Implementation of European Legislations for Cell-based Medicinal Products in Germany

Topics

History and Responsibilities of PEI

Cell-based Medicinal Products:
- Opportunities, Challenges, Examples
- Regulatory Framework in the EU
- Implementation in Germany

Ralf Sanzenbacher

Paul-Ehrlich-Institut
Federal Agency for Sera and Vaccines
Division of Medical Biotechnology
Section Tissue-Engineering & Somatic Cell Therapeutics
D-63225 Langen/Germany
E-mail: sanra@pei.de

History of the Paul-Ehrlich-Institut (PEI)

1972	Establishment as Federal Agency
1994	Responsibility for Blood and Blood Derivates
2000	Accreditation as Notified Body for IVD Testing
Juli 2004	Responsibility für Somatic Cell Therapy and Gene Transfer MP acc. to § 77 AMG
Aug 2004	Responsibility for Clinical Trial Authorisation
Juni 2005	WHO Collaborating Centre for Quality Assurance of Blood Products and IVD
Sept 2005	Responsibility for Tissue Preparations

1896:
Institute for Serum Research
and Serum Testing (Berlin-Steglitz)
First Director: Paul Ehrlich

1900

2000

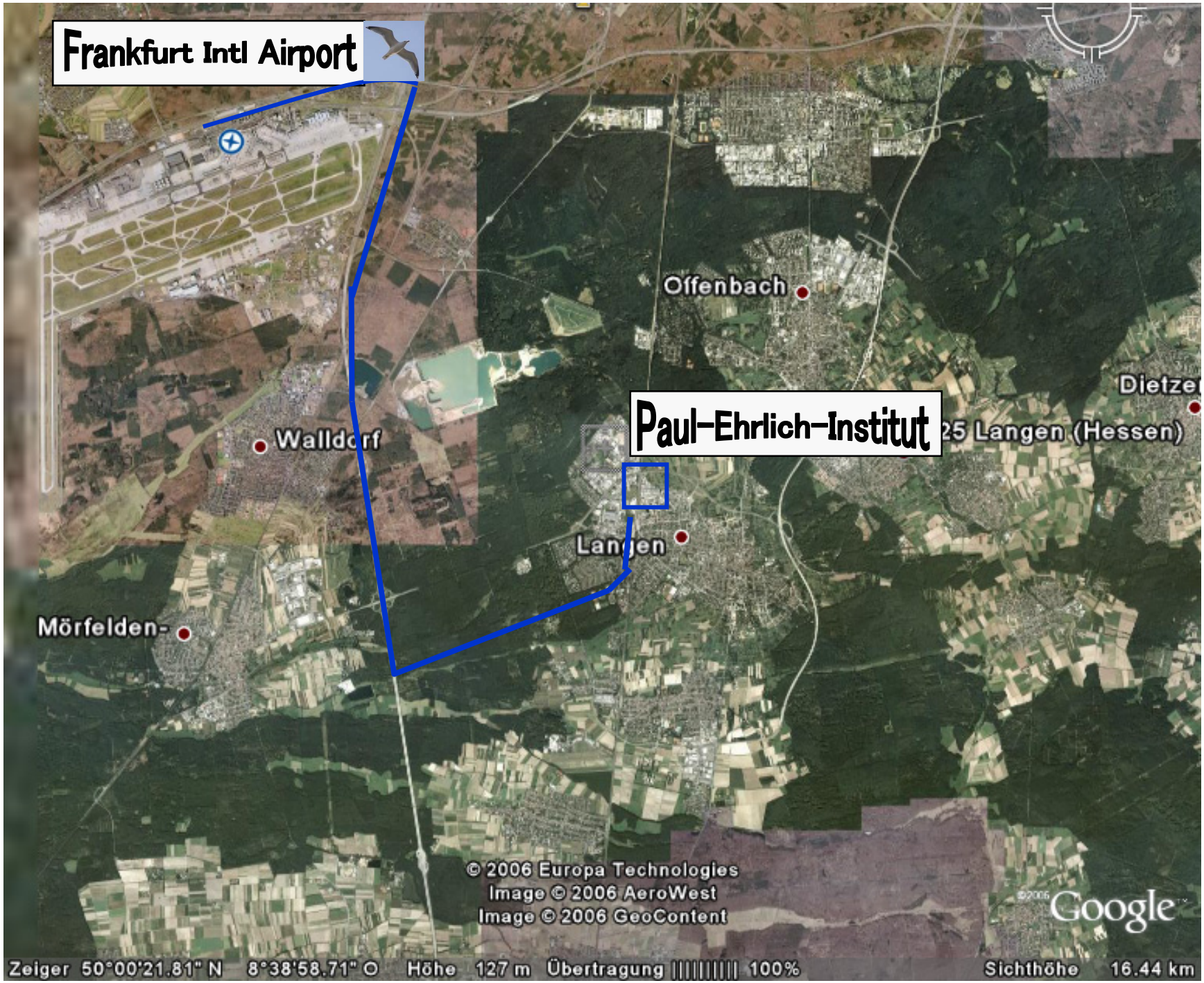
1899:
Royal Institute for
Experimental Therapy
(Frankfurt am Main)

1906:
Georg-Speyer-Haus
(Frankfurt am Main)

1947:
Paul-Ehrlich-Institut
(Frankfurt am Main)

1990:
PEI moves to Langen

today


Frankfurt Intl Airport
Offenbach
Paul-Ehrlich-Institut
Langen (Hessen)
Walldorf
Langen
Mörfelden-
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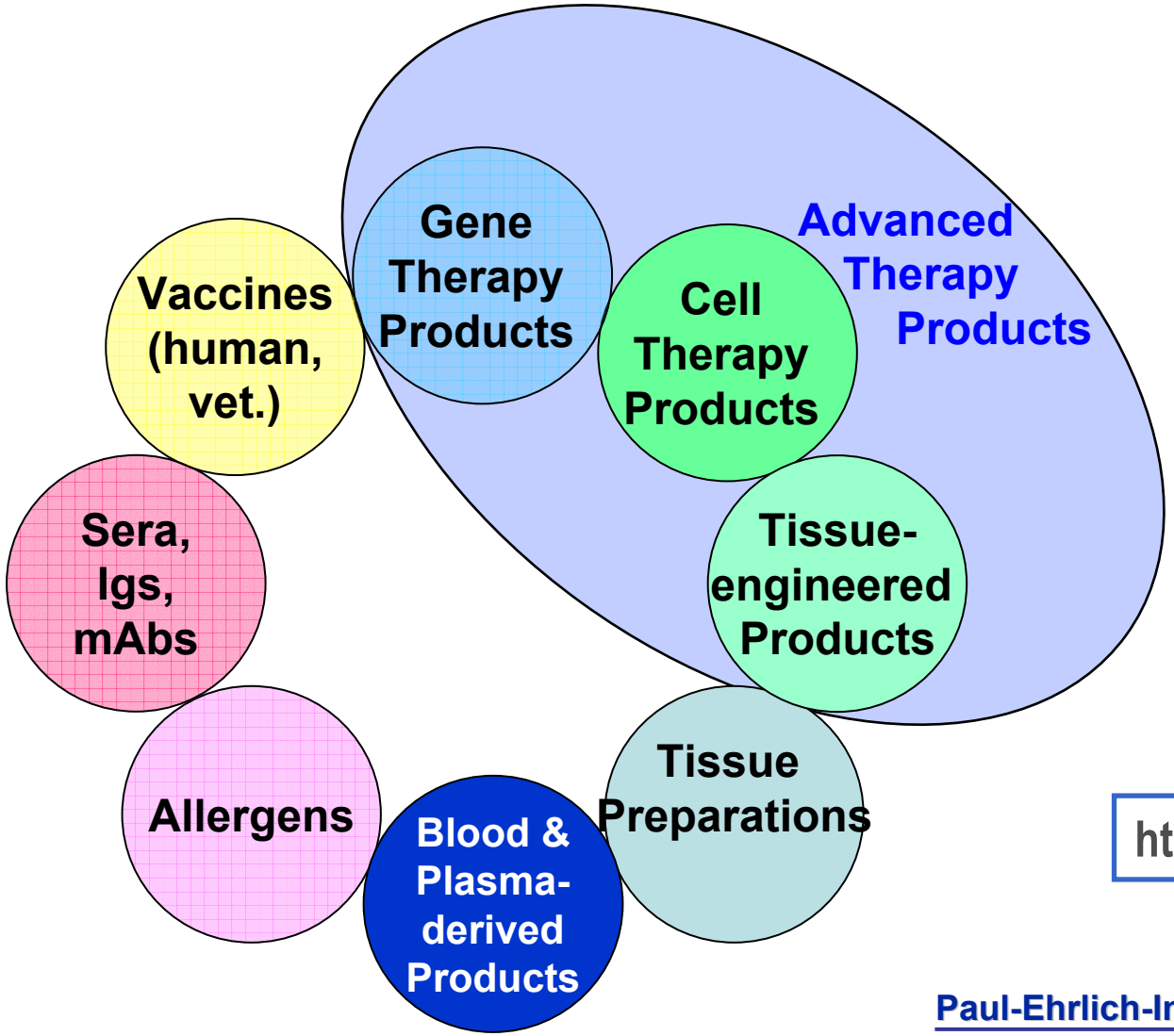
Google
Zeiger 50°00'21.81" N 8°38'58.71" O Höhe 127 m Übertragung 100% Sichthöhe 16.44 km

Medicinal Product Responsibility of the Paul-Ehrlich-Institut (PEI)



http://www.pei.de

Paul-Ehrlich-Institut
Federal Agency for Sera and Vaccines

PEI: National and International Integration

Federal Ministry of Health

Bundesministerium für Gesundheit

PEI
Paul-Ehrlich-Institut
Federal Agency for Sera and Vaccines

BfArM
Federal Institute for Drugs and Medical Devices

BzgA
Federal Centre for Health Education

DIMDI
German Institute of Medical Documentation and Information

RKI
Robert Koch-Institut
Federal Institute for Disease Control and Prevention

EMEA
European Medicines Agency

European Commission

HMA
Heads of Medicines Agencies

EDQM
European Directorate for the Quality of Medicines

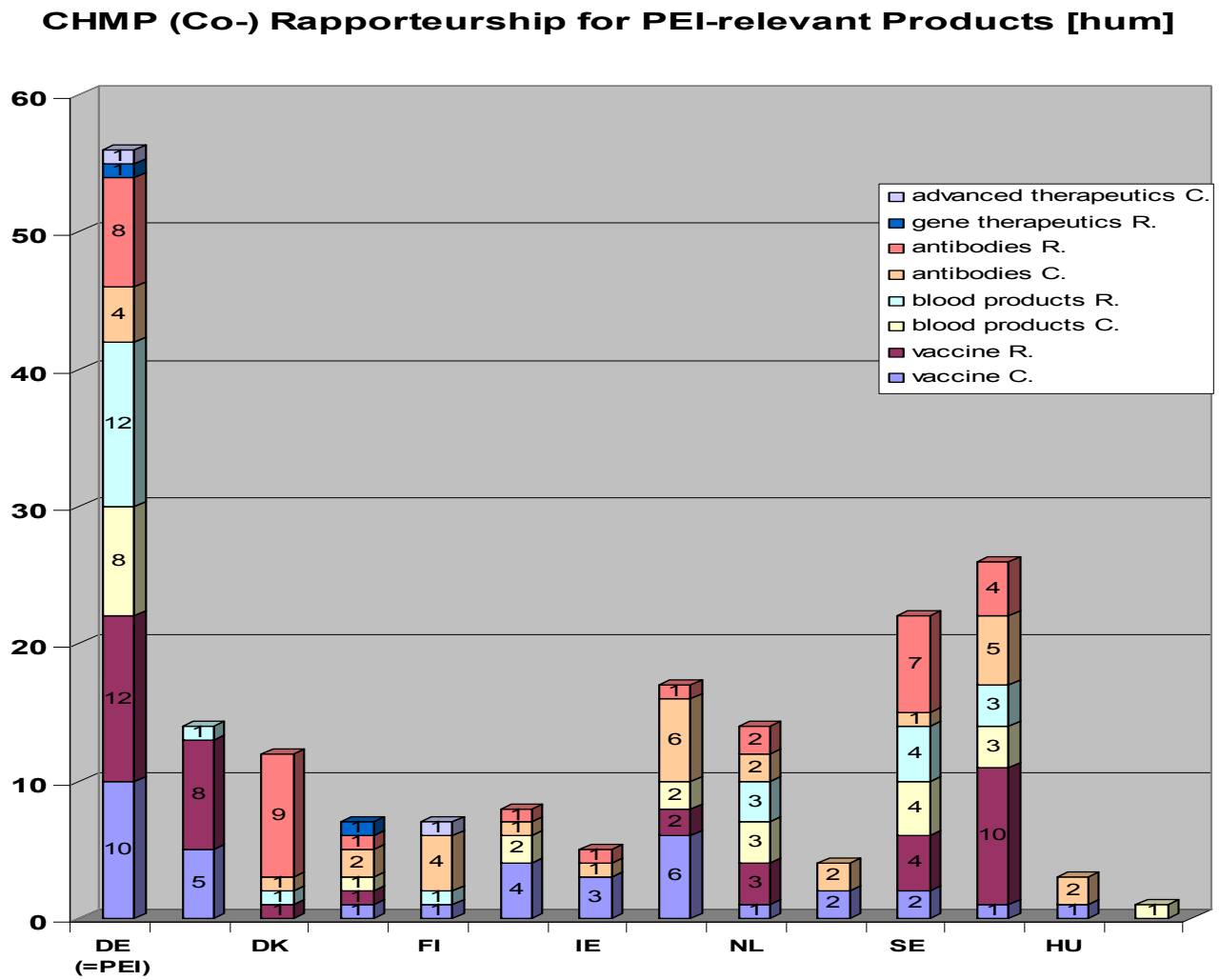
WHO

ICH

Paul-Ehrlich-Institut
Federal Agency for Sera and Vaccines

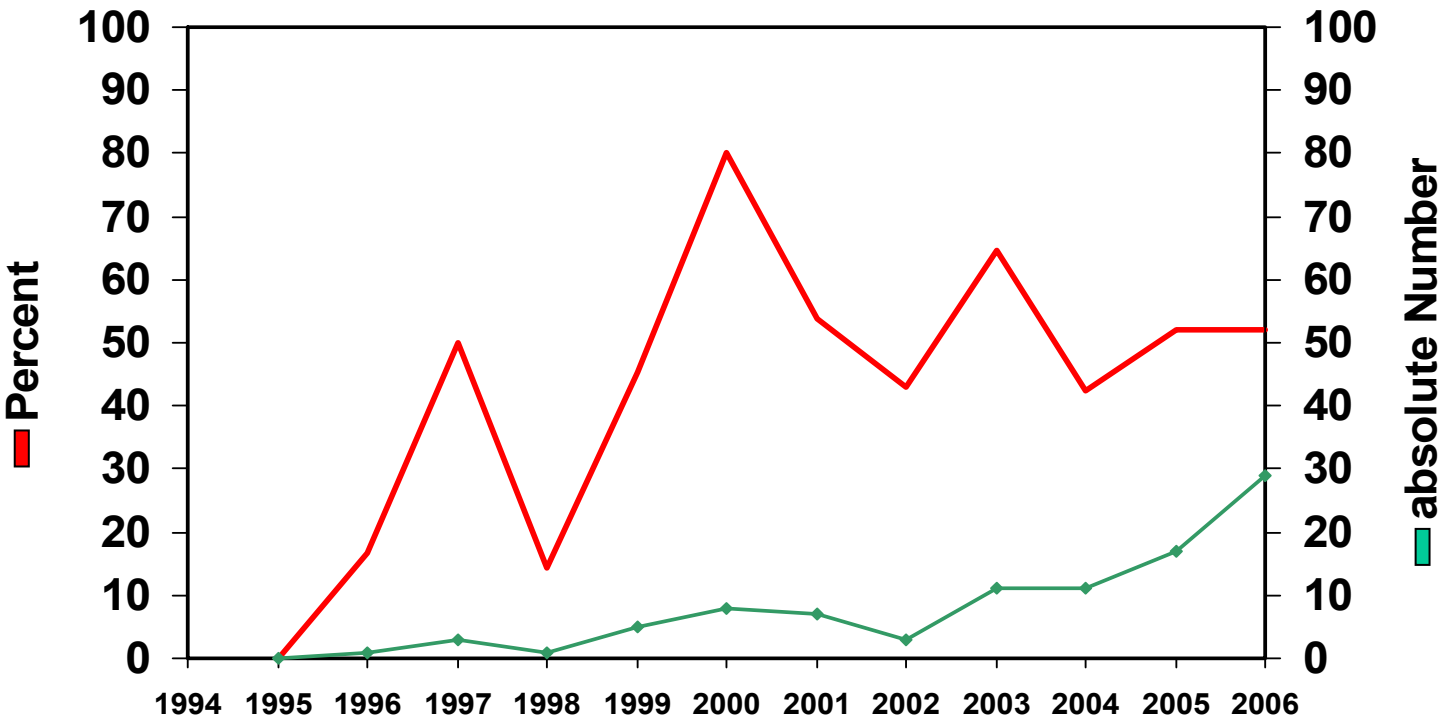
Involvement of PEI in Centralized European Licencing Procedures of Biomedical MPs

Status 31.12.2006



Paul-Ehrlich-Institut
Federal Agency for Sera and Vaccines

Involvement of PEI in EMEA Scientific Advices [Hum] for Biomedical Medicinal Products



Division 6 - Medical Biotechnology (I)

Product Responsibility for MA

Gene Transfer Medicinal Products	(vectors, DNA, gen. mod. cells or micro-organisms)
Somatic Cell Therapy MPs	(human cells; immunotherapy)
Tissue Engineering MPs	(human cells including stem cells)
Xenogeneic Cell Therapy MPs	(xenogeneic cells)
Tissue Preparations	(allogenic tissue)

Working groups

Gene Therapy Working Party

Working Party on Cell-based Products

WHO Clinical Gene Therapy Monitoring Group

others

Medical Biotechnology

Paul-Ehrlich-Institut

Scientific Advice

Manufacture, Clinical Trial

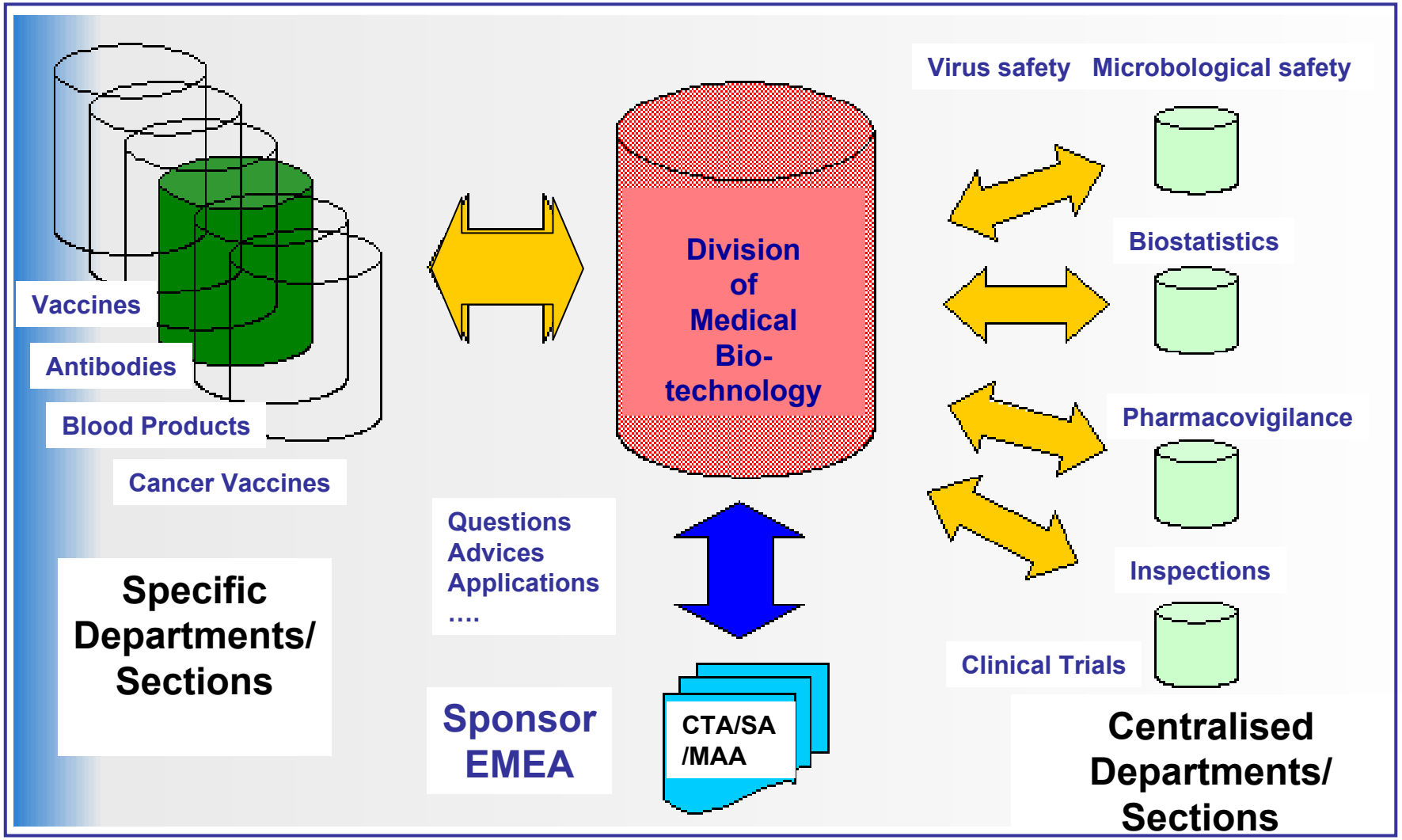
Clinical Trial Advice / Approval Inspections

Advisory service for other authorities and organisations

Basic Scientific Research

Retrovirology	(HIV / SIV and HERV / PERV)
Gene Therapy	(Vector development /AIDS and tumor gene therapy)
Cell Therapy/TE	(Intracellular signaling, stem cell differentiation)

Division 6 - Medical Biotechnology (II)



Implementation of European Legislations for Cell-based Medicinal Products in Germany

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Cell-based Therapies – Opportunities and Challenges (I)

- Promising new treatment concepts and opportunities,
  expected to have major impact on medical practice and public health

- Interdisciplinary medicinal products of high complexity,
  especially when combined with biomolecules, chemical substances,
  biomaterials

- Usually developed by small and medium-sized enterprises,
  universities, hospitals or tissue establishments

- Products in initial phase; limited market but huge potential;
  high risk in product development
  high financial pressure

Cell-based Therapies – Opportunities and Challenges (II)

- Often individualized, patient-specific medicinal products

- Complex, highly science-driven and innovative manufacturing processes specificity of the product often lies within the manufacturing process

- Heterogeneous features of cells from many origins
  - as starting material
  - as active substance of a medicinal product

- Often very limited amount of starting material

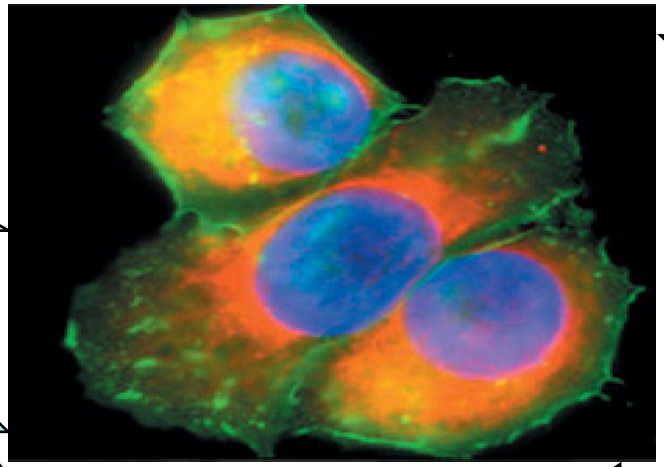
- Special requirements regarding donation, procurement, testing and traceability

- Only partial regulatory framework and regulatory/scientific expertise for evaluation existing

Challenges for approval of cell-based MPs

Source:
donor screening (substitutes for virus inactivation),
microbiology of cell procurement,
banking and history of cell lines,
traceability

Administration:
Final formulation in the clinic,
viability, fragility of product
Relevant function in human
micro environment



Transport to manufacturing facility:
short shelf life
cold chain,
cell viability,
Antibiotics

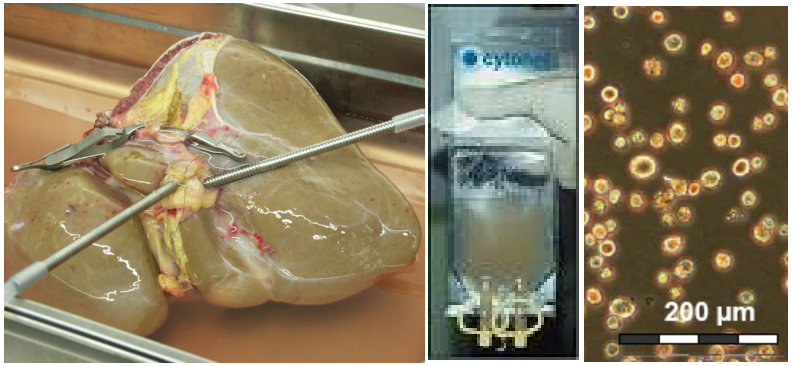
Non-clinical studies:
proof-of-concept,
Identifying of active substance in
cell population
confined localisation
biodistribution
tumorgenicity

Manufacturing:
Microbiological safety concept,
availibility of GMP-grade auxilliary materials and reagents
changes in quality-related cell characteristics upon culturing:
pre-neoblastic transformation, dedifferentiation
validated in vitro surrogate testing methods
robust fast potency assay and release testing methods
Consistency of drug product

Cell Therapy Medicinal Products: Examples

Liver repair

- Allogenic liver cell suspension for treatment of acute sepsis or inherited metabolic liver failure

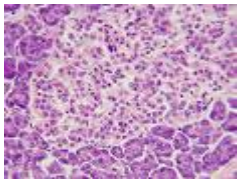


Type I Diabetes

-Allogenic pancreatic islet cell fraction to restore insulin production

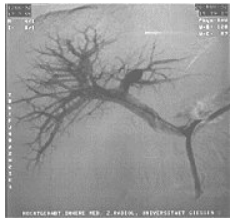
Skin repair

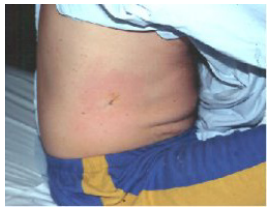
- Different skin cell suspensions for treatment of acute wounds and diabetic foot skin ulcers
- Autologous adipose-derived stem cells for treatment of anal fistula



Immunotherapeutics

- CTLs or NK cell transfer for adoptive immuntherapy





Cell-based therapeutic Vaccines

- Peptide-loaded DC used as tumor vaccines to induce immunity towards tumor-associated antigens
- Fused Tumor/DC hybrid cells

Haematopoetic stem cells

- HSC of different origin, e.g. for haematological indications like AML

Human Tissue Engineered Products: Examples

Cartilage repair

- Autologous chondrocyte transplantation (ACT)
  1st and 2nd generation products

Skin regeneration

- Acute wounds, diabetic foot skin ulcers
- different skin cells (keratinocytes, fibroblasts)
  in combination with a sheet-like matrices/scaffolds

Bone regeneration

- Osteoblasts or bone-marrow-derived stem cells combined
  with ceramic-based scaffolds or biomaterials

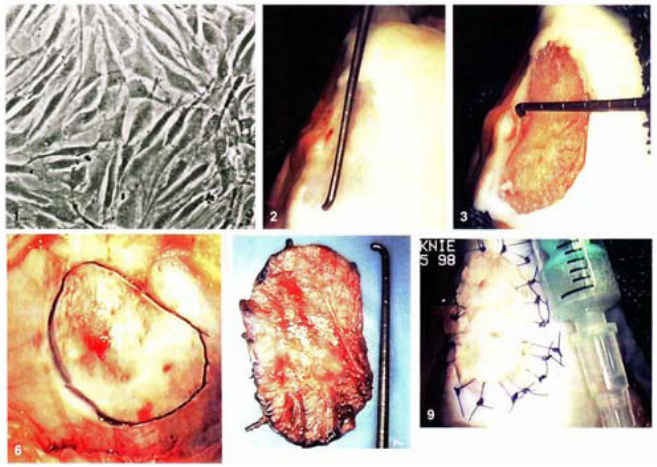
Cardiovascular regeneration

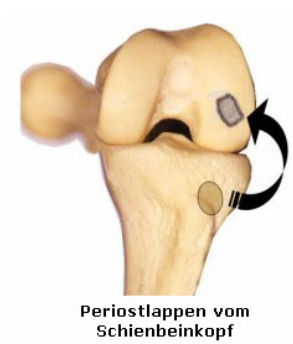
- Hematopoetic stem cells for heart muscle regeneration
- Engineered autologous/allogeneic blood vessels or heart valves

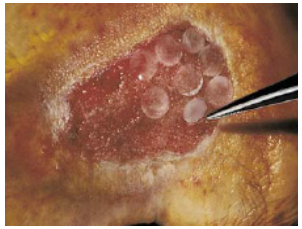
Complete organ engineering

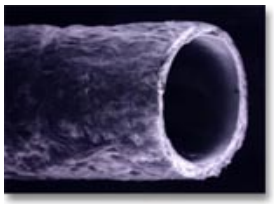
Artificial lymph node

Artificial liver









Cell-based Therapies – The Regulatory Levels

(EC)726/2004: Products for Centralized Procedure

Medicinal products to be mandatory authorised by the Community persuant to Art. 3 and Annex of Reg (EC)726/2004:

- MP developed by means of one of the following biotechnological processes:

- Recombinant DNA technology
- Controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells
- Hybridoma and mAb methods

- MP containing a new active substance, which on the date of the entry into force of this regulation, was not authorised in the Community for the therapeutic indication:

- Acquired immune deficiency syndrome
- Cancer
- Neurodegenerative disorder
- Diabetes
- Auto-immune diseases and other immune dysfunctions*
- Viral diseases *

*[with effect from 20. May 2008]

- Orphan medicinal products persuant to Reg (EC)141/2000

(EC)726/2004: Products for Centralized Procedure

Medicinal products to be optionally authorised by the Community persuant to Art. 3 of Reg (EC)726/2004:

- If the MP contains a new active substance which, on the date of the entry into force of this regulation , was not authorised in the community

- If the applicant shows that the medicinal product constitutes a significant therapeutic, scientific or technical innovation

- If the applicant shows that the granting of authorisation is in the interest of patients at the Community level

Centralised Procedure via EMEA (I)

Pre-Submission Phase

≥ 12 months

Getting information for

- course of actions for centralized procedure
  [www.emea.eu.int/htms/human/presub/index.htm]
- classification request for product at ITF
- possible „Orphan Drug Status“ for product
  [www.emea.eu.int/htms/human/COMP/orphapp.htm]
- possible „Conditional marketing authorisation or „Exeptional circumstances“
- possible „SME Status“ for PU

Scientific Advice(s) / Protocol assistence(s)

- formalised procedure
  [www.emea.eu.int/htms/general/contacts/CHMP/CHMP_SAWP.html]

6-7 months

Nomination of Rapporteur /Co-Rapporteur by CHMP

- formalised procedure

(Pre-Submission Briefing Meeting with Rap/Co-Rap)

Centralised Procedure via EMEA (II)

Submission / Validation Phase

- Application submission in CTD
- EMEA proof of formal completeness and payment of fees
- day 0 — Start of procedure and „Timetable“ by EMEA
- day 80 — AR by Rapporteur /CoRapp
- day 100 — Comments on ARs by CHMP
- day 115 — Discussion and comments by Working parties of CHMP
- day 120 — Adoption of „Consolidated List of Questions“ by CHMP
  Notification to applicant
- ≤ 6 month — clock stop — (Inspection / Company meeting with Rapp/CoRapp on request)
- Submission of Company responses to LoQ

Centralised Procedure via EMEA (III)

Secondary Evaluation Phase

clock stop

day 121 — Resumption of Procedure

day 150 — Evalution of Responses by Rapp/CoRapp / Preparation of „Joint Rapp/CoRapp AR“

day 170 — Comments to Joint AR by CHMP

day 180 — Decision or request for hearing of applicant at CHMP with „List of outstanding issues“

≤ 3 month — clock stop

day 181 — (Hearing at CHMP)

day 210 — Preparation and finalisation of opinion by CHMP ; Adoption of opinion and AR (EN)

Translation of SPC in all MS languages

day 300 — Adoption by European Commission = Marketing authorisation

Cell-based Therapies – The Regulatory Levels

Legislation relevant for
all medicinal products

Directive 2001/83/EC (Nov 2001) amended by 2003/63/EC (Jun 2003)
Community code relating to all medicinal products for human use
Technical requirements with a view to licensing

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

Legislation relevant for
all tissue- and cell-based MP

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

10.12.2007 EN Official Journal of the European Union L 324/121

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)

Advanced Therapies – The new Regulation

Key Elements

Integration of TEMPs as ATMP and therefore MPs

Centralized assessment for ATMPs by European Medicines Agency

Tailored Adaption of GCP-, GMP- and other Guidelines

Mandatory !

Creation of a new expert comittee (CAT) at EMEA

no interference with national ethical decisions on acceptance of the use of specific cell types (i.e. ESCs)

voluntary/unpaid donation; anonymity

post-authorisation follow-up of efficacy, adverse reactions, risk management, long-term traceability

Incentives: SA: 90% fee reduction for SME, ≥ 65% for others)
MAA: 50% fee reduction for SME under spec. circumst

The New ATMP Regulation: Transitional periods

§ 30
Entry into force Regulation applies from **30 Dec 2008**

Extension to Proposal !

§ 29
Transition period products legally on the market in acc. with national or Community legislation on 30 Dec 2008 shall comply with this regulation no longer than

3 y for ATMPs **30 Dec 2011 !**
4 y for TEMPs **30 Dec 2012 !**

….no fee shall be payable to the Agency in respect of applications submitted for the authorisation of ATMPs mentioned above

During transitional period,
centralised MAA has to be submitted,
but is free of fee !

The New ATMP Regulation: EC/EMEA Implementation Plan 2008

Amendment of Annex I (Part IV) of 2001/83/EC

Update of definitions, inclusion of dossier requirements for TEMP and update for GTMP

Composition of of CAT

Rules of procedure, appointment of members and chairperson

Tasks of CAT

Formulation of draft opinions, consultation, advices

Guidelines on GMP specific for ATMP

Guidelines on GCP specific for ATMP

Certification of Q/N-C data (Art. 18)

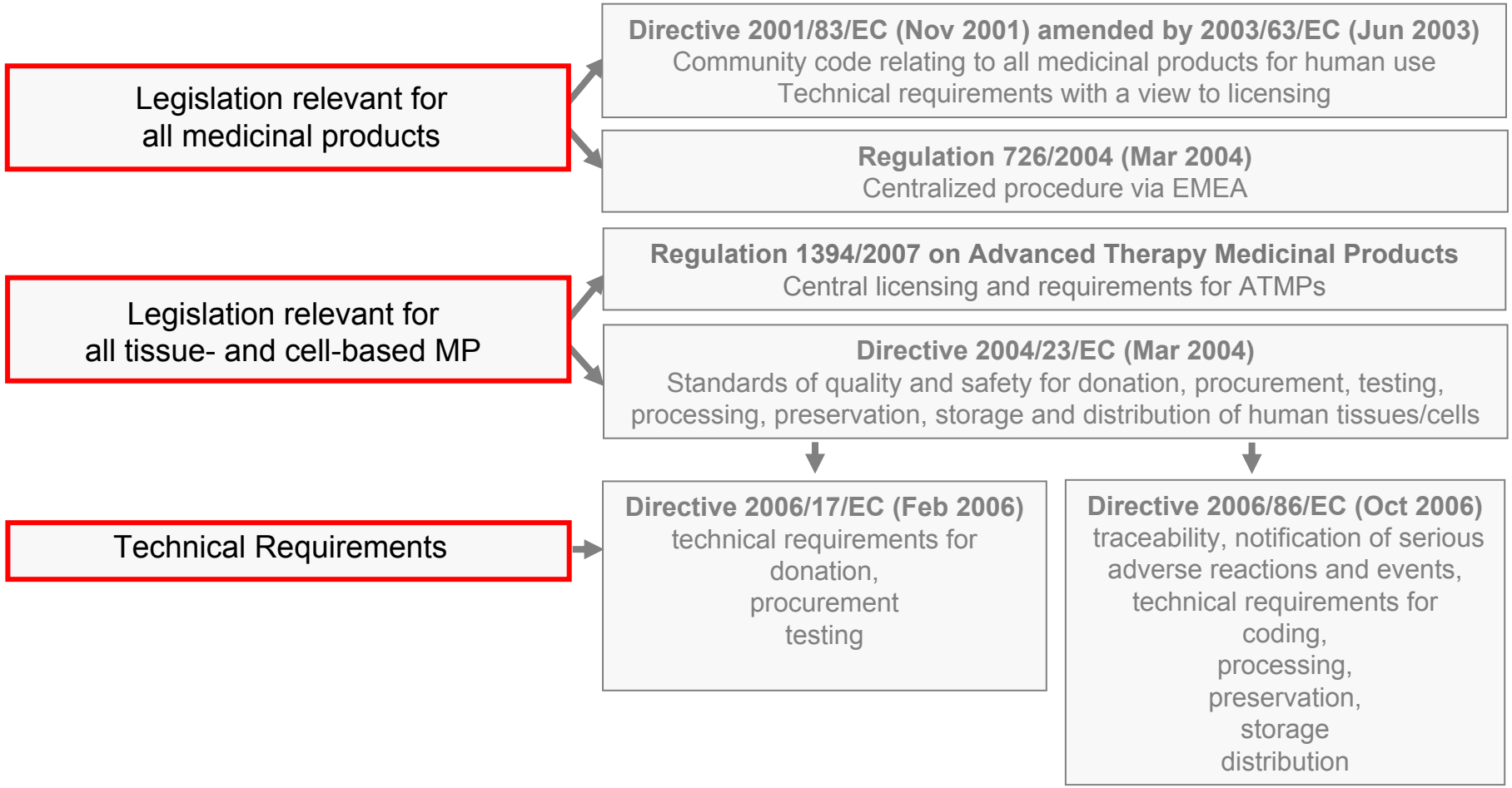
Formulation of procedure, requirements, templates

Traceability

Post authorisation follow-up

Guideline on PM efficacy & safety follow-up and RMP

Cell-based Therapies – The Regulatory Levels



Directive 2004/23/EC (I)

on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells

Applies for Human **tissues** and **cells** and **manufactured products** derived from these for human applications

Including

- HSCs derived from peripheral blood, umbilical cord and bone marrow
- Reproductive cells (sperm, egg)
- Foetal tissues/cells
- Embryonic and adult SCs

Excluding

- Tissues/cells used as autologous graft within same surgical procedure and without any banking
- Blood/blood components as defined by 2002/98/EC
- Human organs/parts of organs, if intended function corresponds to same purpose as entire organ
- Tissues/cells of animal origin
- Tissues/cells used cells used for research purposes

Directive 2004/23/EC (II)

Transposition into national laws

until April 2006 (in Germany : „Gewebegesetz“, and „AMWHV“ 2007)

more stringent national measures possible
(i.e. restriction of source/type of donated cells to be used)

Objectives

provide hormonized framework laying down quality and safety standards

- accreditation and licensing of tissue establishments
- establishement of specific technical requirements for each step in the application process
- establishment of a notification system for adverse events/reactions
- establishment of QM-, traceability- and recall-systems (European coding system, public register of tissue establishments, annual report of tissue establishments to CA)

definition of transparent criteria for access and distribution

promotion of voluntary, non-profit donation system within EU

protection of donors and their personal data

supervision and inspections (≤2y) by MS competent authority

Directive 2006/17/EC

Technical requirements for the donation, procurement and testing of human tissues and cells

ANNEX I Selection criteria for donors of tissues/cells (except reproductive cells)

Selection criteria for donors based on

- *risk evaluation related to application of product and established documented criteria*
- *medical/behavioural history (questionnaire and interview)*
- *physical examination*
- *testing*

General exclusion criteria

- cause of death unknown or disease with unknown aetiology
- HIV-1/2, HBV, HCV, HTLV-I/II
- risk of transmission of prion disease
  (CJD, vCJD, degenerative neurological systemic infection)
- certain malignant diseases, ie. carcinoma when influencing quality
- certain chronic systemic autoimmune disease when influencing quality
- transplantation with xenografts
- recent vaccination with live attenuated virus when risk of transmission

Not necessarily for autologous use

Directive 2006/17/EC

Technical requirements for the donation, procurement and testing of human tissues and cells

ANNEX II Laboratory tests for donors of tissues/cells (except reproductive cells)

HIV-1/-2	anti-HIV-1/2	
HBV	HBsAg anti-HBc	further tests when anti-HBc$^+$ and HBsAg$^-$
HCV	anti-HCV-Ab	
Syphilis	validated specific or non-specific test	
HTLV	anti-HTLV	only for high-risk donors
RhD, HLA, Malaria CMV, Toxoplasma, EBV, Trypanosoma cruzi		„may be required“

-test on serum/plasma

-qualified/authorized lab

- validated tests

Also for autologous donors when cells are stored or cultured !

Directive 2006/86/EC

Implementing 2004/23/EC as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells

Transposition
into national laws until Sept 2007/2008

Requirements for tissue establishments

Requirements for cell preparation processes

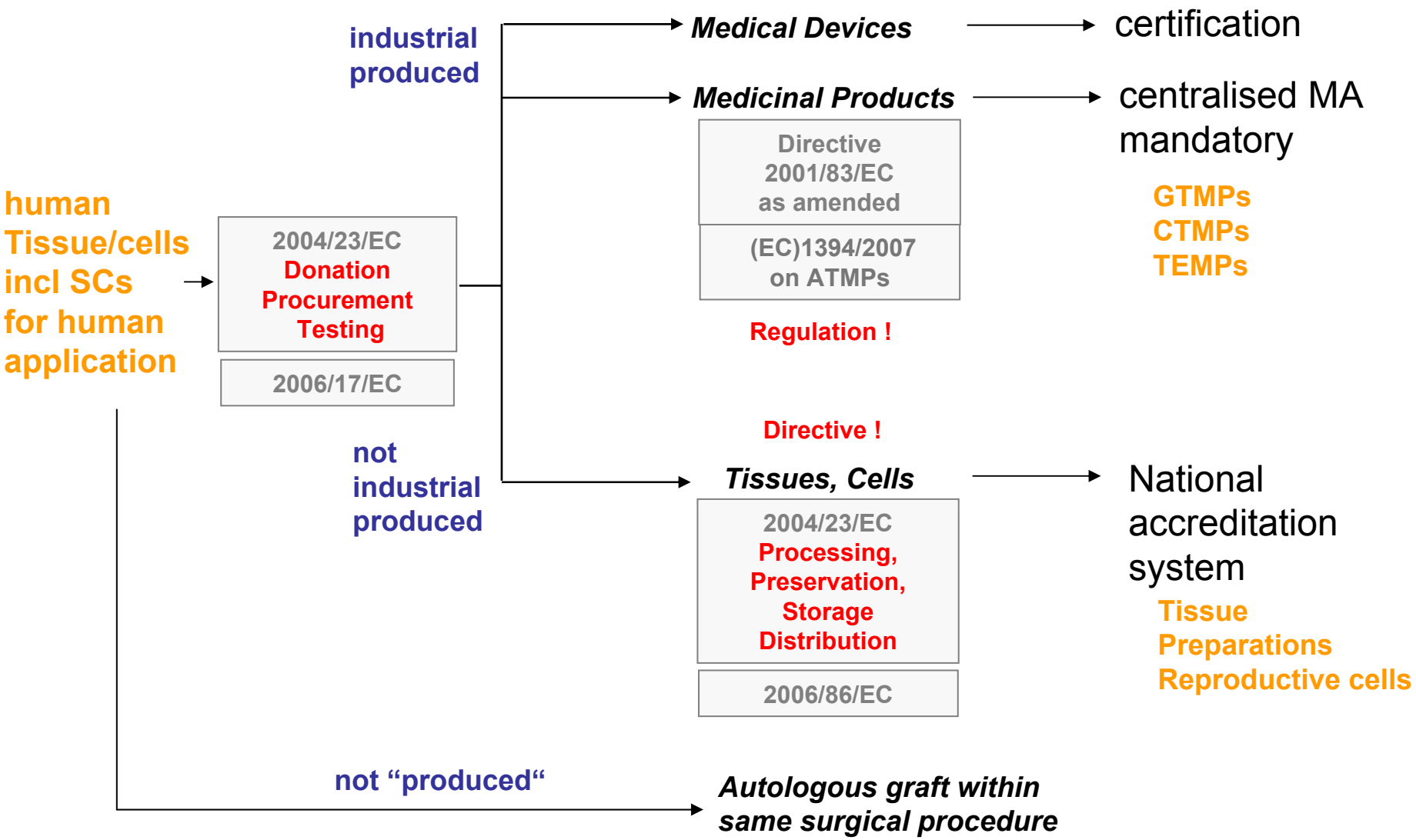
Establishement of procedures for notification on serious adverse reactions/events

Annual reports of MS to Comission about notifications

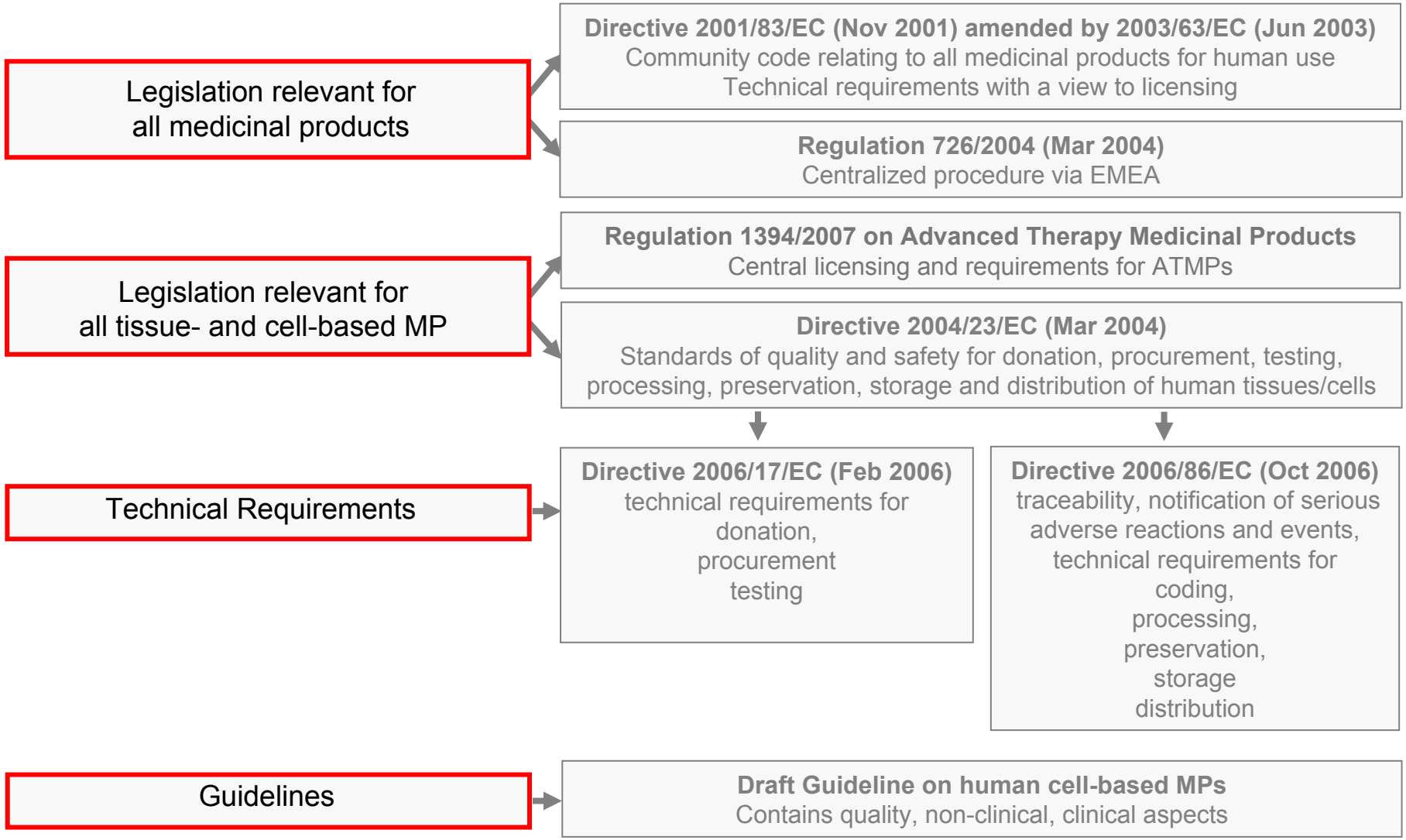
Traceability (≥ 30y)

Development of a european coding system for donated tissues and cells

2004/23/EC Requires National Implemetation in MS



Cell-based Therapies – The Regulatory Levels



Draft Guideline on Cell-based Medicinal Products

European Medicines Agency

London, 11 January 2007
Doc. Ref. EMEA/CHMP/410869/2006

COMMITTEE FOR HUMAN MEDICINAL PRODUCT (CHMP)

DRAFT

GUIDELINE ON HUMAN CELL-BASED MEDICINAL PRODUCTS

DRAFT AGREED BY CPWP AND BWP	December 2006
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	25 January 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 July 2007

This guideline replaces guideline CPMP/BWP/41450/98 Points to Consider on the Manufacture and Quality Control of Human Somatic Cell Therapy Medicinal Products.

Comments should be provided using this template to patrick.celis@emea.europa.eu
Fax +44 20 7418 8545

KEYWORDS	Human cell-based medicinal products, quality and manufacturing aspects, Non-clinical development, Clinical development.

To be finalized in 2Q 2008

Draft Guideline on Cell-based Medicinal Products

Scope

Addresses development, manufacturing, quality, risk-analysis, non-clinical and clinical aspects of CBMPs

intended for products entering the MAA;
principles may be considered for clinical trials

1-3. Background, Scope, Legal Basis
4.1. Risk analysis
4.2. Quality & manufacturing aspects
4.3. Non-clinical development
4.4. Clinical development

Applies for

Viable human CBMPs
- allogeneic or autologous
- undergoing a manufacturing process,
- may be genetically modified
- may be combined

Applies not for

- Non-viable cells/cellular fragments
- CBMPs containing xenogeneic cells

4.1. Risk analysis approach to justify development & evaluation plans

The risk is dependent on the origin of the cells, the manufacturing process, the non cellular components and on the specific therapeutic use.

The results of the risk analysis should be used:

- to identify risk factors associated with quality and safety of the product
- to determine the extent and focus of the data required during non-clinical and clinical development;
- to establish the need for risk minimisation activities,
- to determine the post market risk management activities to be specified in the pharmacovigilance plan.

Following 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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Cell-based Medicinal Products:

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- Regulatory Framework in the EU

- **Implementation in Germany**

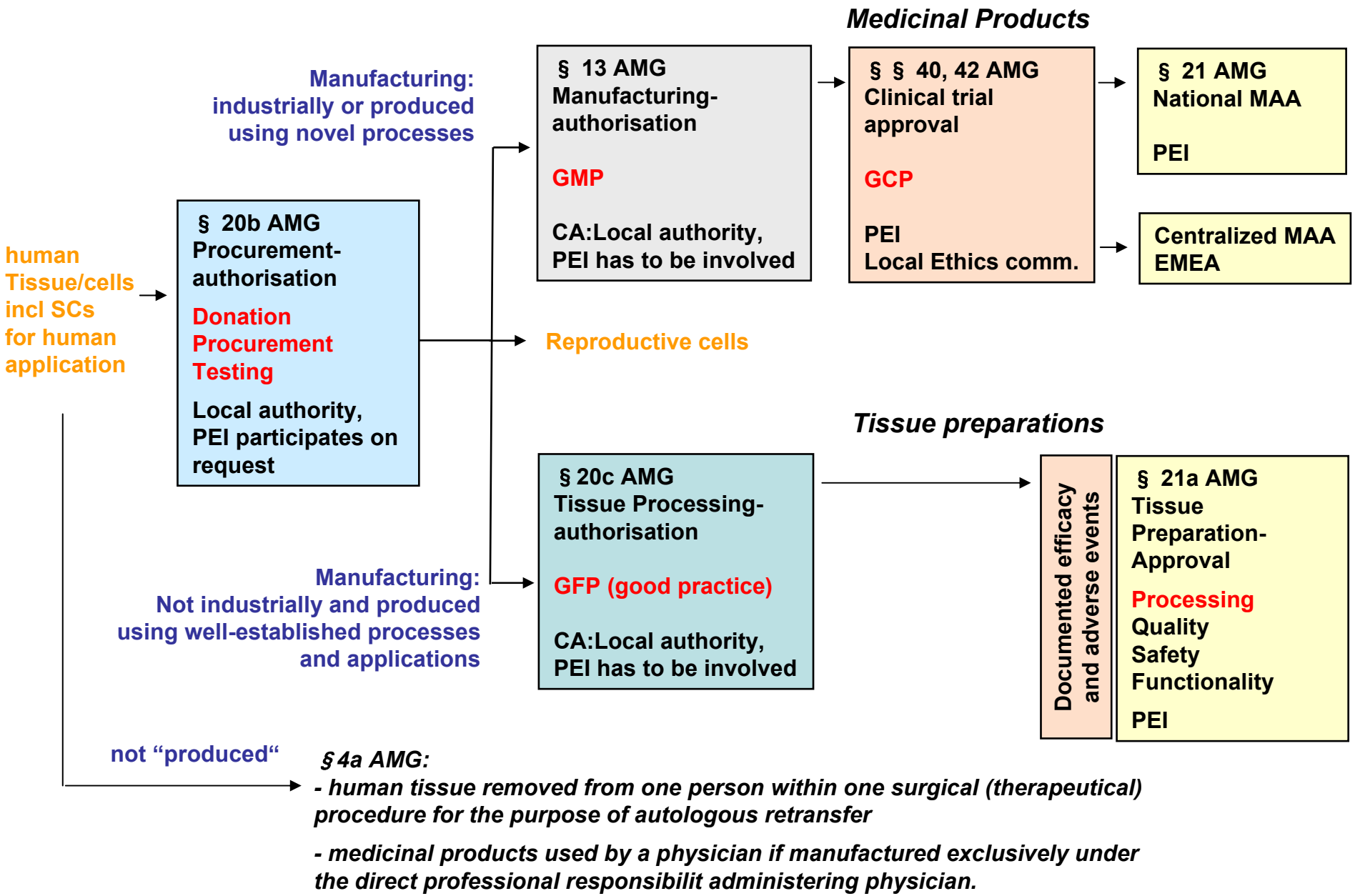
Implementation in Germany:
„Tissue Law“ from 1st August 2007

No stand-alone law, but integrates EU Provisions by changing several existing national legislations *(“omnibus bill“)*, e.g.

- ☞ **Drug Law**
- ☞ **Transplantation Law**
- ☞ **Transfusion Law**
- ☞ **Regulation for manufacturing pharmaceuticals and active pharmaceutical substances**

Update of Definitions, integration of Donation and Procurement of human Organs and Tissues,….

National Implemetation in German Drug Law (AMG)



Tissue Preparations: Examples

Musculo-sceletal Tissue

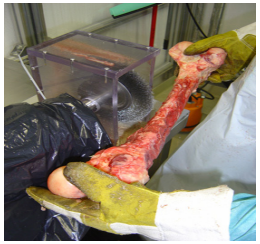
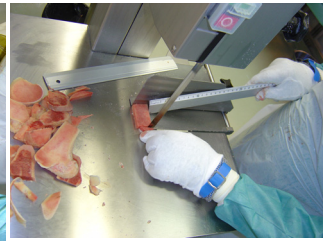
bone tissue

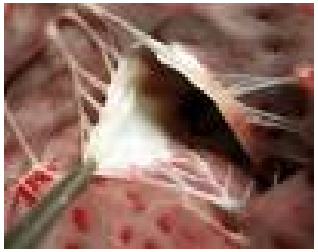
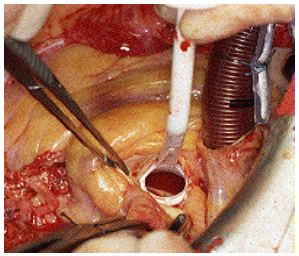
femoral head

Soft tissues, tendon

(Dura mater)

Avitalised skin

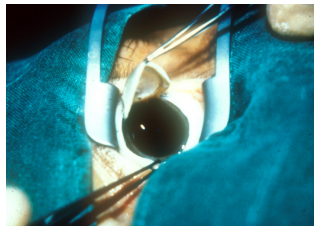



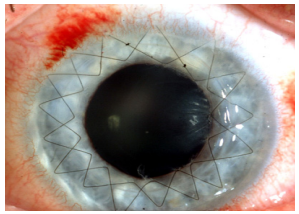
Heart valves

Blood stem cells for hematopoetic reconstitution

Foetal, embryonic, adult

Cornea



Requirements for Placing on the German Market

	Manufacturing Authorisation	*Clinical trial*	*Marketing authorisation*
Gene transfer MP Somatic Cell Therapy MP	local authority, PEI on request	Approval by PEI	centralised by EMEA
Tissue-Engineering MP		Approval by PEI from 12/2012	centralised by EMEA from 12/2012
Human Tissue	local authority, PEI on request since 9/2006	/	/
Human Tissue Preparations	local authority, PEI on request since 1997 (except Cornea)	(PEI since)	national by PEI

EudraCT Clinical Trial Applications in the EU
(3Q 2005 to 3Q 2007)

Somatic cell therapy MPs	*3Q 2005*	*3Q 2006*	*3Q 2007*
(trials / original products)	*(25 / 13)*	*(73 / 59)*	*(132/112)*
cancer immunotherapy	3	23	45
cardio-vascular	4	17	31
skin/liver/lung/eye/diabetes/intestine/bone TE	5	12	28
neurological	1	4	5
lymphohistiocytosis (HLH)	–	1	1
AIDS	–	1	1
infertility	–	1	1
	13	40	112

Implementation of European Legislations for Cell-based Medicinal Products in Germany

Thank you for your Attention

Ralf Sanzenbacher

Paul-Ehrlich-Institut
Federal Agency for Sera and Vaccines
Division of Medical Biotechnology
Section Tissue-Engineering & Somatic Cell Therapeutics
D-63225 Langen/Germany
E-mail: sanra@pei.de