The new Regulation (EC) 1394/2007 on Advanced Therapy Medicinal Products
Update on Cell Therapy and Tissue Regeneration Products in Germany

Topics

CELL-BASED PRODUCTS:

Responsibilities and History of PEI
Product examples
Quality issues

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Update on Cell Therapy and Tissue Regeneration Products in Germany

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PEI: National and International Integration

German Federal Ministry of Health

PEI: National and International Integration

- 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

Outside Institutions

- EMEA: European Medicines Agency
- European Commission
- HMA: Heads of Medicines Agencies
- EDQM: European Directorate for the Quality of Medicines
- WHO
- ICH
History of the Paul-Ehrlich-Institut (PEI)

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

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

1900:

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

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

1972: Establishment as Federal Agency
1994: Responsibility for Blood and Blood Derivates
2000: Accreditation as Notified Body for IVD Testing
July 2004: Responsibility für Somatic Cell Therapy and Gene Transfer MP
Aug 2004: Responsibility for Clinical Trial Authorisation
June 2005: WHO Collaborating Centre for Quality Assurance of Blood Products and IVD
Sept 2005: Responsibility for Tissue Preparations

1990: PEI moves to Langen

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

- Vaccines (human, vet.)
- Sera, Igs, mAbs
- Allergens
- Blood & Plasma-derived Products
- Tissue Preparations
- Advanced Therapy Products
- Gene Therapy Products
- Cell Therapy Products
- Tissue-engineered Products

http://www.pei.de

Paul-Ehrlich-Institut
Federal Agency for Sera and Vaccines
Tissue Preparations: Examples

Musculoskeletal Tissue

- Bone tissue
- Femoral head
- Soft tissues, tendon
  (Dura mater)
- Avitalised skin

Heart valves

Blood stem cells for hematopoietic reconstitution

- Foetal, embryonic, adult

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

Type I Diabetes
- Allogenic pancreatic islets to restore insulin production

Skin
- Different skin cell suspensions for treatment of acute wounds
- Autologous adipose-derived stem cells for treatment of anal fistula

Immunotherapeutics
- CTLs or NK cell transfer for adoptive immunotherapy

Cell-based therapeutic Vaccines
- Peptide-loaded DC used as tumor vaccines
- Fused Tumor/DC hybrid cells

Adult stem cells
- MSC and HSC of different origin, e.g. for haematological indications like AML
- Treatment of anal fistula
Human Tissue Engineered Products: Skin Replacement

EpiDex
(Euroderm, Germany)

www.euroderm-biotech.com

TisCover
(A-Skin, NL)

www.A-skin.nl

Apligraf
(Organogenesis, USA)

www.organogenesis.com
www.apligraf.com

www.euroderm-biotech.com

ulcer

week 24

Paul-Ehrlich-Institut
Federal Agency for Sera and Vaccines
Human Tissue Engineered Products: Cartilage Repair 1st, 2nd, 3rd Gen

BioSeed-C
(BioTissue Technologies, Germany)

Chondrosphere
(co.don AG, Germany)

Novocart / Novocart 3D
(TETEC AG, Germany)

Hyalograft-C
(Fidia Advanced Biopolymers, Italy)

ChondroCelect
(TiGenix, Belgium)

Carticel / MACI
(Genzyme, USA)
Human Tissue Engineered Products: Vessel Replacement

Lifeline
(Cytograft, USA)

(Vasotissue, Germany)

www.cytograft.com

www.vasotissue.com
Human Tissue Engineered Products: Examples

Cartilage repair
- Autologous chondrocyte transplantation (ACT, ACI)

Skin regeneration
- Acute wounds, diabetic foot skin ulcers, veinous ulcer
- different cell types (keratinocytes, fibroblasts)
  - in combination with a sheet-like matrices/scaffolds
- MSC-like cells for hair regeneration (androgenetic alopecia)

Bone regeneration
- Osteogenic or bone-marrow-derived stem cells combined
  with scaffolds or biomaterials

Cardiovascular regeneration
- Hematopoetic stem cells for heart regeneration
- Engineered autologous/allogeneic blood vessels or heart valves,
- Endothelialised stents

Complete organ engineering
Artificial lymph node
Artificial liver
Division 6 - Medical Biotechnology (I)

Product Responsibility for

- 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

Advisory Service for Authorities, Organisations

Medical Biotechnology
Paul-Ehrlich-Institut

MAA Assessment
Scientific Advice
Clinical Trial
Advice/Inspections/Approval
Manufacturing
Advice/Inspections

Basic Scientific Research

- Retrovirology (HIV / SIV and HERV / PERV)
- Gene Therapy (Vector development / gene therapy)
- Cell Therapy/TE (Intracellular signaling, stem cell differentiation)
Division 6 - Medical Biotechnology (II)

Product-specific Departments/Sections

- Vaccines
- Immunology
- Blood Products
- Cancer Vaccines

Questions
Advises
Applications

Sponsor
EMEA

Centralised Departments/Sections

- Virus safety
- Microbiological safety
- Biostatistics
- Pharmacovigilance
- Inspections
- Clinical Trials

Division 6
PTL Core Team

CTA/SA/MAA

Paul-Ehrlich-Institut
Federal Agency for Sera and Vaccines
The Regulatory Levels in the EU on Human Tissues and Cells

Human Tissues/Cells for Human Application
- incl. SCs
- excl. Blood Blood Components

- not "prepared"
- not industrially prepared produced using well known process

Tissues, Cells
- Dir 2004/23/EC
  - Processing, Preservation, Storage, Distribution,…
- Dir 2006/86/EC

National Accreditation System
- Tissue Preparations (bone, heart valves, cornea)
- SCs for Haematopoietic Use

- Autologous Grafts within same Surgical Procedure
- Parts of Organs for Homologous Use

Reproductive Cells
- Dir 2006/17/EC

Medicinal Products
- industrially prepared produced using novel process
- new active substance
- specific indications
- (EC)1394/2007 on ATMPs
- Dir 2001/83/EC

Centralised MA
- ATMPs

Paul-Ehrlich-Institut
Federal Agency for Sera and Vaccines
## Requirements and CA‘s for Placing on the German Market

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

Paul-Ehrlich-Institut
Federal Agency for Sera and Vaccines
Involvement of PEI as Rap/CoRap in Centralized European Licencing Procedures of Biomedical MPs

Status 31.12.2007
Involvement of PEI in EMEA Scientific Advices [Hum] for Biomedical Medicinal Products

The graph shows the involvement of PEI in EMEA Scientific Advices [Hum] for Biomedical Medicinal Products from 1994 to 2007. The y-axis represents the percent and absolute number of involvements, while the x-axis represents the years. The involvement is indicated by the red line on the graph.
## EudraCT Clinical Trial Applications in the EU
### (3Q 2005 to 3Q 2008)

<table>
<thead>
<tr>
<th>Somatic cell therapy MPs</th>
<th>3Q 2005</th>
<th>3Q 2006</th>
<th>3Q 2007</th>
<th>3Q 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>(trials / original products)</em></td>
<td>(25 / 13)</td>
<td>(73 / 59)</td>
<td>(132/112)</td>
<td>(213/171)</td>
</tr>
<tr>
<td>cancer immunotherapy</td>
<td>3</td>
<td>23</td>
<td>45</td>
<td>70</td>
</tr>
<tr>
<td>cardio-vascular</td>
<td>4</td>
<td>17</td>
<td>31</td>
<td>44</td>
</tr>
<tr>
<td>skin/liver/lung/eye/diabetes/intestine/bone TE</td>
<td>5</td>
<td>12</td>
<td>28</td>
<td>48</td>
</tr>
<tr>
<td>neurological</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>lymphohistiocytosis (HLH)</td>
<td>–</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>AIDS</td>
<td>–</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>infertility</td>
<td>–</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

| **Total**                                        | **13**  | **59**  | **112** | **171** |
## EudraCT Clinical Trial Applications in the EU (3Q 2005 to 3Q 2008)

<table>
<thead>
<tr>
<th>Gene therapy/transfer MPs (trials / original products)</th>
<th>3Q 2005 (19 / 9)</th>
<th>3Q 2006 (51 / 23)</th>
<th>3Q 2007 (69 / 35)</th>
<th>3Q 2008 (124 / 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cancer</td>
<td>4</td>
<td>13</td>
<td>20</td>
<td>29</td>
</tr>
<tr>
<td>cardio-vascular</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>metabolic diseases (diabetes)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>autoimmune diseases</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>HIV vaccine</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>infectious disease</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>(chronic Hepatitis C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>neuronal</td>
<td>–</td>
<td>1</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>vaccines (monovalent, combi-)</td>
<td>–</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

| Total Applications                                      | 9                | 23               | 35               | 59               |
Procedures for tissue/cell-products at PEI Div 6
(without Therapeutic Tumor Vaccines)
(without non-manipulated HSC)
Discussion of scientific principles, development strategies

Briefing meeting EMEA ITF, GTWP/CPWP

Discussion of scientific principles & classification

Discussion of specific questions for MAA formal answered by CHMP

Product specifications

MAA

national SA

EMEA SA

Phase III

Phase II/III

Large-scale GMP manufacture

Phase I/II

Orientation phase

Non-clinical studies

Small-scale GMP manufacture

Manufacturing authorisation

First proof-of-concept in animal

In vitro findings

Paul-Ehrlich-Institut
Federal Agency for Sera and Vaccines
From bench to bedside: How much do we need to know?
Issues to be addressed for approval of cell-based MPs

- Procurement
- Administration
- Transport
- Clinical
- Non-clinical
- Manufacturing
CBMPs – Quality aspects

Starting material – How to guarantee „external“ control of cell sourcing?

- Limited time and amount of tissue available for testing of acceptance criteria
- Control of donation: Intensive donor screening must substitute for virus inactivation
- Getting consent in time
- Banking and history of cell lines
- Training of procurement team for specific needs
- Microbiology of cell procurement
- Assure consistent isolation of cells/tissues
- Linking different traceability systems, e.g. in hospitals

2006/17/EC Selection criteria for donors based on...
- risk evaluation related to application of product and established criteria
- Medical/behavioural history (questionnaire, interview)
- Physical examination
- Testing
### ANNEX II  Laboratory tests for donors of tissues/cells (except reproductive cells)

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1/2</td>
<td>anti-HIV-1/2</td>
</tr>
<tr>
<td>HBV</td>
<td>HBsAg, anti-HBc, further tests when anti-HBc+ and HBsAg+</td>
</tr>
<tr>
<td>HCV</td>
<td>anti-HCV-Ab</td>
</tr>
<tr>
<td>Syphilis</td>
<td>validated specific or non-specific test</td>
</tr>
<tr>
<td>HTLV</td>
<td>anti-HTLV, only for high-risk donors</td>
</tr>
<tr>
<td>RhD, HLA, Malaria</td>
<td>„may be required“</td>
</tr>
<tr>
<td>CMV, Toxoplasma, EBV, Trypanosoma cruzi</td>
<td>-test on serum/plasma</td>
</tr>
<tr>
<td></td>
<td>-qualified/authorized lab</td>
</tr>
<tr>
<td></td>
<td>- validated tests</td>
</tr>
</tbody>
</table>

Also for autologous donors when cells are stored or cultured!
CBMPs – Quality aspects

Reagents, other materials, excipients – Where to get?
– How to test?
– How control costs?

✘ Certificates for animal-derived reagents (eg, origin, TSE, adv. agents)

✘ Change to non-animal derived products not always possible or may have major impact on product

✘ For many reagents no pharmaceutical grade available

✘ Identity testing on small batches, e.g. collagenase
Challenges in microbial safety of CBMPs

Sterility of source material can not be guaranteed
Comparabre to transfusion medicine where 0.2 to 0.5 %
of cellular blood components (Thrombocytes)
are bacterially contaminated, e.g. Staph. epidermidis
Skin as tissue source
Increasing incidence of multi-resistant hospital strains
(MRSA, Acinetobacter, Vancomycin-resistant Enterococci)
Non- sporocidal disinfection procedures

Source material cannot be sterilised

Final products cannot be sterilised
e.g. by heat, gas, γ-rays, filtration, 0.2 µm filters
Use of antibiotics only masks bacterial contamination,
concentration might be lower in patient
Challenges in microbial safety of CBMPs

Sterility testing underlay “sampling error”

i.e. the potential result “The test sample is sterile!” gives no significant information on the whole volume of product/intermediate

Antibiotics in culture medium

Short shelf life of final product

Established methods for sterility testing are not always applicable:
- Conventional sterility testing (Pharm Eur 2.6.1.Sterility) takes 14 day; turbidity
- Automated sterility testing (Pharm Eur 2.6.27) takes 7 days

Results are not available at time of release / application to patient
Growth of *Pseudomonas fluorescens* in BacT/Alert at 32°C, 34°C und 35°C

T. Montag-Lessing, PEI
Sven Deutschmann, Roche Diagnostics

no growth at 36 and 34°C
Challenges in microbial safety of CBMPs

Consequences:

Need for a complex strategy in microbial safety of cell products (taking over of experiences of transfusion medicine ?)

Need for specific assessment for product and manufacturing process as a whole, including procurement

Need for development of novel reliable rapid test systems

Need for revision of current guidelines
CBMPs – Quality aspects

Manufacturing

– Product is the Process!
– Primary cells are not GMP grade!

✘ Ensuring consistency of final product while allowing variability in some process steps due to variability of primary cells

✘ Ensuring comparability upon process changes / upscaling

✘ Process optimization automatisation sometimes not feasable „Scale out manu-facturing“
training of staff

✘ In-process controls optimal tests: measure process variables meaningful, realtime, rapid, quantitative, objective, robust

How much „similarity“ do we need?
CBMPs – Quality aspects

Example Cell culture expansion – Which parameters are critical / important? – Which are needed / suitable as IPCs?

✘ Viability
✘ Population doublings, survival
✘ Morphology
✘ Confluency
✘ Functional stability / (de-) (re-) differentiation ?
✘ Senescence
✘ Genetic / epigenetic stability

http://www.biotissue-tec.com
CBMPs – Quality aspects

Characterisation / Release Specifications

✗ Tumorgenicity (pre-neoblastic transformation, karyotype)
✗ Structural characteristics, if essential
✗ Stability
✗ ✗ Cell viability
✗ ✗ Identity (phenotypic and/or genotypic)
✗ ✗ Cell purity
✗ ✗ Impurities (product-/process-related, degradation products, adventitious agents)
✗ ✗ Potency
✗ ✗ Sterility
✗ ✗ Total cell number
CBMPs – Quality aspects

ICH Q6B: *Potency is the quantitative measure of biological activity based on the attribute of the product, which is linked to the relevant biological properties*

- should be based on the intended biological effect which should ideally be related to the clinical response
- can be *in vitro* or *in vivo* test
- can be surrogate marker
- can also be measured on mode of action (e.g. ectopic model)
- ideally in place when first IMD is produced
- combination of assays may be needed during development
- markers for potency and purity should not be mixed
- reference to preclinical and clinical data may be needed
CBMPs – Quality aspects

Transport – How to keep the product „alive“?

✗ Fragility / short shelf life of cells and/or whole product

✗ Product is likely sensitive to temperature changes, light, vibration, pH shifts, ….

✗ Identification of a qualified shipping contractor

✗ Logistics at end user, e.g. appropriate storage, cooling,…

Administration – Hospital as „final manufacturing facility“?

✗ Need for on-site preparation step?

✗ Need for „GMP-status“ at hospital?

✗ Logistics, critical time of delivery
4.3. Non-Clinical Development

**General aspects**

– Conventional requirements of Dir 2001/83/EC for pharmacological & toxicological testing may not always be appropriate; deviation should be justified.

– Objectives of the non-clinical studies are to demonstrate **proof-of-principle**, define the pharmacological & toxicological effects predictive of the human response.

– The **goals of non-clinical studies** include:
  - provide information to select safe doses for clinical trials
  - support route of administration & application schedule
  - support duration of follow-up time
  - identify target organs for toxicity
  - identify parameters to monitor in patients
Issues to be addressed for approval of cell-based MPs

**Administration**
- on-site preparation
- logistics

**Procurement**
- Donor screening
- Microbiology of procurement
- Banking and history of cell lines
- Traceability systems

**Transport**
- Validation

**Manufacturing**
- Antibiotics
- Microbiological safety
- Availability of GMP-grade materials
- Quality-related cell characterisation (e.g., pre-neoablasic transformation, dedifferentiation)
- Consistency
- Valid predictive potency test
- Robust fast release specifications

**Clinical**
- ensure relevant function in human microenvironment
- validity of dose finding
- endpoints
- comparators
- long-term follow up

**Non-clinical**
- Selection of suitable (homologous) animal models
- evaluation of relevant function in vitro / in vivo
- confined localisation
- Biodistribution
- secretion of other biologically active molecules
- Tumorigenicity, immunogenicity

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Federal Agency for Sera and Vaccines
Cell-based Therapies – Progressive adjustment of regulatory demands in the course of product development

fast evolving science and legislation

Procurement authorisation

GMP
Manufact. license

QA, QC
Preclinical

Phase I

QA, QC
Clinical

Phase II

GMP-status
Product specifications

Phase III

„Complete“

MAA

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Federal Agency for Sera and Vaccines
Regulatory framework is (co)evolving constantly.
Keep track! Use expert counsel! Products and regulations might not fit together!

Interact early and constantly with regulatory bodies.
Prepare your questions precisely! Use data-driven approach!
Regulatory bodies will not do your product development!
Keep in mind: due to the novelty of products and regulations regulatory procedures might move on slower than you expect.

Know your manufacturing process.
Keep it as simple as you can!
Install early an effective quality system!

Characterise your product as best as you can as early as you can.
Define potency! Think about consistency!
Prospectively think of comparability: Every change may have regulatory impacts!

Identify most relevant preclinical models.

Think prospectively of the clinical development program.

Highlight the advantages of your product compared to competitors.
Update on Cell Therapy and Tissue Regeneration Products in Germany

Thank you for your Attention,

and special thanks to
C. Schneider, PEI
T. Montag-Lessing, PEI

Ralf Sanzenbacher

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Section Tissue-Engineering & Somatic Cell Therapeutics
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