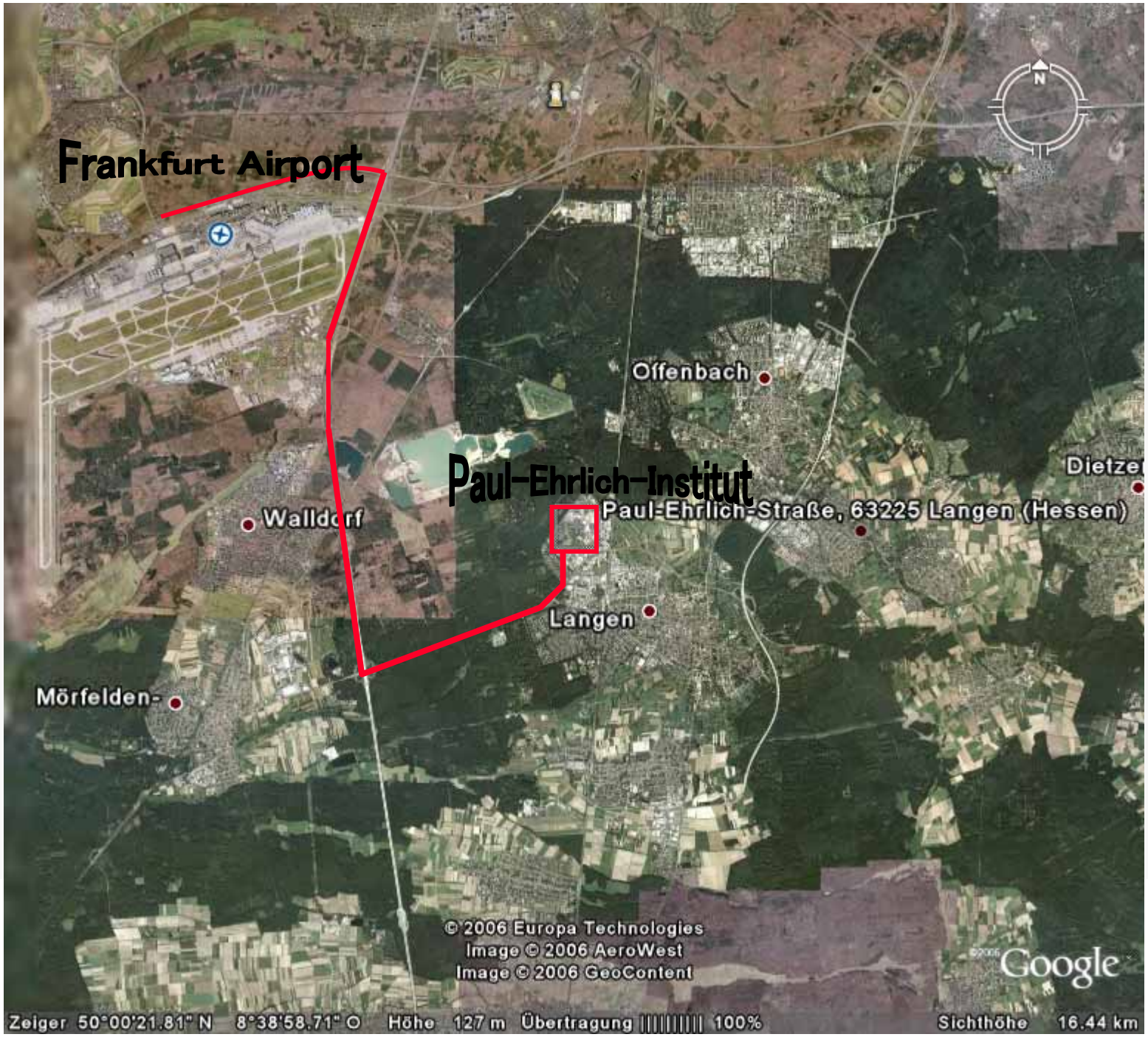
Advanced Therapy Medicinal Products: Present and Future Regulation in the EU

- Current Advanced Therapy Regulations in the EU
- GTMP Regulations
- CTMP Regulations
- Proposal of the EC for a Regulation on Advanced Therapies

Klaus Cichutek
Paul-Ehrlich-Institut, 63225 Langen, Germany
Chair, CHMP/EMEA GTWP

E-mail: **cickl@pei.de**
Tokyo, 15 February 2007


Frankfurt Airport
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Zeiger 50°00'21.81" N 8°38'58.71" O Höhe 127 m Übertragung 100%
Sichthöhe 16.44 km

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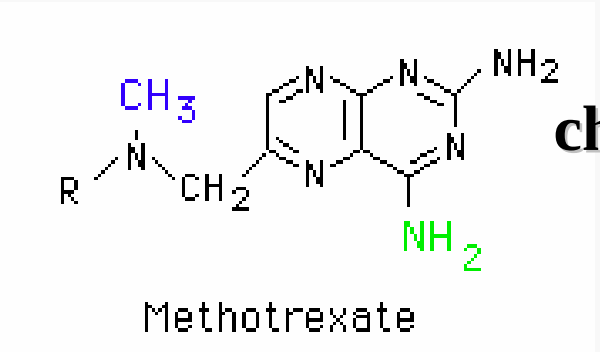
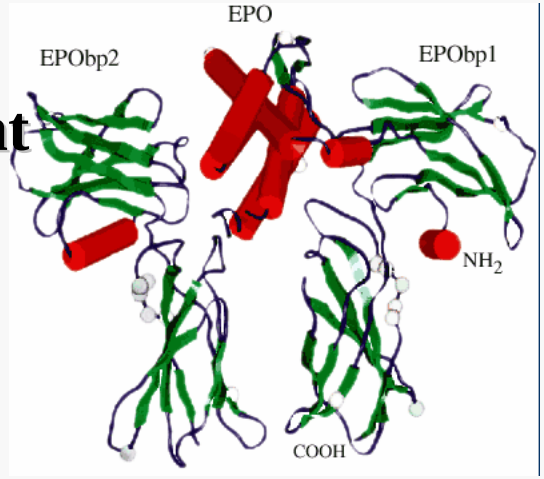
A change in paradigm: genes and manipulated cells as products

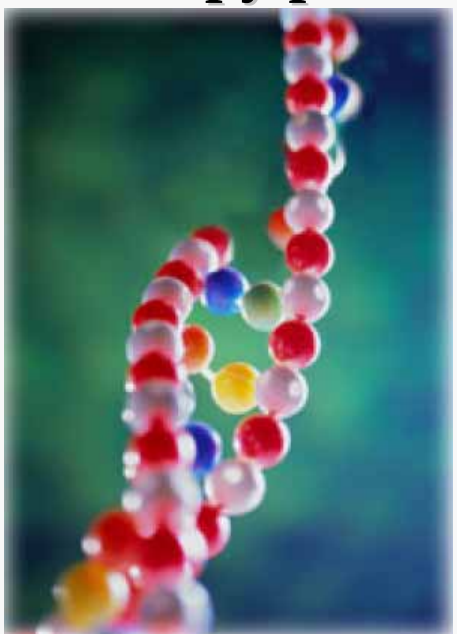


chemicals

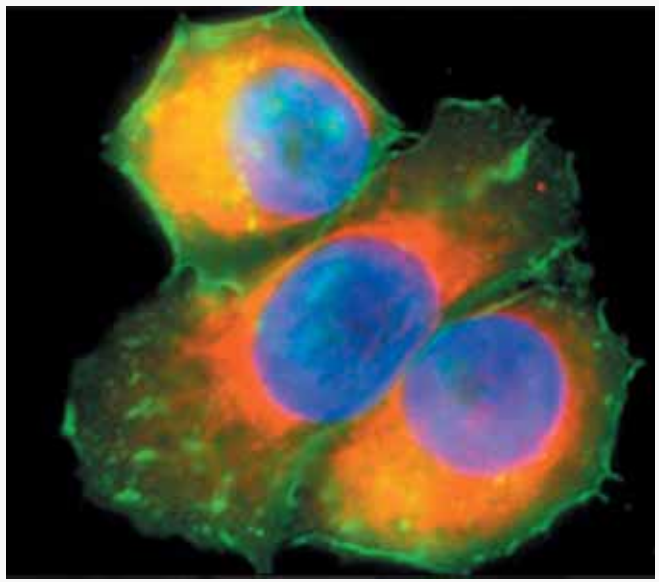
recombinant proteins



gene therapy products



somatic cell therapy products



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

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.

-> New Annex I, Part IV, to Directive 2001/83/EC

Advanced therapy products at present: gene therapy and somatic cell therapy products

- Legal EU definition according to Directive 2001/83/EC

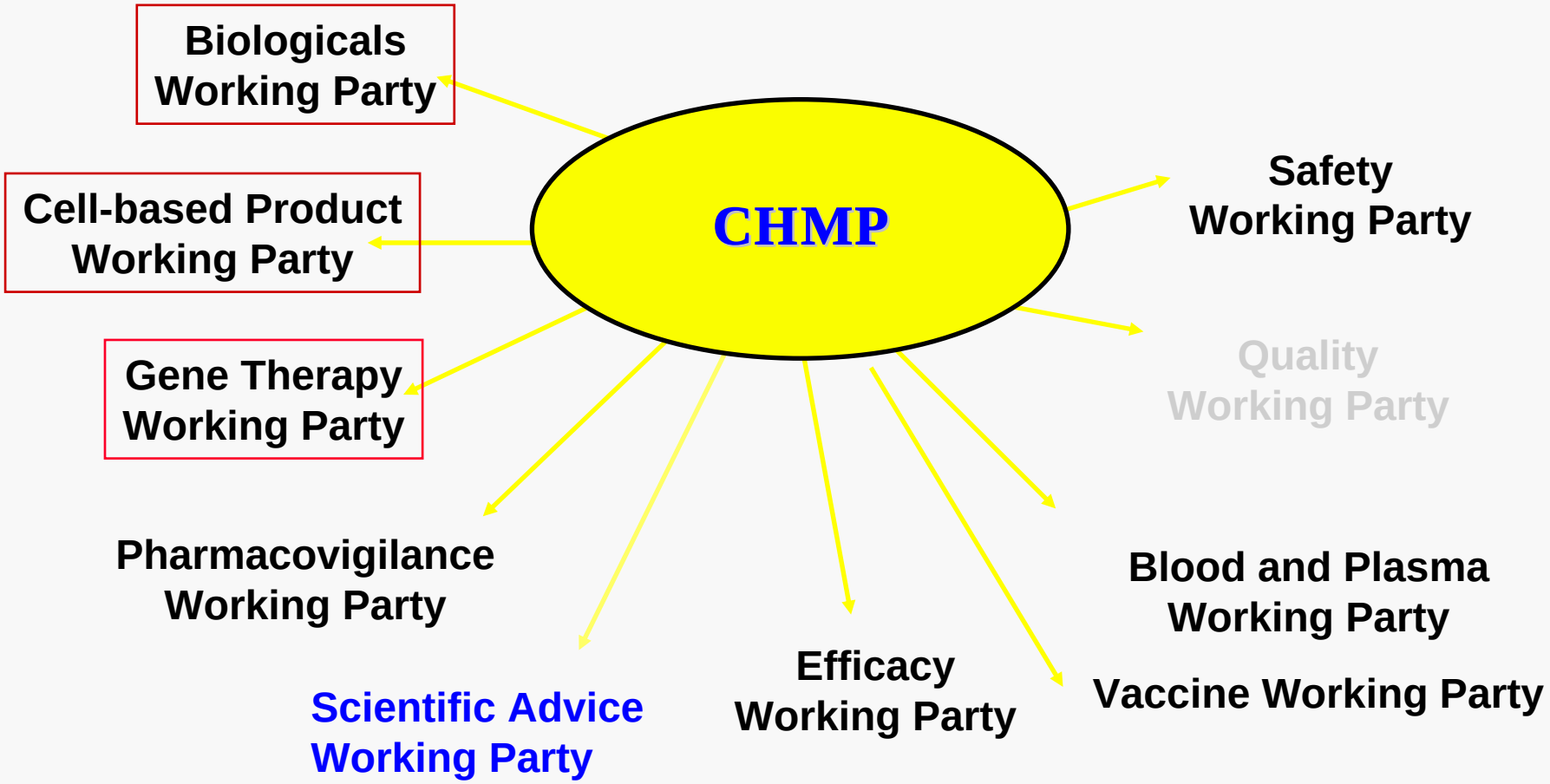
  - Gene Therapy Medicinal Products

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.

  - Somatic Cell Therapy Medicinal Products

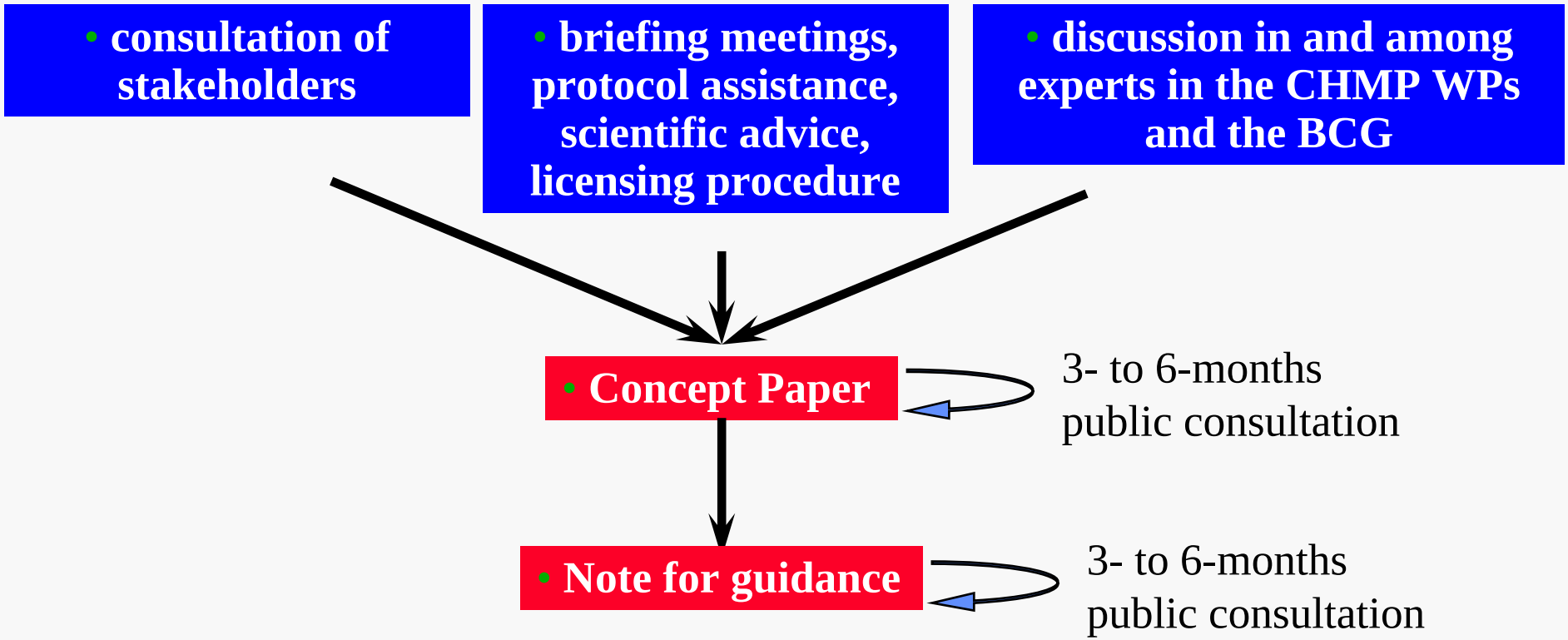
For the purposes of this Annex, somatic cell therapy medicinal products shall mean the use in humans of autologous (emanating from the patient himself), allogeneic (coming from another human being) or xenogeneic (coming from animals) somatic living cells, the biological characteristics of which have 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).

CHMP and WPs collaborate in support of advanced therapy product development

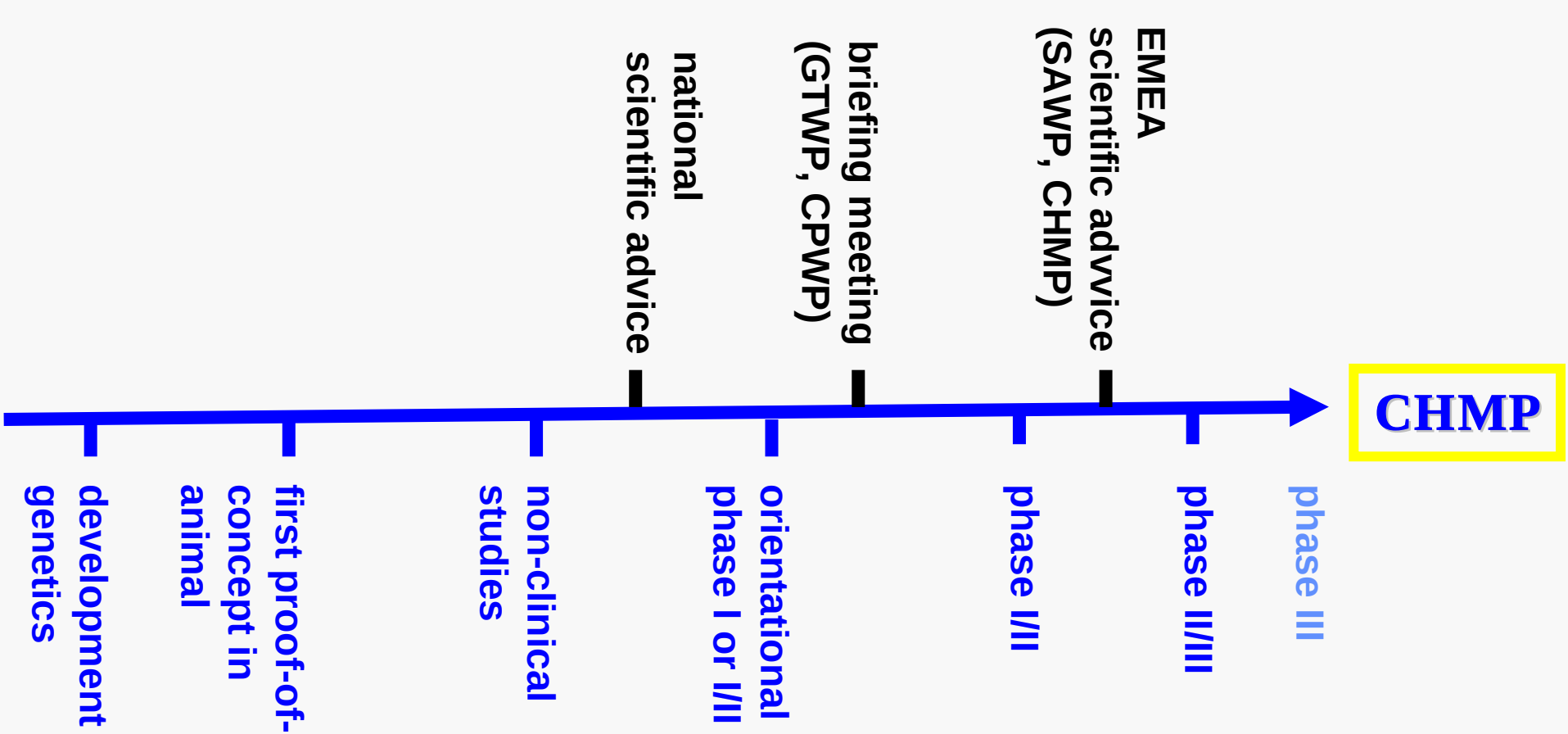


+ Specific ad-hoc working groups or sub-group meetings when needed

Concept Papers notify the public about guideline development



Scientific advice during MP development



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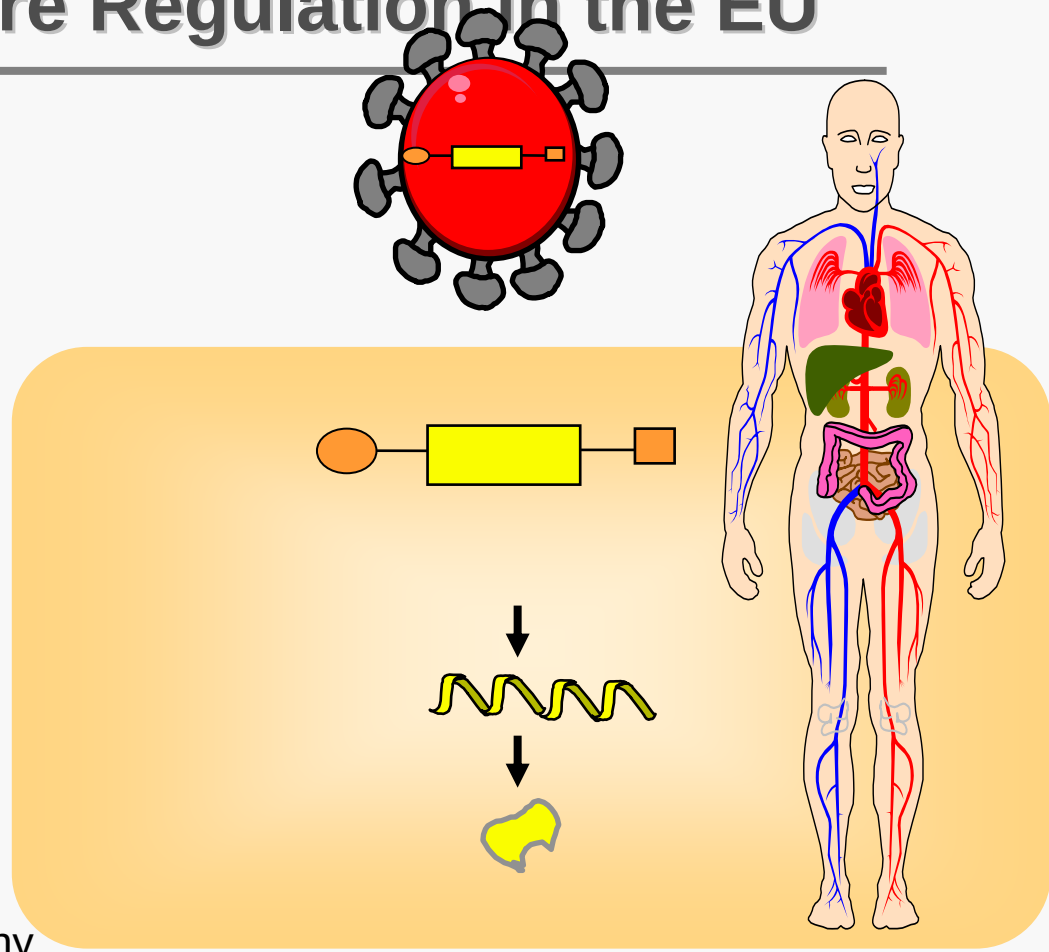


Klaus Cichutek
Paul-Ehrlich-Institut, 63225 Langen, Germany
Chair, CHMP/EMEA GTWP

E-mail: **cickl@pei.de**
Tokyo, 15 February 2007

Challenges for clinical trial approval: preclinical testing program of GTMPs

- Vector and therapeutic gene
  - Preclinical testing program to be performed with vector and therapeutic gene in its final version intended for administration to the patient.
- Animal model
  - Animal model should mimick disease situation in humans as close as possible
    - Animal model for human adenovirus vector use
    - Animal model for oncolytic conditionally replicating viruses
- Vector development
  - Scientifically used vectors are further developed compared to vectors ready for clinical use.
  - Vectors used in initial clinical trial are changed in later phases of development.

Challenges for clinical trial approval: preclinical testing program of GTMPs

- Acute and chronic toxicity study in an animal model incldg. dosing regimen and worst-cas scenario
  - GLP
  - Addressing the major safety concerns
- Biodistribution and germline transduction/transmision
  - Novel vectors with theoretical potential of transducing germline (resting) cells
- Long-term follow-up
  - Follow-up beyond end of clinical trial
  - Cancer risk follow-up (insertional oncogenesis)

History and activities of the CHMP Gene Therapy Working Party

- Scientific Reports on Insertional Oncogenesis and Other Issues(January and June 2003, GTWP)
  - EMEA/CHMP/183989/04 Report from the CHMP Gene Therapy Expert Group Meeting 14-15 October 2004
    EMEA/CHMP/127803/04 Report from the CHMP Gene Therapy Expert Group Meeting 17-18 June 2004
    EMEA/CPMP/1879/04 Report from the CPMP Gene Therapy Expert Group Meeting 26-27 February 2004
    EMEA/22880/03 Report from the Ad hoc meeting of CPMP Gene Therapy Expert Group 26-27 June 2003
    EMEA/5382/03 Report from the Ad hoc meeting of CPMP Gene Therapy Expert Group 23-24 January 2003
  - One published as a scientific paper in J. Mol. Med.
- EMEA Training of Assessors in Gene Therapy (2004; GTWP)
- Consultations with stakeholder and external experts (regularly in 2003 – present; GTWP)
- Briefing meetings with stakeholders
- **ICH-Gene Therapy Discussion Group**
  - ICH Considerations General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors (October 2006)
  - Workshops during ICH Conferences (Insertional oncogenesis (Frederick, USA, 2003, Okayama 2004, Oncolytic viruses (Chicago, 2005), Virus shedding (planned for 2007),

•EMEA/CHMP guidance documents
(Webpage 02-2007)

•CPMP/BWP/3088/99 Note for Guidance on the Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products

•EMEA/273974/05 Guideline on Non-Clinical testing for Inadvertent Germline transmission of Gene transmission of Gene Transfer Vectors (Adopted by CHMP November 2006)

- Overview of Comments received on the above draft

•EMEA/CHMP/203831/05 Concept Paper on Scientific Requirements for the Environmental Risk Assessment of Gene Therapy Medicinal Products (Released for Consultation November 2005)

•EMEA/CHMP/GTWP/203821/05 Concept Paper on the Development of a Guideline on the Non-Clinical Studies prior to Clinical Use of Gene Therapy Medicinal Products (Released for Consultation November 2005)

•CPMP/BWP/2458/03 CPMP Position Statement on Development and Manufacture of Lentiviral Vectors

European Medicines Agency
Evaluation of Medicines for Human Use

London 17 November 2005
Doc. Ref. EMEA/CHMP/203831/2005

COMMITTEE FOR THE MEDICINAL PRODUCT FOR HUMAN USE (CHMP)

Draft

CONCEPT PAPER ON SCIENTIFIC REQUIREMENTS FOR THE ENVIRONMENTAL RISK ASSESSMENT OF GENE THERAPY MEDICINAL PRODUCTS

European Medicines Agency
Evaluation of Medicines for Human Use

London, 17 November 2005
Doc. Ref. EMEA/CHMP/GTWP/203821/2005

COMMITTEE FOR THE MEDICINAL PRODUCT FOR HUMAN USE (CHMP)

Draft

CONCEPT PAPER ON THE DEVELOPMENT OF A GUIDELINE ON THE NON-CLINICAL STUDIES PRIOR TO CLINICAL USE OF GENE THERAPY MEDICINAL PRODUCTS

Prior-to first human use: non-clinical requirements (draft guideline under discussion)

- First human dose establishment
- Toxicity studies
- Integration studies
- Germline transmission studies
- Target tissue selectivity/ biodistribution
- Immunogenicity/immunotoxicity

- Delivery devices
- Reproductive toxicology

- Oncogenicity, if applicable

- Environmental risk/shedding
- No carcinogenicity studies in general

Prior-to first human use: non-clinical requirements (draft guideline under discussion)

First human dose establishment	rational; biological effects in animal
Toxicity studies	repeated dose tox. study endpoints
Integration studies	DNA vectors entering nucleus
Germline transmission studies	declining vector DNA signal in germline
Target tissue selectivity/ biodistribution	non-target effects
Immunogenicity/immunotoxicity	vector particle/gene products, imm rel. proteins, aberrant gene products
Delivery devices	contribution to GT/safety
Reproductive toxicology	only with foreseeable risk and fertile patient population
Oncogenicity, if applicable	chromosom. Integrating vectors with tumour enhancer/promoter potential
Environmental risk/shedding	Nfg av., not with genet. mod. cells
No carcinogenicity studies in general	with ancillary products carrying risk

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

London, 17 November 2005
Doc. Ref. EMEA/273974/2005

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

<DRAFT>

NOTE FOR GUIDANCE ON THE QUALITY, PRECLINICAL AND CLINICAL ASPECTS OF GENE TRANSFER MEDICINAL PRODUCTS

ANNEX ON NON-CLINICAL TESTING FOR INADVERTENT GERMLINE TRANSMISSION OF GENE TRANSFER VECTORS

ICH INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

25 October 2006

ICH Considerations

General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors

- state: adopted by ICH Steering Committee, published

ICH Considerations on Germline Integration of Vectors

- Regulatory agencies represented at ICH agree that gene therapy studies intended at allowing germline integration should not be performed.

- Risk of germline integration should be minimised because of the potential of transmitting vector DNA to progeny.

- Vector DNA integration
  - Required in some approaches
  - Non-desirable in non-target cells -> minimize
  - Concern in gonadal tissue,
    particular concern in germline cells -> avoid, minimize risk

Non-clinical studies addressing germline integration: biodistribution

- Observe general principles of guideline ICH S6 (nonclinical studies for biotechnology-derived pharmaceutical products)

- Biodistribution studies
  - Address vector distribution to target and non-target cells
  - Should include gonads (testes and ovaries)
  - Vector can be detected by testing for nucleic acid sequences.
  - Testing should be done using at least one sensitive assay, such as, e.g., q-PCR.
  - No prescription for assay sensitivity: 50 copies per ug DNA may be standard?

- Vector used in biodistribution studies
  - Should be conducted with the product that is intended for clinical use.
  - Studies with vector containing other transgenes could be used to support early phase clinical development.

Non-clinical studies addressing germline integration: outcome of biodistribution studies

- If vector is not detected in gonads
  - Further germline integration studies might not be warranted.

- If vector is detected in the gonads
  - Assess whether vector levels fall below the assay´s limit of detection at later time points
  - If vector is persistently detected in the gonads, it might be warranted to elucidate whether germline cells are transduced.
  - If vector is detected in germline cells, talk to your regulatory authority.

Studies during clinical use addressing germline integration: patient monitoring

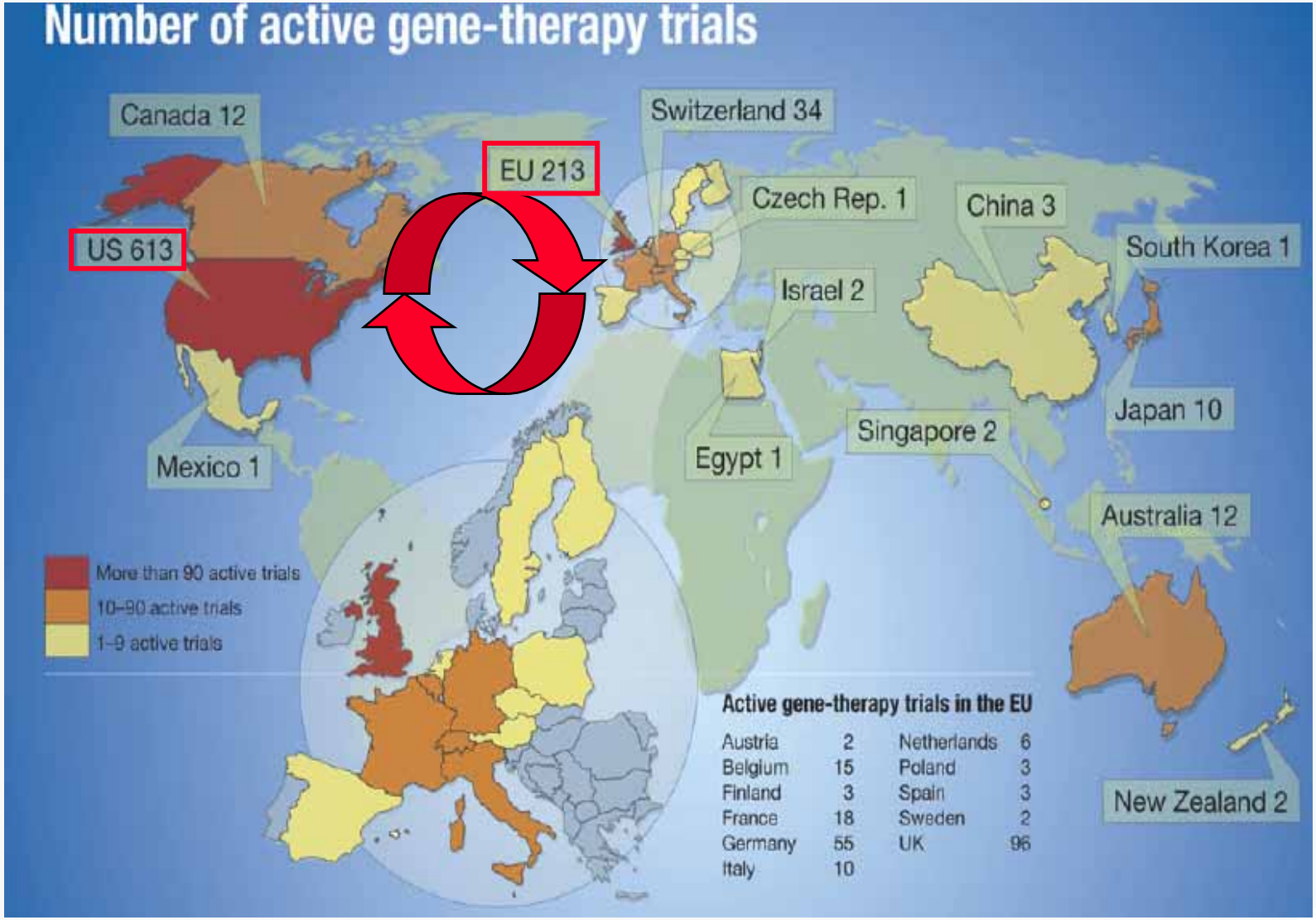
- If, in animal studies, vector is transiently detected in gonads
  - Consider assaying patient semen for presence of vector
  - This may not be warranted if patients are definitely sterile or have a severe disease condition with short life expectancy.

- Semen testing
  - Preferably to be done at several time points extending over 64-74 days (cycle of spermatogenesis)
  - If samples are positive, notify regulatory authority.

- Risk assessment for women may be exclusively based on non-clinical data.

- Contraceptive measures are usually recommended during clinical trial.

> 6.000 patients have been enrolled in GT trials



Ark Therapeutics

Ark Therapeutics Grp - Regulatory Application

RNS Number:2904T
Ark Therapeutics Group PLC
28 October 2005

CereproTM Marketing Authorisation Application

Review Commences in Europe

- Dossier for potentially the world's first gene therapy product 1 accepted by EMEA as 'valid' -

28 October 2005: Ark Therapeutics Group plc ('Ark') today announces that its Marketing Authorisation Application (MAA) for CereproTM, a novel gene-based therapy for operable malignant glioma (brain cancer), has been filed with the European medici
been accepted f

+ 2 gene transfer medicinal products on the Chinese market:
- Since 2003: adv-p53
- Since 2005: Onyx-like oncolytic replicating adv (Oncorine)

The applicatior
requirements of
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EMEA had appoir
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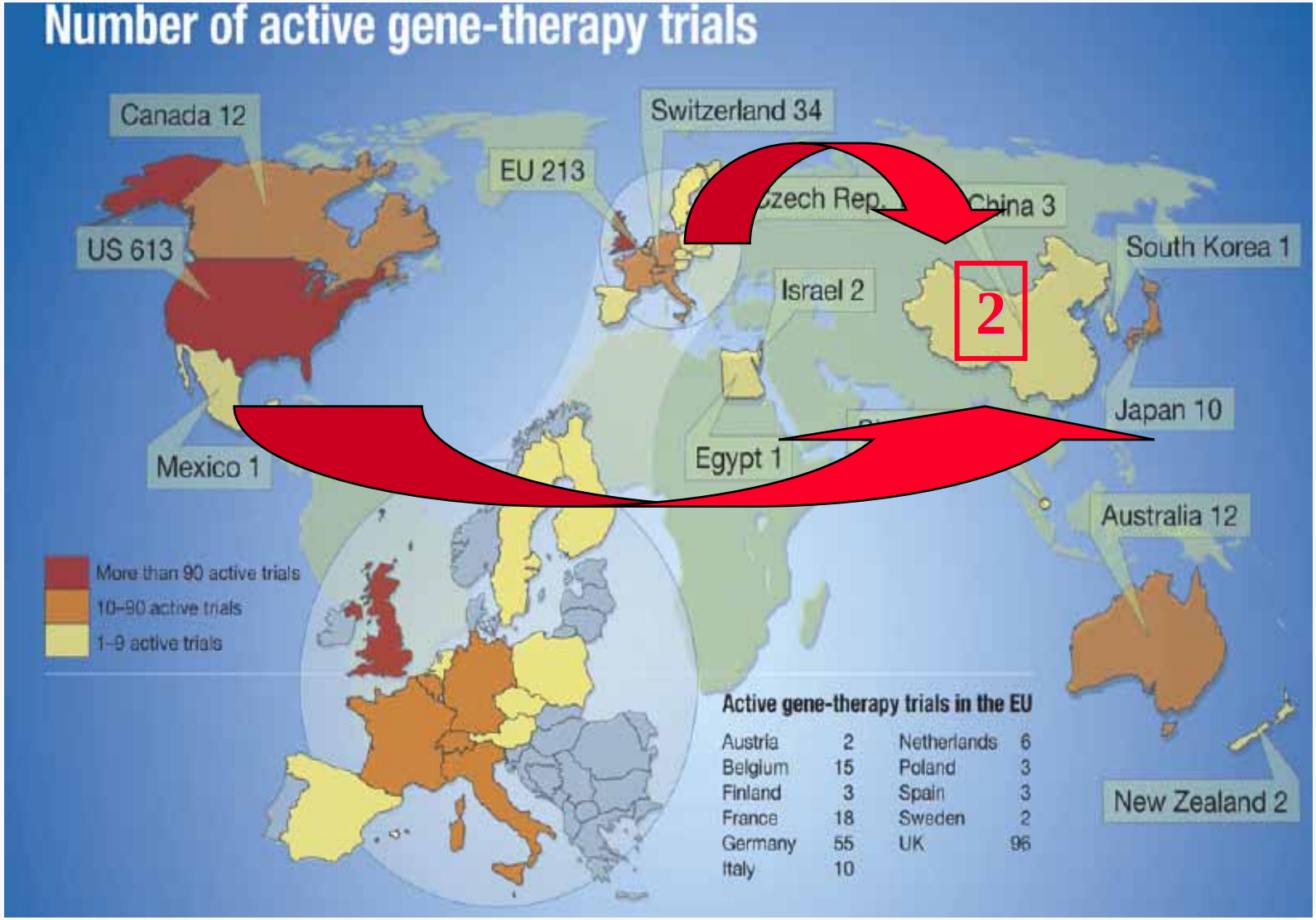
CereproTM, a novel gene-based medicine, has undergone three clinical studies during its development to date, a Phase I study establishing safety and posology (dosing and method of administration) and two safety and efficacy studies. In these studies CereproTM treatment produced an average extension of 7.5 months of

China´s marketed gene therapy products attract attention from abroad patients



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E-mail: **cickl@pei.de**
Tokyo, 15 February 2007

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

London, 26 January 2006
Doc. Ref. EMEA/CHMP/CPWP/323774/2005

Committee for Human Medicinal Products (CHMP)

DRAFT

CONCEPT PAPER ON GUIDELINE FOR HUMAN CELL-BASED MEDICINAL PRODUCTS

AGREED BY CPWP	6 October 2005
AGREED BY BWP	7 December 2005
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	23 January 2006
END OF CONSULTATION (DEADLINE FOR COMMENTS)	17 April 2006

The proposed guideline will replace guideline CPMP/BWP/41450/98 Points to Consider on the Manufacture and Quality Control of Human Somatic Cell Therapy Medicinal Products

Challenges for clinical trial approval: preclinical testing program of CTMPs

- Biodistribution
  - Migration of cells to target organs
- Differentiation to the intended cell type
  - In micro-environment
- Malignant transformation
  - hESCs and long-term cultured progenitor cells may transform to malignancy
- Virus/microbial safety
  - Donor testing substitutes for virus inactivation
  - Procurement procedures

Cell-based product guideline: risk criteria

- 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.

Directive 2006/17/EC
of the European Commission of 8th Feb 2006

Implementing 2004/23/EC as regards certain technical requirements for the donation, procurement and testing of human tissues and cells

ANNEX II Laboratory tests for ALL donors of tissues/cells (except reproductive cells) <u>including</u> autologous donors when cells are stored or cultured

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

Cell-based product guideline: General credo of non-clinical development

- Objectives of non-clinical studies
  - demonstrate proof-of-principle
  - define pharmacological and toxicological effects to be expected during human use
  - select a safe dose for human use
  - support route of administration and application schedule
  - measure duration of exposure (half-life of cells and their effect in vivo)
  - define reasonable follow-up time to detect adverse reactions
  - detect target organs of toxicity and parameters for patient monitoring in subsequent clinical trials
- Use relevant animal models and justify:
  - Expression level of biologically active molecules,
  - route of administration,
  - dosage…
    - …should reflect the intended human use.
- Consider ICH S6 Guideline on the safety of biotechnology-derived pharmaceuticals
- Demonstrate safety and suitability of all components for all intended functions.

Cell-based product guideline: secondary and safety pharmacodynamics of cells (2)

- Secondary pharmacodynamics:
  Investigate potential undesired effects of the cell-based product:
  - homing to other than the intended organs,
  - secretion of other bioactive molecules beside the protein(s) of interest,
  - undesirable effects of the protein(s) of interest,
  - undesirable targets of the protein(s) of interest.

- Safety pharmacodynamics:
  Due to secretion of pharmacologically active substances from cells, there may be
  - CNS dysfunctions,
  - cardiac dysfunctions,
  - respiratory dysfunctions,
  - renal dysfunctions
  - gastrointestinal dysfunctions.

- Watch ICH S7A Note for guidance on safety pharmacology studies for human pharmaceuticals (CPMP/ICH/539/00), when applicable.

Cell-based product guideline: kinetics, migration persistance of cells (4)

- Conventional ADME studies are genrally not relevant.
- Relevant are measurements of
  - tissue distribution,
  - viability,
  - trafficking,
  - growth,
  - phenotype and
  - any alteration of phenotype due to factors in the new environment.
- With respect to produced systemically active biomolecules. study
  - the distribution,
  - duration and
  - amount of expression of these molecules and
  - the survival and
  - the functional stability of the cells at target sites.

Cell-based product guideline: cliinical development (11)

- The clinical development plan should include
  - pharmacodynamic studies,
  - pharmacokinetic studies,
  - mechanism of action studies,
  - dose finding studies and
  - RCTs
  - in accordance with the existing general guidances and specific guidances for the condition evaluated.

- Risk Management Plan:

  The long-term safety issues should be addressed, such as
  - infections,
  - immunogenicity/immunosuppression,
  - malignant transformation,
  - durability of the associated medical device/biomaterial component.

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Ready for action: custom-made gene vectors are held for use in a gene-therapy trial.

Klaus Cichutek
Paul-Ehrlich-Institut, 63225 Langen, Germany
Chair, CHMP/EMEA GTWP

E-mail: **cickl@pei.de**
Tokyo, 15 February 2007

COMMISSION OF THE EUROPEAN COMMUNITIES

Brussels, 16.11.2005
COM(2005) 567 final

2005/0227 (COD)

Proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

Advanced therapy products will also include tissue-engineering products

Definitions

1. In addition to the definitions laid down in Article 1 of Directive 2001/83/EC and in Article 3, points (a) to (l) and (o) to (q) of Directive 2004/23/EC, the following definitions shall apply for the purposes of this Regulation:

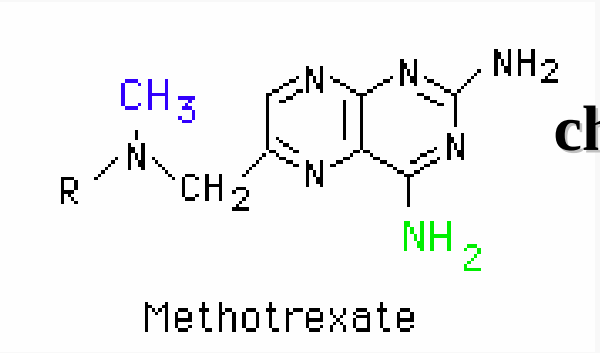
(a) advanced therapy medicinal product means any of the following medicinal products for human use:

- 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:

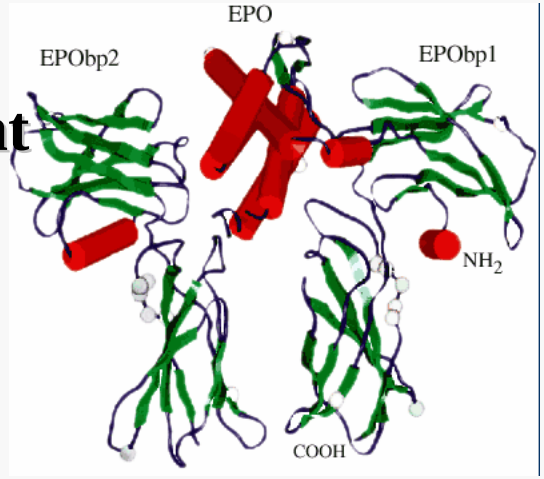
- contains or consists of engineered cells or tissues; and
- is presented as having properties for, or is used in or administered to human beings with a view to, regenerating, repairing or replacing a human tissue;

A change in paradigm: genes and manipulated cells as products



chemicals

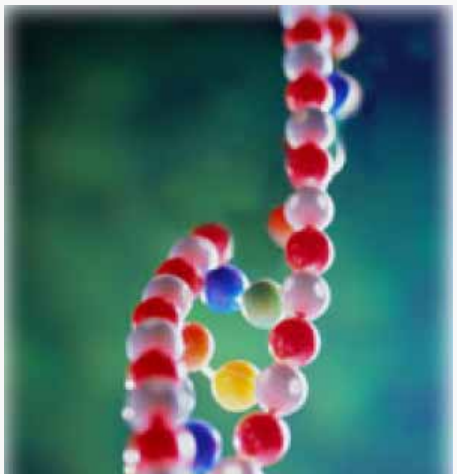
recombinant proteins

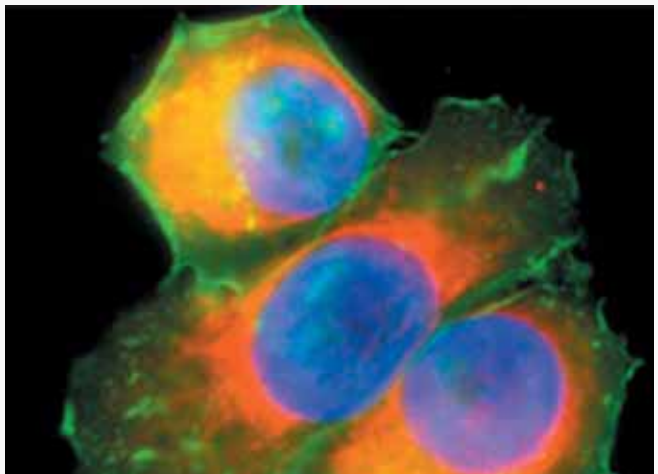


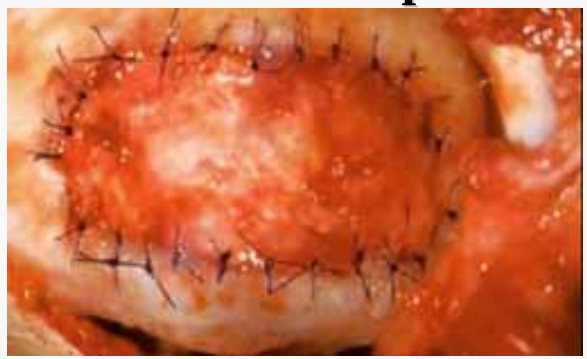
gene therapy products
- cells and vectors

somatic cell therapy products
- DCs, CTLs, NK cells

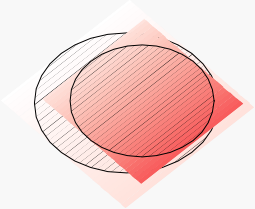
tissue engineered products
- ACT, stem cells for tissue repair



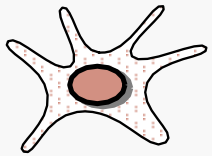




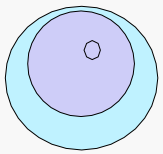
Examples of Cell Therapy Medicinal Products



Cell-based vaccines
(e.g. peptide-loaded DC used as tumor vaccines)

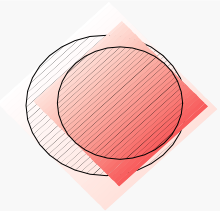


Immunotherapeutics
(e.g. CTLs or NK cell transfer used for adoptive immunotherapy)

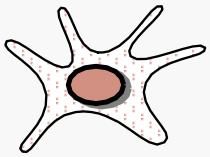


Cell/tissue regenerative medicinal products
(e.g. cultured chondrocytes for cartilage repair; hepatocytes for treatment of acute liver failure; adipose-derived and mesenchymale stem cells …)

Examples of somatic cell therapy medicinal products

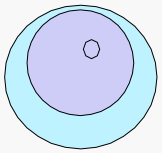


- *peptide loaded dendritic cells (DCs)*
- *DC / tumor hybrid cells*



- *antigen-specific T-cells*
- *killer cells (CTLs, NK cells)*

Human Somatic Cell Therapy Products for immunotherapy



- *CD34+ cells for heart muscle regeneration*
- *chondrocytes for cartilage repair (may include scaffolds)*
- *pancreatic islet cells to restore function*
- *liver cells to restore liver function during sepsis*
- *neuronal cells for treatment of Parkinson´s disease*

manipulated: TEPs

not manipulated: cell-containing medicinal products

Changes accrdg. to the EC ATMP Proposal

- Centralized licensing procedure for all ATMPs
  - Gene therapy products
  - Human somatic cell therapy products
  - Xenogeneic somatic cell therapy products
  - Tissue engineering products
- Autologous and directionally used medicinal products will undergo licensing
  - cell banks
  - industrially produced
- Tissue engineered products and somatic cell therapy products will undergo central licensing,
  - live (viable) and
  - substantially altered or engineered

Issues of the EC ATMP Proposal under discussion

- Inclusion of all or only substantially manipulated cells in the definition of cell therapy and tissue engineering products?
  - Virus/microbial safety, tumourigenicity are common major safety issues already present with viable cells which have not been substantially manipulated.

- Presentation of the CAT
  - Ethics member needed?
  - Physician rather than surgeon as expert member
  - Include only experts, not equal EU MS representatives
  - CHMP/CAT relationship

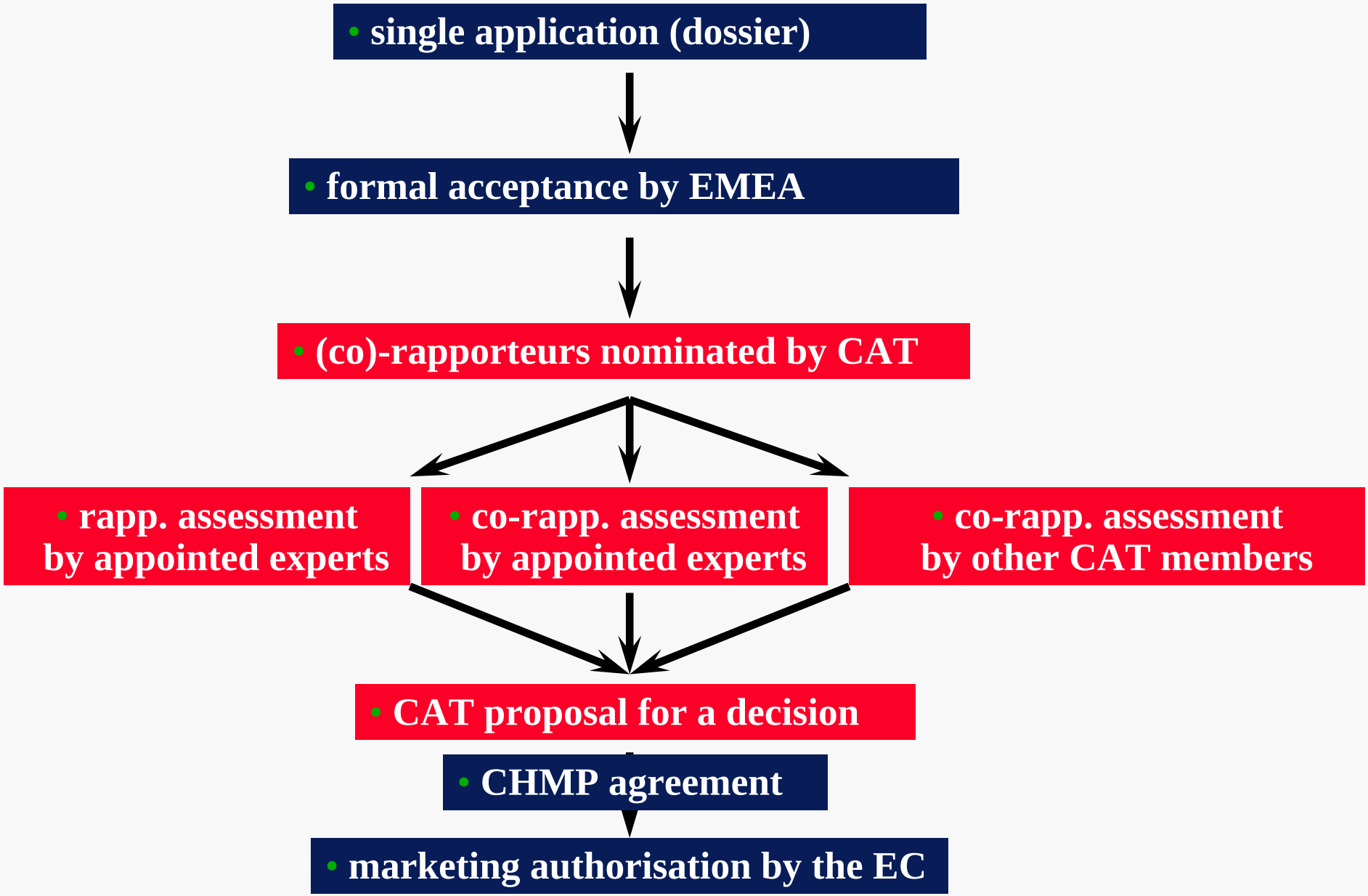
- Borderline products
  - Classification of combination products as
    - medical device or
    - medicinal product

- Hospital exemption

- Transition time until centralized procedure becomes mandatory

Future centralized procedure for ATMPs

(Directive 726/2004/EC)



Cell-based Advanced Therapies – The Regulatory Levels

1

Regulation addressing all Advanced Therapy Medicinal Products

→ **Proposal: Regulation on Advanced Therapy Medicinal Products (ATPs)**
Definition of ATPs including TE products
Central licensing requirement

Existing Legislation on Tissues & Cells, (Medical Devices) and Medicines

→ **Directive 2001/83/EC (Nov 2001) amendend 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

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

2

Technical Requirements

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

Directive 2006/??/EC (Fall 2006)
technical requirements for coding, processing, preservation, storage, distribution

3

Guidelines

→ **Concept paper for a Guideline on Cell-based Products including TEP**
(Fall 2007/2008)
Contains quality, non-clinical, clinical aspects
Will replace Points to Consider on manufacture and quality control of human somatic cell therapy MP (CPMP/BWP41450/98)

CHMP GTWP

Avanced Therapy Clinical Trial Applications in the EU since August 2004 (07.09.2005, EudraCT)

clinical use	number
Somatic cell therapy MPs	*25/13 original products*
cardio-vascular	4
cancer immunotherapy	3
skin/liver/diabetes/bone TE	5
neurological	1
Gene therapy/transfer MPs	*19/9 original products*
cancer	4
cardio-vascular	2
neuronal	1
HIV vaccine	2
Biologicals (EU)	*184*

Advanced Therapy Medicinal Products: Present and Future Regulation in the EU

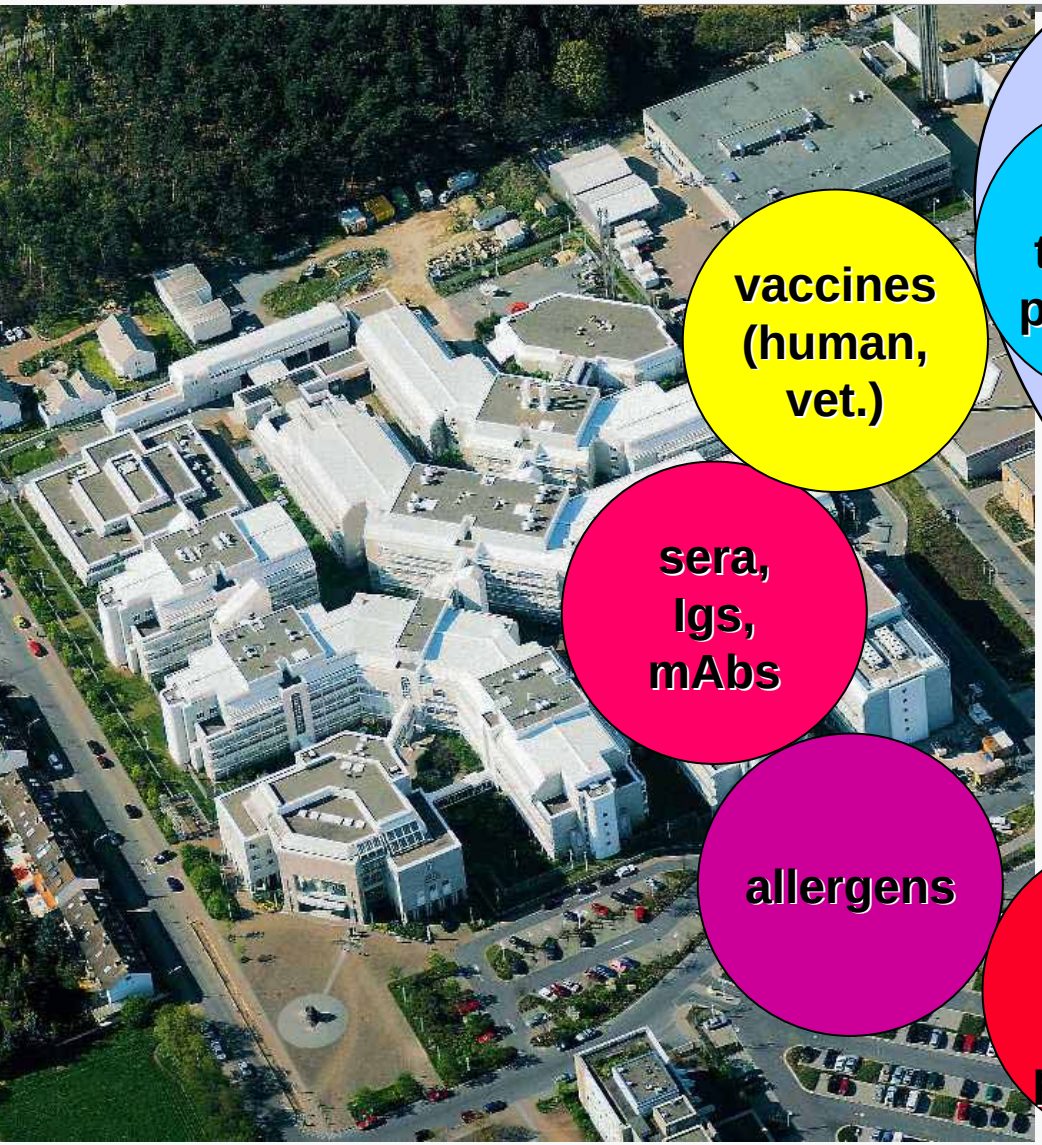
- Current Advanced Therapy Regulations in the EU
- GTMP Regulations
- CTMP Regulations
- Proposal of the EC for a Regulation on Advanced Therapies

Calculated risk: the use of viral vectors to deliver corrective genes to a patient can cause side effects.

Klaus Cichutek
Paul-Ehrlich-Institut, 63225 Langen, Germany
Chair, CHMP/EMEA GTWP

E-mail: **cickl@pei.de**
Tokyo, 15 February 2007

Medicinal product responsibility of the PEI



vaccines (human, vet.)

sera, Igs, mAbs

allergens

blood a. plasma-derived products

tissue preparations

advanced therapy products

gene therapy products

cell therapy products (human, xeno)

tissue-engineering products