Regulatory framework in procurement, manufacturing and application of Advanced Therapy Medicinal Products (ATMP)

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TECHNISCHE UNIVERSITÄT DRESDEN

CRTD
Center for Regenerative Therapies Dresden

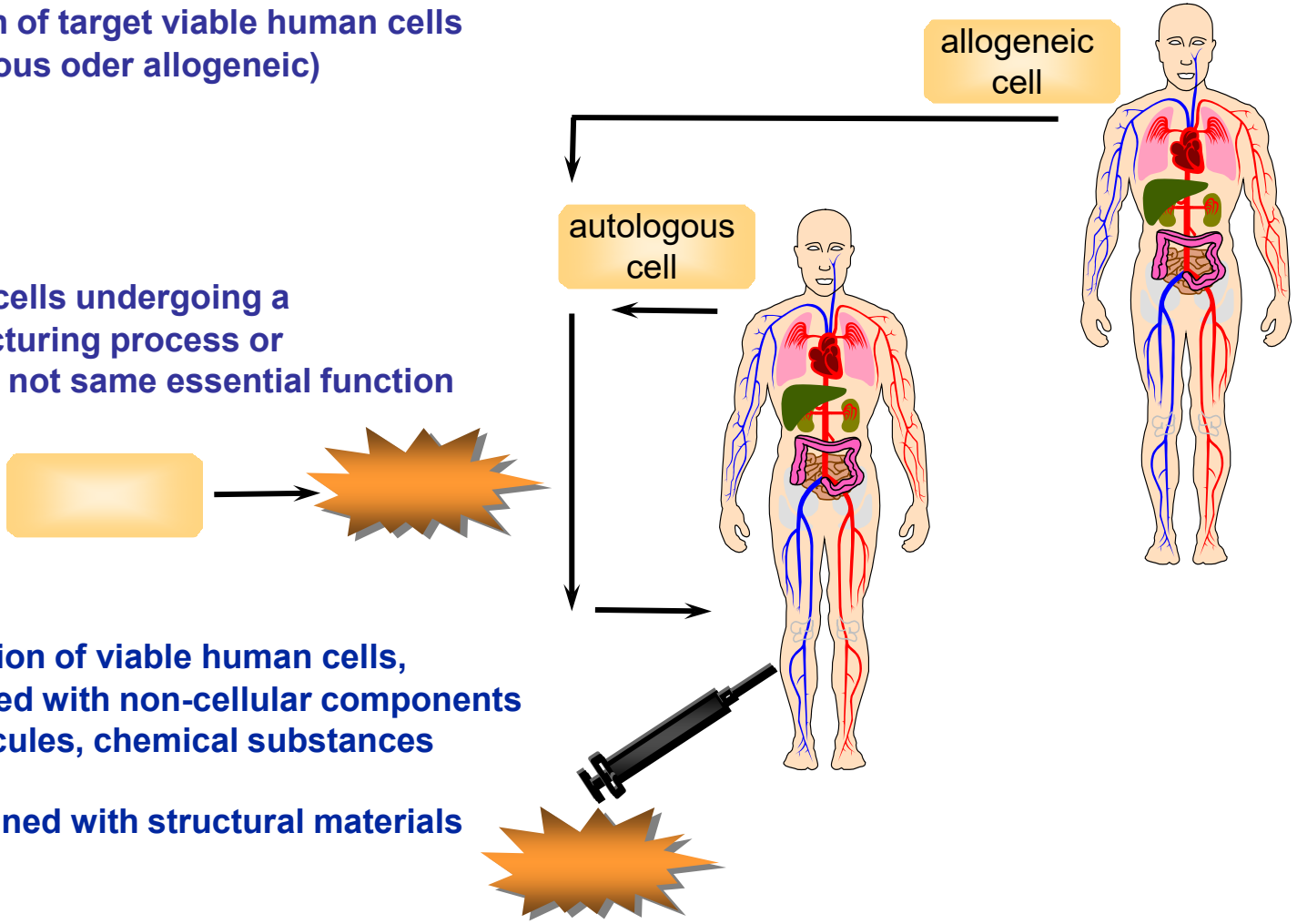
Cell-based Medicinal Products (CBMP)

1) Isolation of target viable human cells (autologous oder allogeneic)

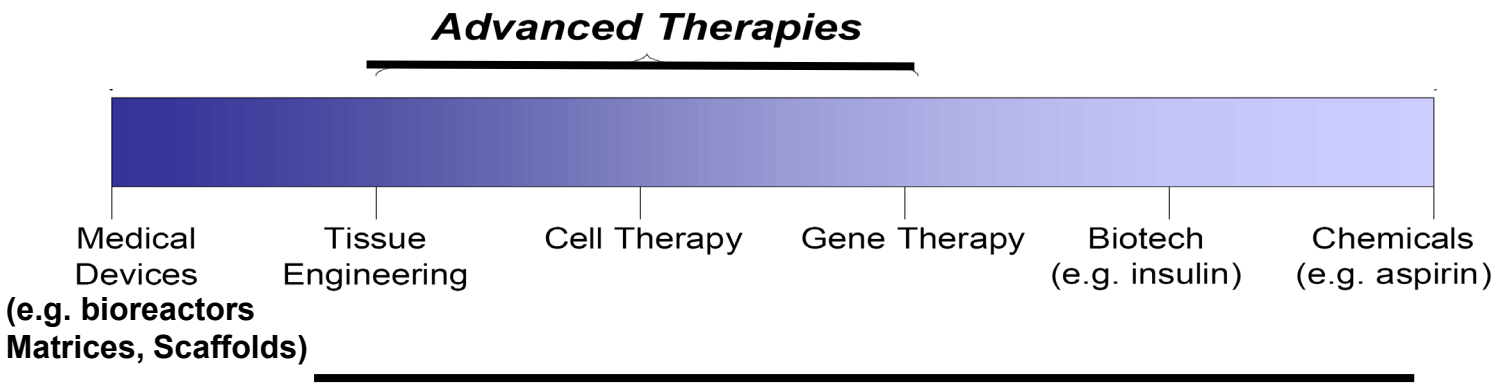
2) Human cells undergoing a manufacturing process or used for not same essential function

3) Re-Infusion of viable human cells, associated with non-cellular components biomolecules, chemical substances

or combined with structural materials



Current overall regulatory picture



Medicinal Products comprise

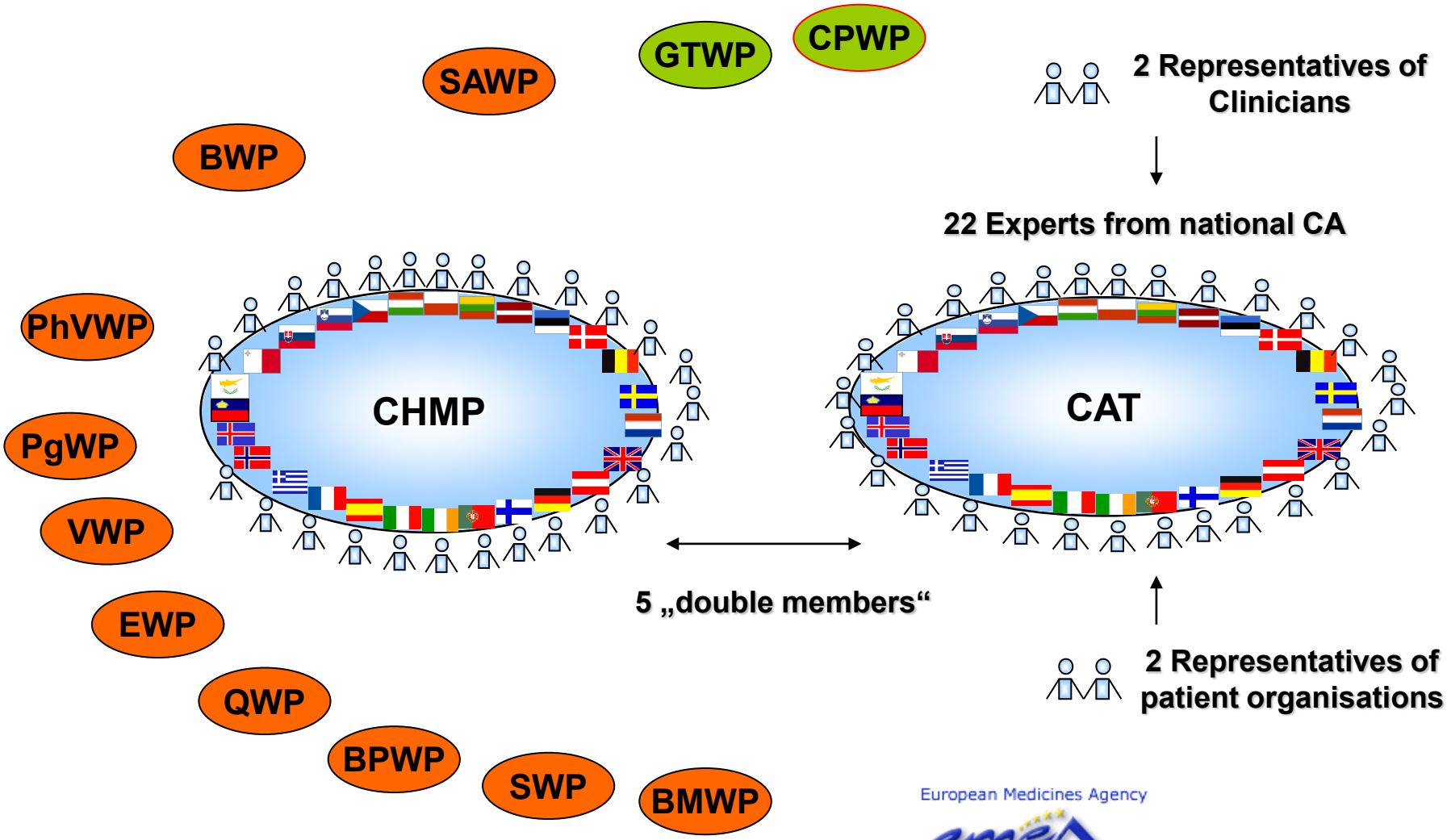
Advanced Therapy Medicinal Products (ATMP)

Tissue Engineering
Cell Therapy

Gene Therapy

Cell-Based Medicinal Products (CBMP)

Committee for Advanced Therapies (CAT)



European Medicines Agency

CAT and CPWP

- Scientific draft opinions ATMP applications,

- Certification,
- Classification,
- Involvement in scientific advice,
- Post-Authorisation procedures,
- Advising CHMP, EC other stakeholders.

- Prepare, review & update guideline

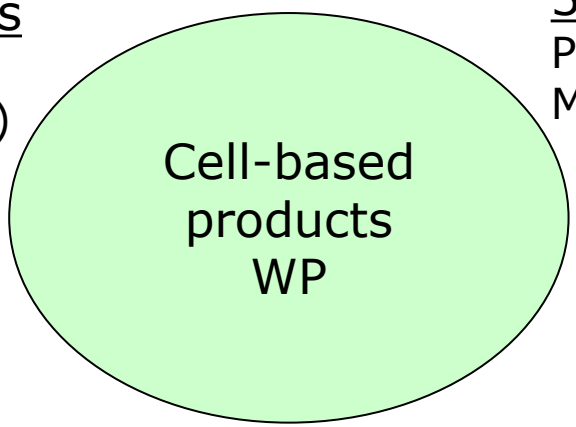
awareness on scientific issues

- Upon request by CAT:

-Product-related issues
-Briefing meetings
-Stakeholder/international organisation contact

Cell-based products WP – Core members

<u>3 nonclinical experts</u>
Egbert Flory (CAT)
Tiina Palomaeki (SWP)
Carla Herberts



<u>3 quality experts</u>
Paula Salmikangas (CAT)
Margarida Menezes-Ferreira (BWP)
Louise Bisset

<u>4 clinical experts</u>
Romaldas Maciulaitis (CAT)
Giovanni Migliaccio (CAT)
Torsten Tonn
Lisbeth Barkholt

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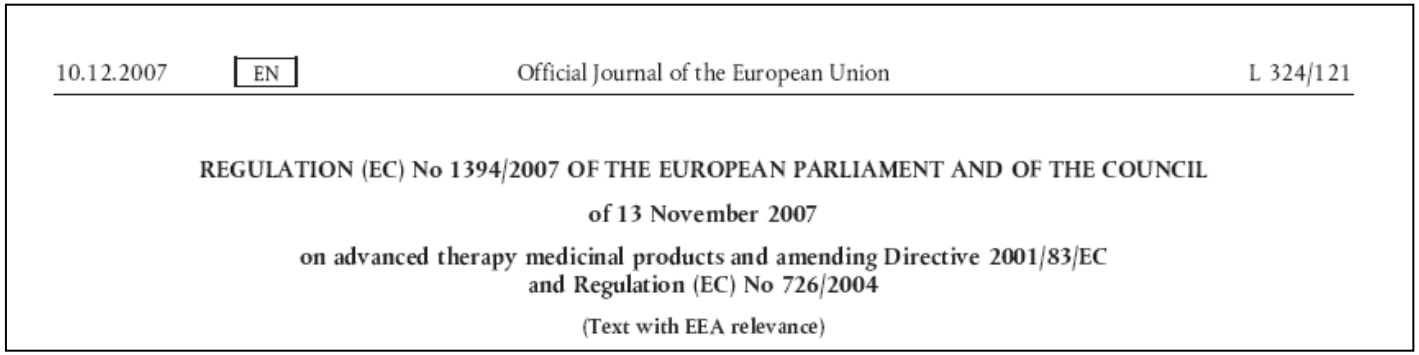
EC Regulation 1394/2007 on ATMP



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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

(Text with EEA relevance)

Tissue Engineered Medicinal Product

Contains or consists of engineered cells or tissues of human or animal origin, or both.

Having properties for, or is used in or administered to human beings with a view to replace, repair or regenerate a human tissue

The cells or tissues may be viable or non-viable.

May contain additional substances, such as cellular products, bio-molecules, bio-materials, chemical substances, scaffolds or matrices.

ATMP Regulation: Definitions

Cells or tissues shall be considered engineered if they fulfill at least one of the following points:

Have been subject to substantial manipulation, so that their original biological characteristics, physiological functions or structural properities relevant for the intended regeneration, repair or replacement are altered.

The cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.

The cells or tissues form part of a combined medicinal product.

Manipulations not considered as substantial manipulations:

- ***Cutting and grinding***
- ***Sterilization / irradiation***
- ***Cell separation, purification, concentration***
- ***Soaking in antibiotic / antimicrobial solutions***
- ***Shaping and centrifugation***
- ***Filtering / lyophilization***
- ***Freezing / cryopreservation***

The Regulatory framework

Legislation relevant for
all medicinal products

Legislation relevant for
all cell-based MP

Technical Requirements

Guidelines

The Regulatory framework

Legislation relevant for all medicinal products

Directive 2001/83/EC (Nov 2001) amended by 2009/120/EC (Jun 2009)
Community code relating to all medicinal products for human use
Requirements with a view to MA

Regulation 726/2004 (Mar 2004)
Centralized MA procedure via EMEA

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Legislation relevant for all cell-based MP

Regulation 1394/2007 on Advanced Therapy Medicinal Products
Central licensing and requirements for ATMPs

Directive 2004/23/EC (Mar 2004)
Standards of quality and safety for donation, procurement, testing, processing, preservation, storage and distribution of human tissues/cells

REGULATION (EU) 2024/…
on standards of quality and safety for substances of human origin intended for human
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Technical Requirements

- **Directive 2006/17/EC (Feb 2006)**
  technical requirements for
  donation,
  procurement
  testing
- **Directive 2006/86/EC (Oct 2006)**
  traceability, notification of serious adverse reactions and events, technical requirements for
  coding,
  processing,
  preservation,
  storage
  distribution

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Technical Requirements

Directive 2006/17/EC (Feb 2006)
technical requirements for donation, procurement testing

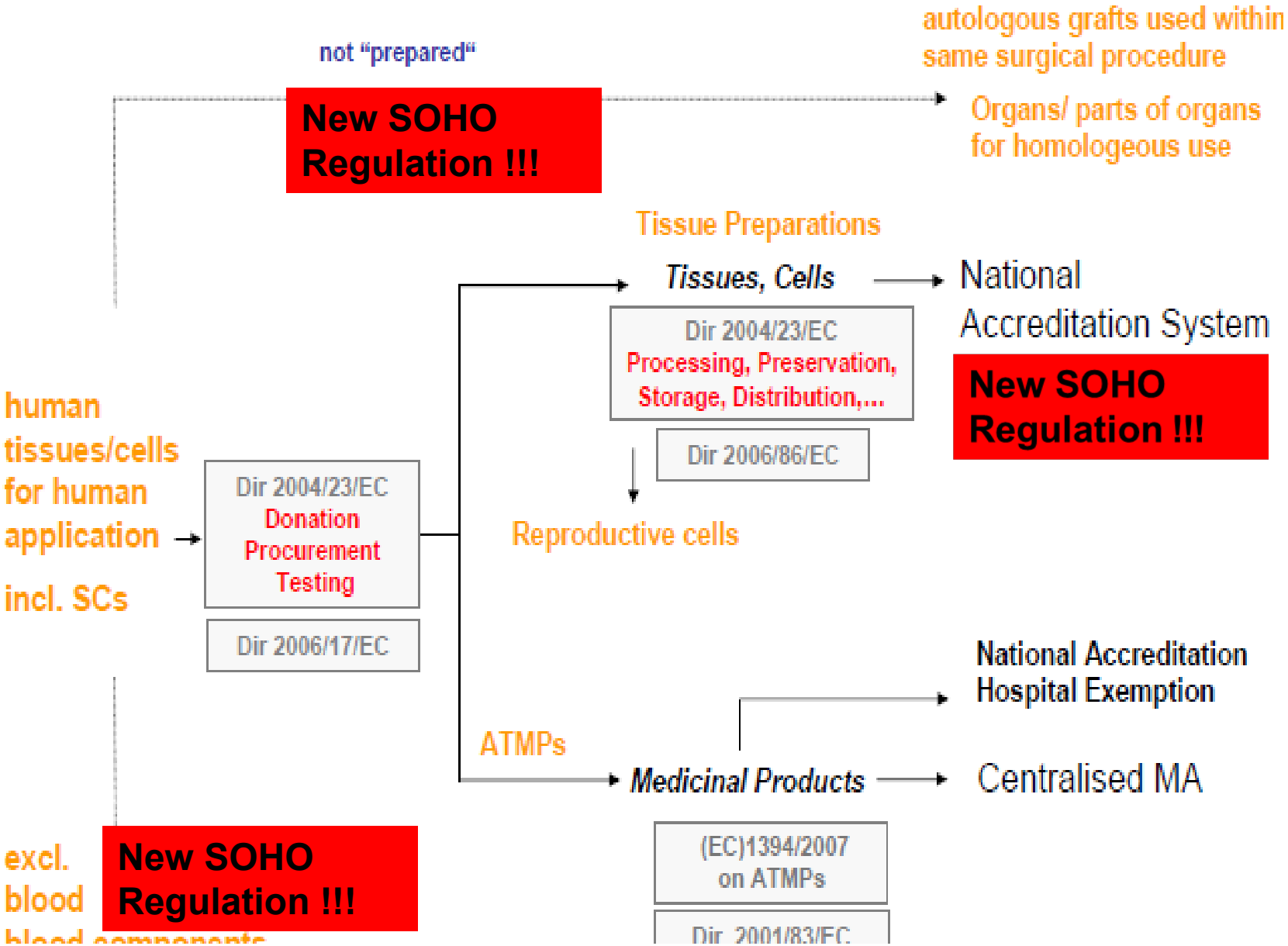
Directive 2006/86/EC (Oct 2006)
traceability, notification of serious adverse reactions and events, technical requirements for coding, processing,

Guidelines

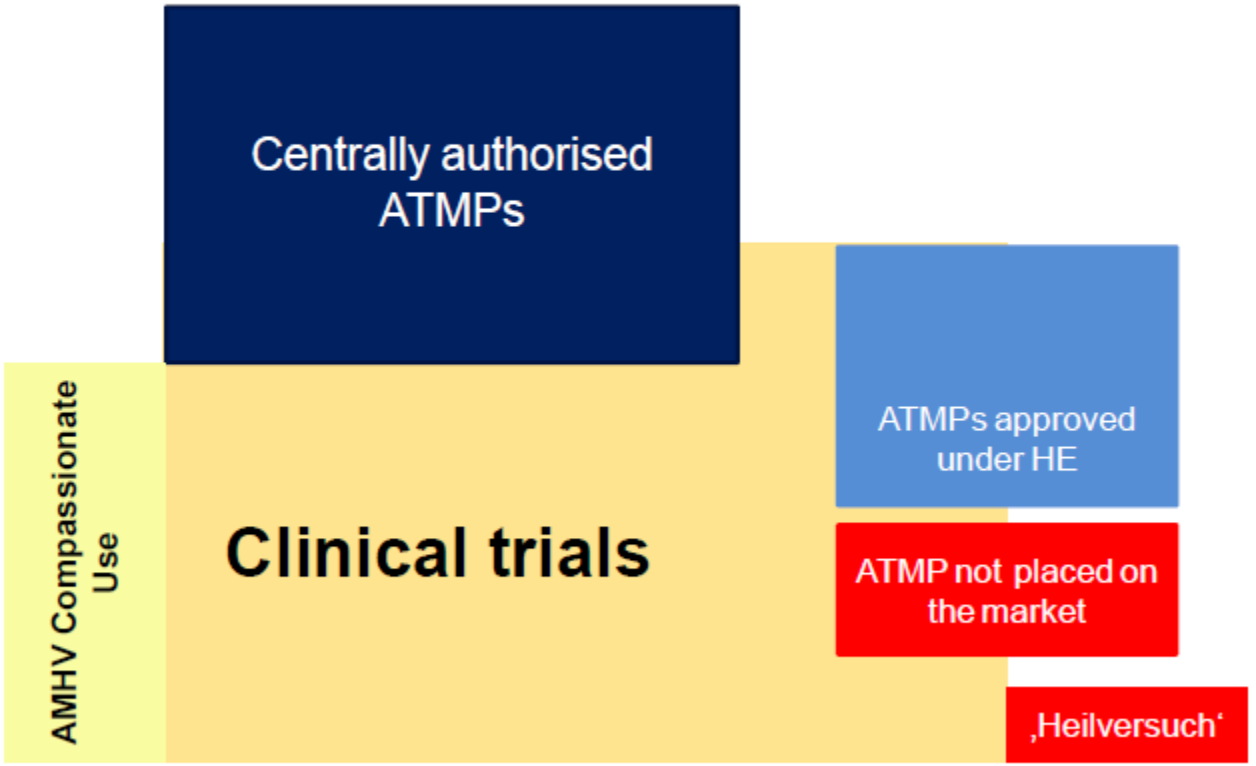
Guideline on human cell-based MPs (Sept. 2008)
Contains quality, non-clinical, clinical aspects

Concept paper on Risk-based approach for ATMP (2009, in prep.)
Reflection paper on human stem cells including HSC, MSC, iPS and embryonic (2010)

Regulatory Levels in the EU on Human Tissues and Cells



Availability of ATMPs



The Hospital Exemption

Genehmigung für das IVB gem § 4 b AMG

Umsetzung der HE im AMG

§ 4b Sondervorschriften für Arzneimittel für neuartige Therapien

(1) Für Arzneimittel für neuartige Therapien, die im Geltungsbereich dieses Gesetzes

1. als individuelle Zubereitung für einen einzelnen Patienten ärztlich verschrieben,

2. nach spezifischen Qualitätsnormen nicht routinemäßig hergestellt und

3. in einer spezialisierten Einrichtung der Krankenversorgung unter der fachlichen Verantwortung eines Arztes angewendet

werden, finden der Vierte Abschnitt *(Zulassung von AM)*, mit Ausnahme des § 33 *(Kosten)*, und der Siebte Abschnitt *(Abgabe von AM)* diesesGesetzes keine Anwendung.

Es gelten aber u.a.

Abschnitt 3 Herstellung
Abschnitt 6 Schutz des Menschen bei der klinischen Prüfung
Abschnitt 10 Pharmakovigilanz
Abschnitt 11 Überwachung

Vorgesehene Änderungen

§ 4b Abs. 2 zu nicht-routine-mäßiger Herstellung

Bisher:
(2) Nicht routinemäßig hergestellt im Sinne von Absatz 1 Satz 1 Nummer 2 werden insbesondere Arzneimittel,
1. die in geringem Umfang hergestellt werden, **und bei denen auf der Grundlage einer routinemäßigen Herstellung Abweichungen im Verfahren vorgenommen werden, die für einen einzelnen Patienten medizinisch begründet sind**, oder
2. die noch nicht in ausreichender Anzahl hergestellt worden sind, so dass die notwendigen Erkenntnisse für ihre umfassende Beurteilung noch nicht **vorliegen**.

Neu:
(2) Nicht routinemäßig hergestellt im Sinne von Absatz 1 Satz 1 Nummer 2 werden insbesondere Arzneimittel,
1. die in so geringem Umfang hergestellt und angewendet werden, dass **nicht zu erwarten ist, dass hinreichend klinische Erfahrung gesammelt werden kann, um das Arzneimittel umfassend bewerten zu können**, oder
2. die noch nicht in ausreichender Anzahl hergestellt und angewendet worden sind, so dass die notwendigen Erkenntnisse für ihre umfassende Bewertung noch nicht **erlangt werden konnten**.

‚Hospital Exemption' is not for the race horses

... it‘s for the ponies

Hospital Exemption– German Situation

- German Drug Act (AMG) §4b
- *Warrants an authorization from the PEI and a manufacturing license from the federal state authority (e.g. Full GMP !)*

www.PEI.de > Genehmigung von nicht routine-mäßig hergestellten ATMP nach § 4b AMG

Central Marketing Authorisation

Regular market access for ATMP via EU-wide Marketing Authorisation

Challenging with respect to

- **data and paperwork to be generated and submitted**
- **regulatory experience**
- **workload for handling the procedure**
- **time lines and costs**
- **EU wide marketing**

→ **PRIME**

Summary

- Full GMP applies and has to be granted by a manufacturing authorisation (National Authority, Landesbehörden)
- In addition a hospital exemption will be required which will be granted by the national authority (PEI)
- Investigational medicinal products do not fall under 2001/83 EC. They require an IND Filing with the national authority.
- Compassionate Use in Germany may require a permission granted by the PEI (21Abs.2 Nr. 6 AMG) (www.PEI.de)

- Thank you very much for the attention !

Achknowledgements:
Thanks to Egbert Flory and Lucia D`Apote (CAT) for providing slides