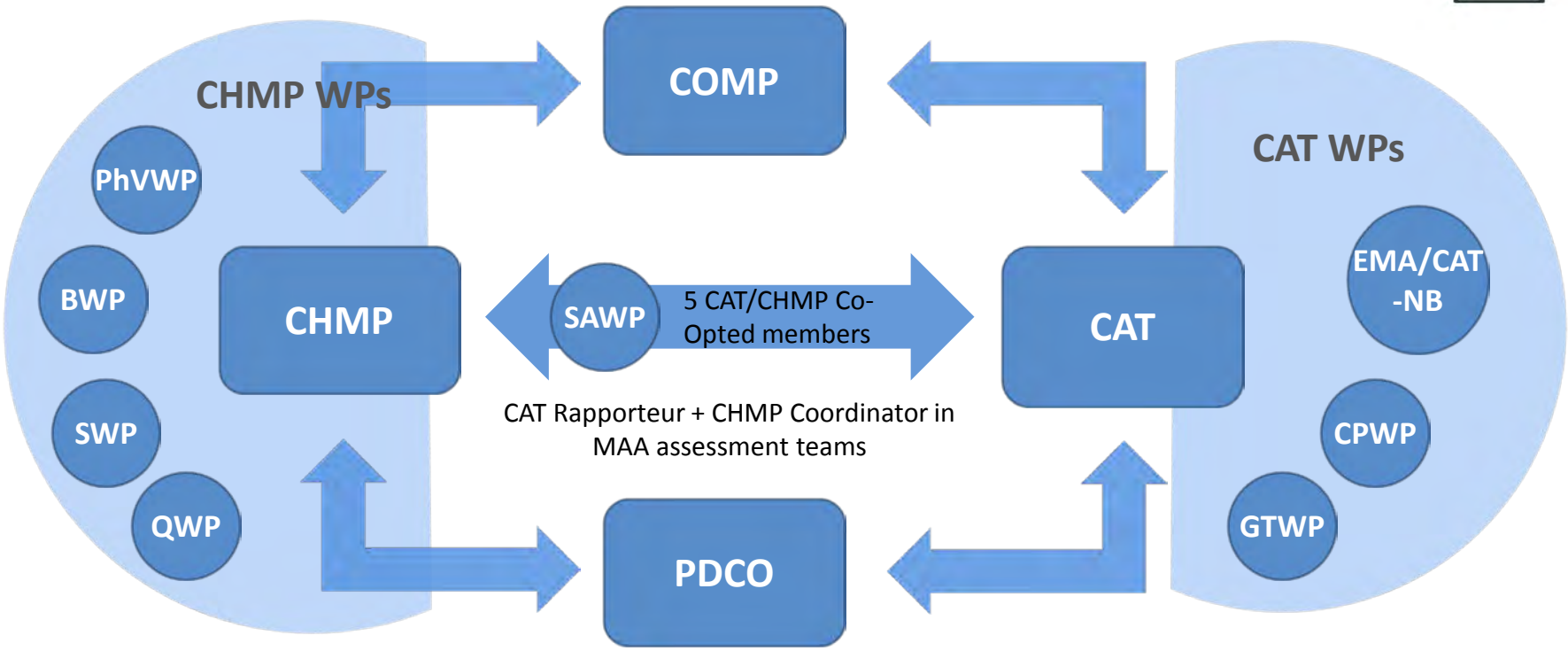
- **Scientific Advice**

  Provide scientific advice for ATMPs / provide input on ATMP related questions form other committees (CHMP / PDCO)

- **Certification procedure**

  Assessment of early quality and non-clinical data

Primary tasks of the Committee for advanced therapies (CAT)



COMP = Committee for Orphan Medicinal Products

CHMP = Committee for medicinal products for human use

PDCO = Pediatric committee

CAT = Committee for Advanced Therapies

GTWP = Gene Therapy WP

CPWP = Cell-based products WP

BWP = Biologics WP

QWP = Quality WP

SWP = Safety WP

PhVWP = Pharmacovigilance WP

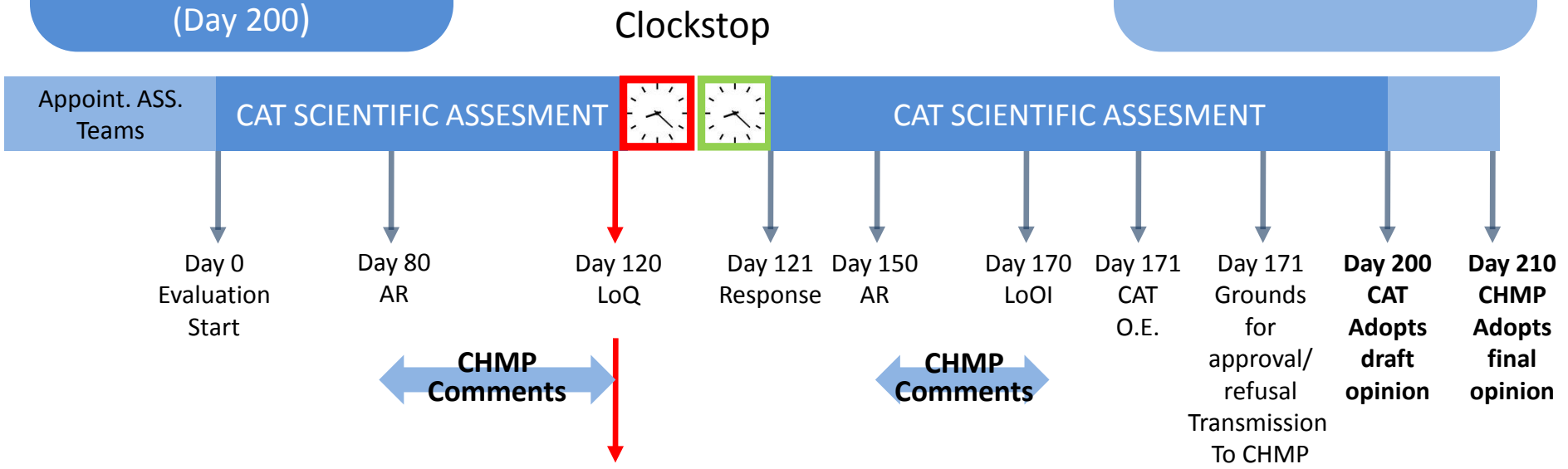
EMA/CAT-NB =

EMA/CAT and Medical Devices' Notified Body Collaboration Group

Evaluation of ATMP MAAs

CAT
- Scientific Assessment (incl. Day 80/150 AR, Adoption LoQ, LoOI)
- Adopt draft opinion (Day 200)

CHMP
- Appoints Rapporteur)
- Adopts Final CHMP opinion (Day 210)



Evaluation of ATMP MAAs

What is different for ATMPs?

- Rapp/CoRapp are from CAT, not CHMP
- Scientific discussion on LoQ/LoOI/OE at CAT
- CAT adopts LoQ, LoOI and draft opinion
- CHMP fully informed of progress of CAT evaluation
- Circulation of Rapps AR to CHMP, discussion of LoQ/LoOI etc.
- CHMP will adopt the final opinion at Day 210

ATMP evaluation procedure builds on full transparency between CAT and CHMP to avoid divergent views

Tasks of the assessment team members

CAT (Co) Rapporteur

- coordinates the procedure & discussions at CAT
- preparation of assessment reports

CHMP (Co) Coordinator

- responsible for flow of information between CAT & CHMP
- discussion/adoption of opinion

Peer review by one CHMP member and at least one CAT member

There should be adequate and sufficient interaction and communication between the two Committees, CAT and CHMP, via the Assessment Team members*

*CAT RULES OF PROCEDURE, EMEA/CAT/ EMEA/454446/2008

Classification Procedure

The CAT provides a recommendation:

- as to whether the product in question falls within the ATMP definition
- And if so, to which ‘subclass’ of ATMP it belongs (GTMP, SCMP, TEP)
- Takes up to 60 Days, possibility of ‘clockstop’ at day 30

Available to all applicants

- Gain understanding of required regulatory pathway at an early stage of development
- Widely adopted => approximately 90 classification requests finalized since coming into force of the ATMP regulation

Certification Procedure

ATMPs are mostly developed by small to medium sized enterprises (e.g. university spin-offs) which:

- largely depend on venture capital
- often lack the resources to conduct ‘full scale’ clinical trails
- Do not know how to successfully navigate the regulatory landscape

Thus the CAT offers a certificate regarding the quality and/or preclinical data of an ATMP in order to support SMEs when they are:

- Rallying for new investors
- Looking for support from bigger pharmaceutical companies
- Try to obtain approval for a CTA from national competent authorities

Not widely adopted => only two applications for certification procedure

- In 2012 EMA conducted a survey to assess the reasons for the slow adoption among stakeholders
- Main points identified were
  - limited added value as compared to scientific advice
  - Certification only available to SMEs

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Problems identified

- Since coming into force of the ATMP regulation in December 2008 until November 2013 only 10 initial MAAs have been received at the EMA and only five positive opinions have been issued by the CAT resulting in approval of four ATMPs
    - During the same period the number of positive opinions for new chemical entities (excluding ATMPs) was approximately 35 per year
- Incentives in the ATMP regulation are specifically tailored to and exclusively available for small to medium sized enterprises
- The EMA has engaged in a consultation with relevant stakeholders in order to revise the current ATMP regulation. The consultation was finalized in 2012.

EMA consultation – Major points identified

MAA Dossier requirements are still designed for conventional medicinal products
Any tailoring for ATMP specific requirements would be beneficial

- Especially the drug substance requirements for autologous cell based therapeutics should be clarified
- Hospital exemption deters the pursuit of an MAA in certain circumstances
  - Should not be available in indications where an ATMP is already approved
- Incentives for any ATMP related regulatory procedure should be opened to non-commercial entities such as academia and charity organizations to better reflect the actual stakeholders in the ATMP field
- Further clarification on applicability / necessity of animal models in pre-clinical development is required

In summary

- Stakeholders appreciate the establishment of the regulatory framework for ATMPs as the regulatory processes and requirements to obtain a MAA are now clearly mapped out

- The current framework is in need to adopt some of the previously outlined changes in order to better accomodate the characteristics spefic to ATMPs and to better recognise the resource constraints of the involved stakeholders

- The upcoming revision of the ATMP regulation is a chance to keep Europe at the heart of biotech innovation

- If however the identified gaps are not addressed properly a stifling of innovation is likely to occur