EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Advanced Therapy Medicinal Products (ATMPs)

European Experience and Challenges

ASEAN training. Kuala Lumpur. 31 May 2011

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European Medicines Agency

Content

- European Medicines Network
- Definition of ATMPs
- Guidance on Cell products
- Development of a (stem) cell-based MP
- Case study of an approved ATMP: ChondroCelect
- EMA Regulatory procedures for ATMPs

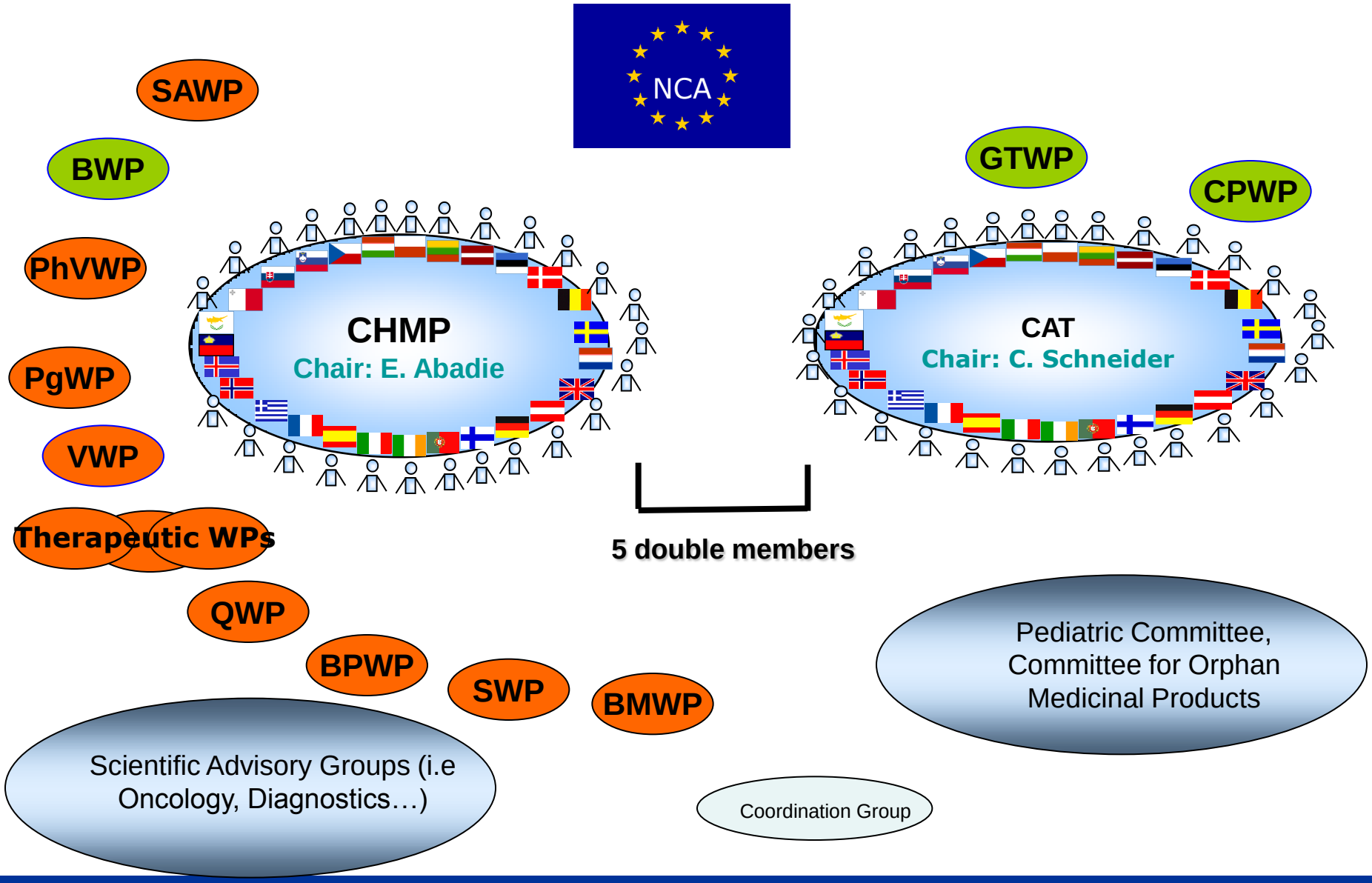
European Medicines Network

EMA and ATMPs

To foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health

- Network of European experts (+3500)
- 6 Scientific Committees (CHMP, CAT, COMP, PDCO, CVMP, HMPC & …)
- Over 15 working parties (human unit)
- Centralised Procedure (for ATMPs): 1 single market
- Motto: Science, Medicines, Health
- Values: Europe, public health, innovation, sense of purpose, quality, transparency, integrity, honesty, objectivity, impartiality (CoI)

CHMP, CAT and working parties



Definitions of Advanced Therapy Medicinal Products

Gene Therapy Medicinal Product

Biological medicinal product with the following characteristics:

a) 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**;

b) 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.

Annex I, part IV of Dir. 2001/83/EC

Cell-based products

Somatic cell therapy medicinal products:

- **substantially manipulation** cells or tissues **or not intended** to be used for **the same essential function**(s);

- administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action.

Tissue engineered product:

- **engineered** cells or tissues, and

- administered to human beings with a view to regenerating, repairing or replacing a human tissue.

Annex I, part IV of Dir. 2001/83/EC & Reg. (EC) No. 1394/2007

Non-substantial Manipulation

- cutting
- grinding
- shaping
- centrifugation
- soaking in antibiotic or antimicrobial solutions
- sterilization
- irradiation
- cell separation, concentration or purification
- filtering
- lyophilization
- freezing
- cryopreservation
- vitrification

Everything else is considered as substantial

ATR 1394/2007, Annex I

Combined ATMPs

Definition:s

Incorporates a medical device (according to Article 1(2)(a) of Dir. 93/42/EEC)

and

Includes viable cells or tissue parts

or

In case of non-viable cellular/tissue part, the primary mode of action is attributed to the cell component as either pharmacological, immunological, metabolic or as repair, replacement, regeneration

Summary of definitions

Gene therapy medicinal product:

- recombinant nucleic acid → to regulating, repairing, replacing, adding or deleting a genetic sequence

Somatic cell therapy medicinal products:

- substantially manipulated cells/tissue → to treat, prevent or diagnose a disease (pharmacological, immunological, metabolic action)

Tissue engineered product:

- substantially manipulated cells/tissue → to regenerate repair or replace a human tissue

Combined ATMP:

- medical device + cell/tissue part

ATMP Classification examples

TISSUE ENGINEERED PRODUCT	SOMATIC CELL THERAPY
Adult skeletal muscle derived cells: female stress urinary incontinence	Human allogeneic fibroblasts and keratinocytes + fibrin (structural component): chronic venous leg ulcers
NOT COMBINED	**COMBINED**
Frozen, cultured allogeneic keratinocytes on a silicone dressing material: acute burn wounds	Autologous osteoprogenitor cells in 3D biodegradable scaffold: regenerating and replacing bone defects in OdontoStomatology

ATMP Classification examples

GENE THERAPY PRODUCT

Genetically modified Lactococcus lactis secreting human IL-10: inflammatory bowel disease

Salmonella typhi strain genetically modified to secrete a fusion protein of the prostate specific antigen (PSA) and a protein leading to an increased antigenicity: prostate cancer

Guidance for (stem) cell-based medicinal products

What is special about ATMPs?

- Classification is dependent not only on the product (substantial manipulation), but also on the application (heterologous use)
- Risk-based approach – Data requirements related to the nature of the product
- Balance between standardisation and case-by-case approach
- Innovative field in rapid progression – Further knowledge required, standards established and guidance developed
- Medicianl products containing/consisting on genetically modified organisms an enviromental risk assessment on the risks to human health and the environment is requested.

Risk-based approach

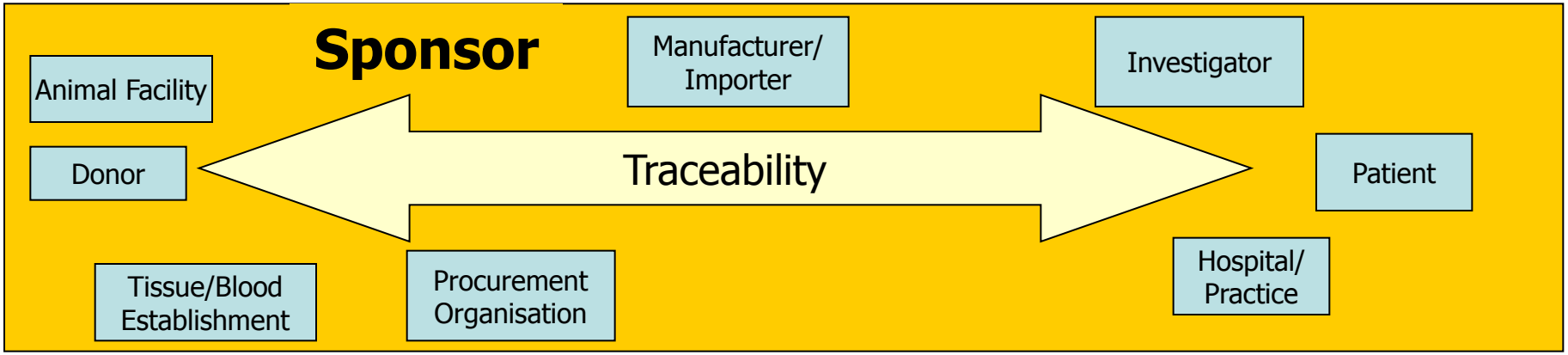
- A risk-based approach may be applied to determine the extent of quality, non-clinical and clinical data for a MAA.
- The risk analysis may cover the entire development.

  Relevant factors: the origin of cells, ability to proliferate and/or differentiate and to initiate an immune response, level of cell manipulation, combination products, nature of gene therapy medicinal products, extent of replication competence of viruses or micro-organisms used *in vivo*, the level of integration, long time functionality, risk of oncogenicity and mode of administration or use.
- Relevant available non-clinical and clinical data or experience with other, related ATMPs may also be considered in the risk analysis.

Product Traceability – Coding System

The ATMP Regulation (art. 15) defines a two tiered system connecting the required traceability from cell donation and procurement to the manufacturer and user

- At the tissue establishment: link between donor and donation
- At the manufacturing site: link between donation and product
- Hospital/practice: link between product and recipient
- The systems should allow full traceability from donor to recipient through anonymous coding systems.
- Manufacturers should establish their coding systems in a rational way, building from the coding system of the tissue establishment, and designing it to facilitate the tracing of the donation to the product and to the patient.



Genetically Modified Organisms (GMO)

Directive 2001/18/EC: Definitions (paraphrased)

An organism is a biological entity capable of replication or of transferring genetic material

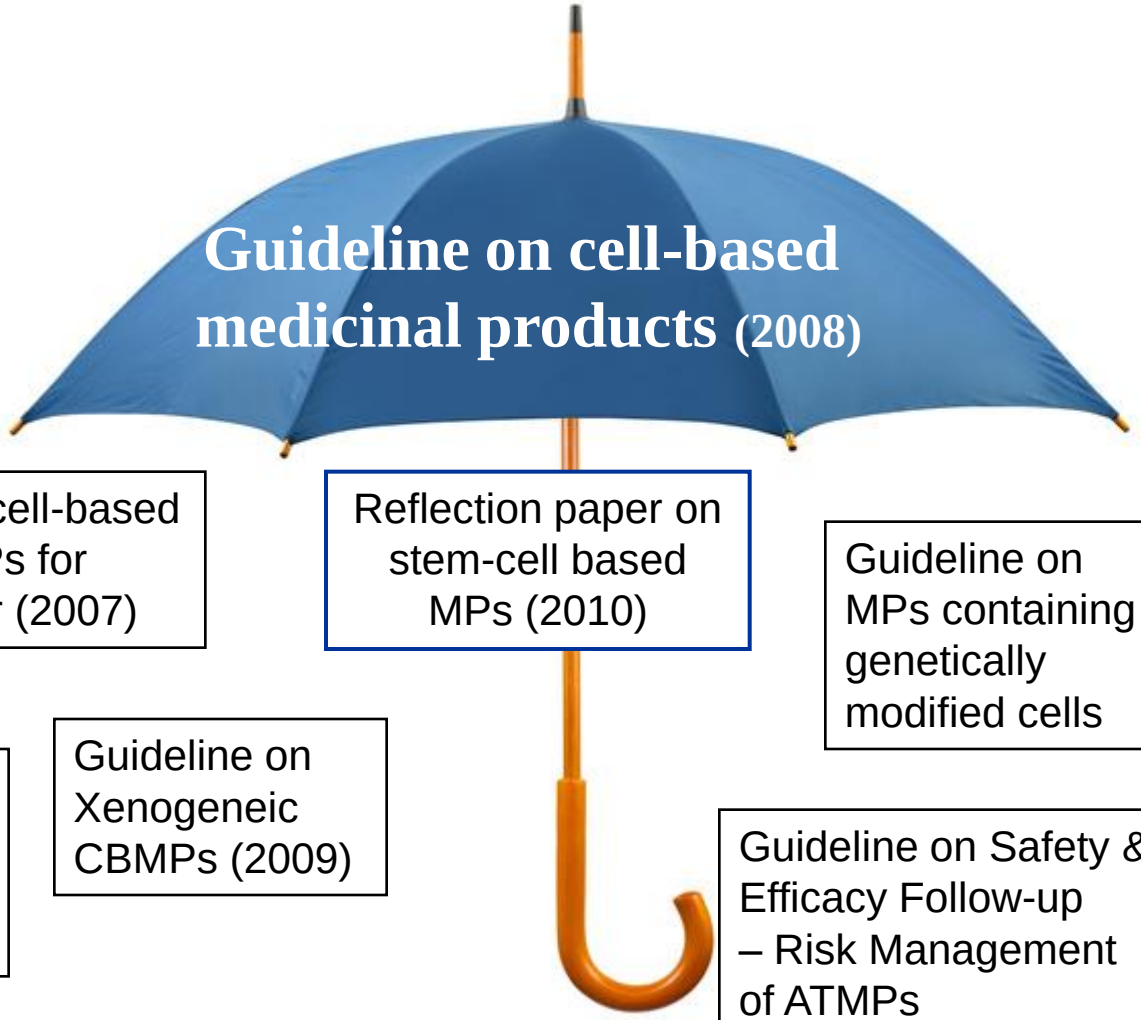
•A genetically modified organism is one in which the genetic material has been altered in a way that does not occur naturally by mating or natural recombination.

Environmental risk assessment means evaluation of the risks to human health and the environment. (Module 1.6.2 of the CTD dossier).

Guidance: Environmental risk assessments for medicinal products containing, or consisting of, genetically modified organisms (GMOs) (Module 1.6.2). EMEA/CHMP/BWP/135148/2004

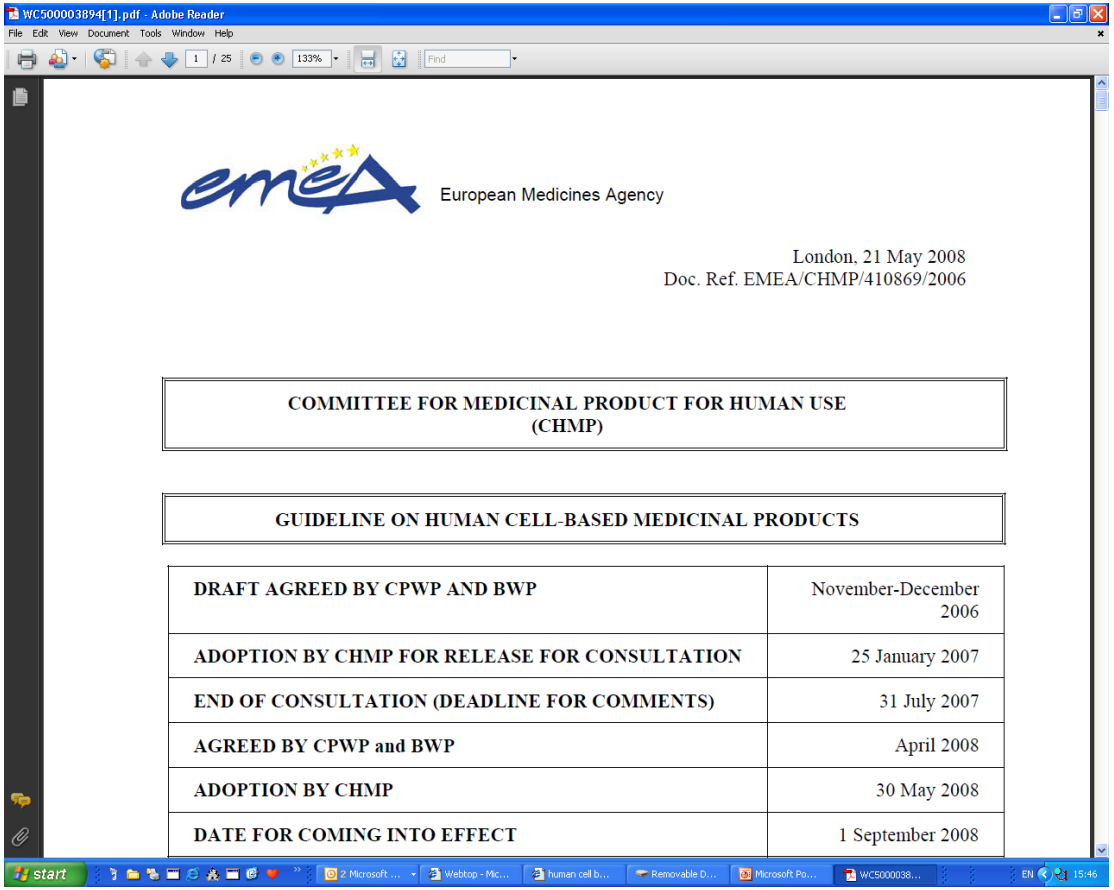
Guideline on scientific requirements for gene therapy medicinal products (EMEA/CHMP/GTWP/125491/2009).

Guidance on cell products



Guideline on human cell-based medicinal products

'Mother guideline'



European Medicines Agency

London, 21 May 2008
Doc. Ref. EMEA/CHMP/410869/2006

COMMITTEE FOR MEDICINAL PRODUCT FOR HUMAN USE
(CHMP)

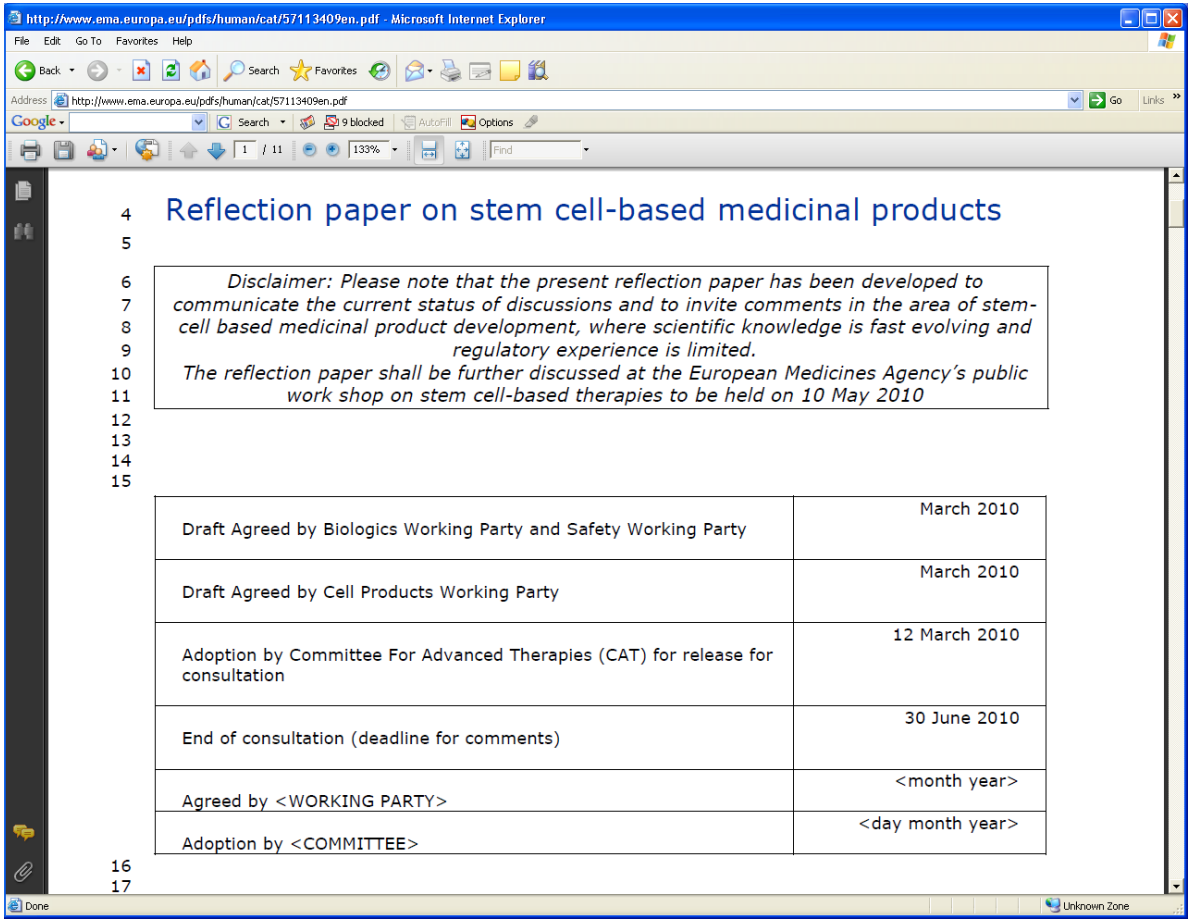
GUIDELINE ON HUMAN CELL-BASED MEDICINAL PRODUCTS

DRAFT AGREED BY CPWP AND BWP	November-December 2006
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	25 January 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 July 2007
AGREED BY CPWP and BWP	April 2008
ADOPTION BY CHMP	30 May 2008
DATE FOR COMING INTO EFFECT	1 September 2008

Human Cell & Tissue engineered products

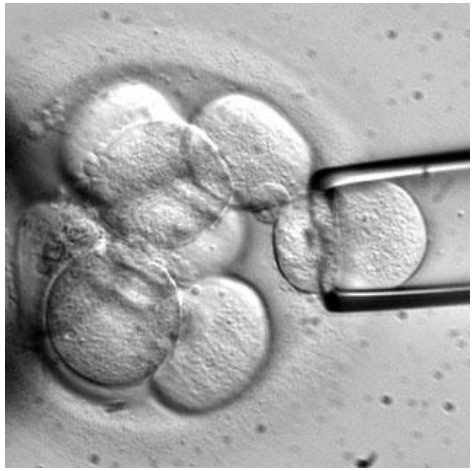
- Quality + manufacturing aspects
- Nonclinical development
- Clinical development

Draft Reflection paper on stem cell-based medicinal products



- quality, preclinical & clinical requirements for specific for stem cell-based products

Scope



- **Embryonic stem cells**

- **Adult or somatic stem cells** including
  - Haematopoietic progenitor /stem cells
  - Mesenchymal/stromal stem cells
  - Tissue-specific progenitor cells with restricted differentiation capacity

- **Induced pluripotent stem cells** and/or their intermediate stages

➢relevant to all MPs using stem cells as starting material.

➢Finished product: terminally differentiated cells, pluripotent stem cells or mixture of cells with varying differentiation profiles

Risk-based approach

- EU legislation (Annex I, part IV of Dir. 2001/83/EC)
- Guidance under development (Concept paper CHMP/CPWP/708420/09)

Approach:

- Use to justify amount of data needed for Q, NC & C
- cover the entire development
- discuss risk profile of product (risk factors) and implication on extent of data in MAA dossier

Development of a (stem) cell-based medicinal product

Quality issues I

- ✓Starting material tested/documented for viral, TSE safety?
- ✓Excipients, reagents and structural components qualified?
- ✓Product consistent and well characterised
- ✓Active moiety identified and quantified?
  - ✓Manufacturing process validated?
  - ✓Potency assay available?
  - ✓Comparability issues?

Quality issues II

Control & validation of the manufacturing process

- Critical steps & limits (i.e. population doublings)
- Control via relevant markers, mRNA, protein expression

Purity

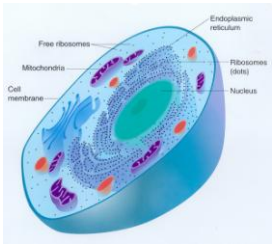
- Maximise active moiety
- Eliminate and control undesired dedifferentiated cells
- ➢ Minimum requirement: consistency

Tumourigenicity

- Limit amount of dedifferentiated cells
- Demonstrate genotypic / phenotypic stability during process

Potency assay

- To utilise quality attributes of the cells to measure biological activity relevant for efficacy/safety in the patient



quality attributes

qualitative
quantitative

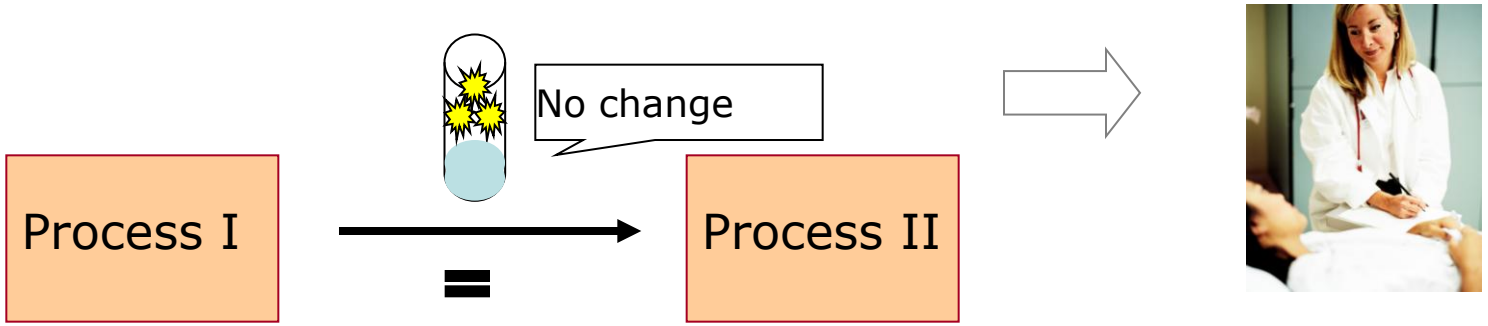
extrapolation

surrogate marker

Clinical effect

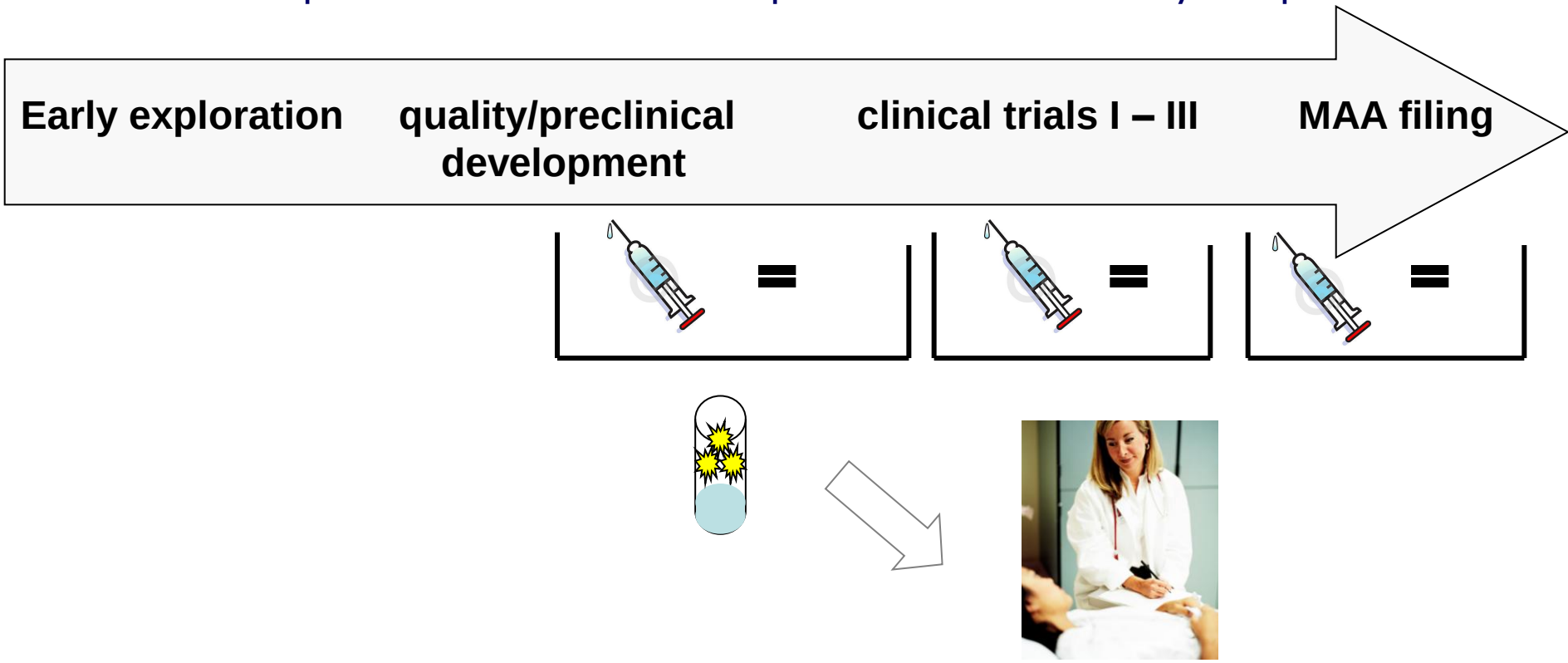
Potency assay & comparability

Aim: control manufacturing & finished product,
- to bridge to the new product following process changes
  - -Scale – up
  - -Site transfer
  - -New/amended starting material (i.e. primary cell culture)



Potency assay

should be in place for clinical development but absolutely for pivotal data



Potency assay

Biological activity

- Cell number
- Differentiation status

+

- Relevant gene/protein expression (i.e. microarray, flow cytometry, immuno-fluorescence, cell cloning, PCR)
- Functional performance *in vivo*
  - tissue regeneration, repopulation (e.g. ectotopic model)
  - Metabolic activity (e.g. secretion of growth factors, metabolites)
  - Immunological activity (e.g. measurable immune response)

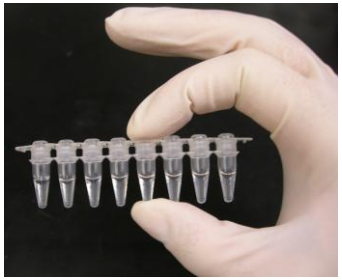
Potency test – practical aspects

- *in vivo assays*
  - tissue regeneration
  - Metabolic activity
  - Immunological activity

- Time consuming
- functional correlation

➢Validation of process /comparability

- *in vitro assays*
  - Gene/protein expression
  - viability
  - Other cell characteristics



- Can be quick
- Based on surrogates
- Should be correlated to functional assays

➢Batch release

Preclinical issues

Animal models

- ✓Species specificity on a molecular, cellular and tissue level
- ✓Animal model suitable & predictive of safety?
- ✓Homologous model / disease model (efficacy/ proof of concept)
- ✓Non-homologous model (immunocompromised?) to test human product
- ✓Biologically relevant animal model available (concomitant treatment immunogenicity, delivery)?

Large animal model necessary
(surgical procedure, tissue regeneration)

Preclinical issues

Biodistribution and Niche

- Important for systemic applications
- Methods for tracking cells *in vivo* to be developed/employed
- Safety requirements

Tumourigenicity & chromosomal stability

- Thorough evaluation before first clinical use
- Study differentiation process / migration *in vivo*
- Manipulated/extensively cultured cell products
- Extent of testing dependent on route of administration, intended clinical use.

Clinical Issues

2 main clinical concerns: Safety
Long-term efficacy

- ✓Non-clinical data available to justify B/R for clinical use?
- ✓Clinical control available/feasible/ethical?
- ✓Standardised collection & delivery procedure?
- ✓Dose available & justified?
- ✓suitable endpoint (clinical indication, TEP specific)?
- ✓Duration of follow-up (efficacy/safety)

Clinical criteria

Dose finding

- Minimally effective dose i.v. applied stem-cell products

Clinical efficacy

- common endpoints recommended in the studied indication (common guidance)
- Additional endpoints: specific structural endpoints

Clinical safety

- caution if stem cell products developed solely using non-clinical homologous model endpoints
- Safety FU combined with Efficacy FU

Pharmacovigilance

Follow-up of safety and lack of efficacy

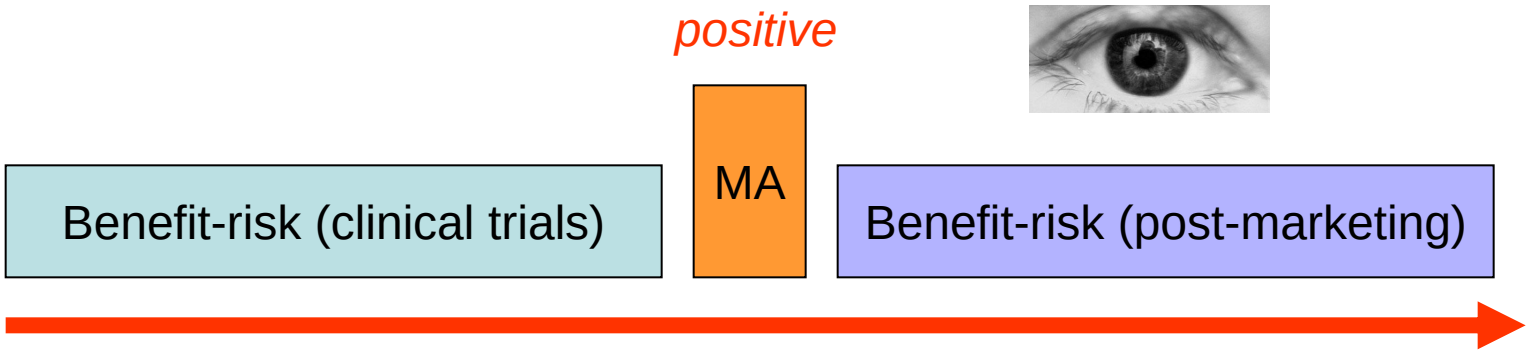
Duration of follow-up → intended therapeutic effect and identified safety risks

Specific surveillance plan for long-term safety

Guideline on the safety and efficacy follow-up – risk management of advanced therapy medicinal products (EMEA/149995/2008)

Follow-up of efficacy & safety post-marketing

- Efficacy as part of Risk-management



Long-term efficacy (tissue regeneration)

Life cycle management

Shift/extension of review procedure

Combined ATMP

Definition:

Incorporates a medical device according to Article 1(2)(a) of Dir. 93/42/EEC

and

Includes viable cells or tissue parts

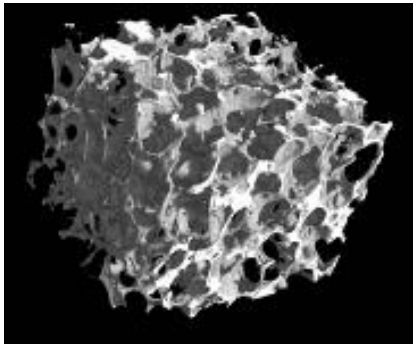
or

In case of non-viable cellular/tissue part, the primary mode of action is attributed to the cell component as either pharmacological, immunological, metabolic or as repair, replacement, regeneration

Combined ATMPs

Validation of cell culture process with respect to integrity of cells/scaffold

- Effect of device on cell growth and activity
- Effect of cells on device function and integrity



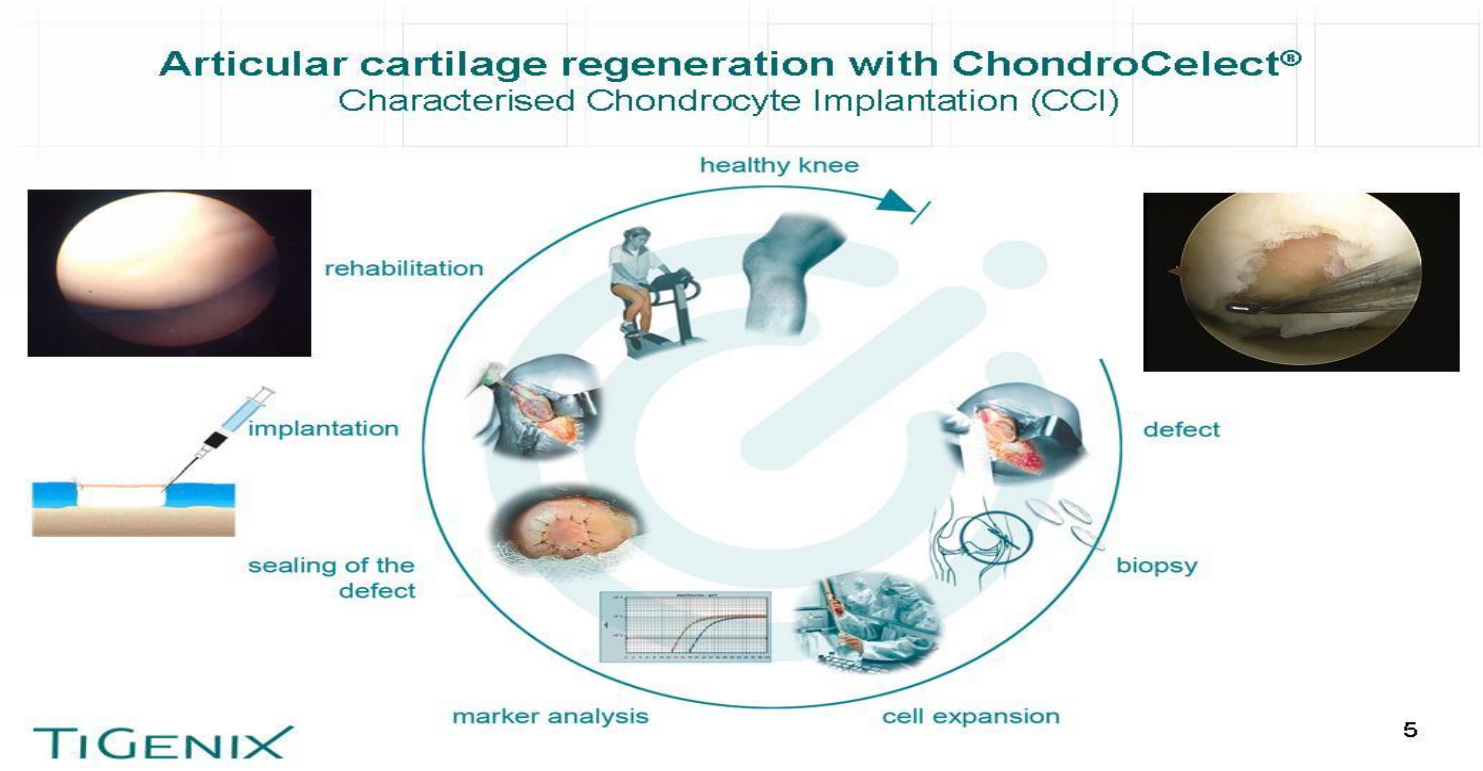
- ✓ Characterisation and testing of cell-device combination
- ✓ Impurities and degradation products from device component
- ✓ CE mark of device component, if possible

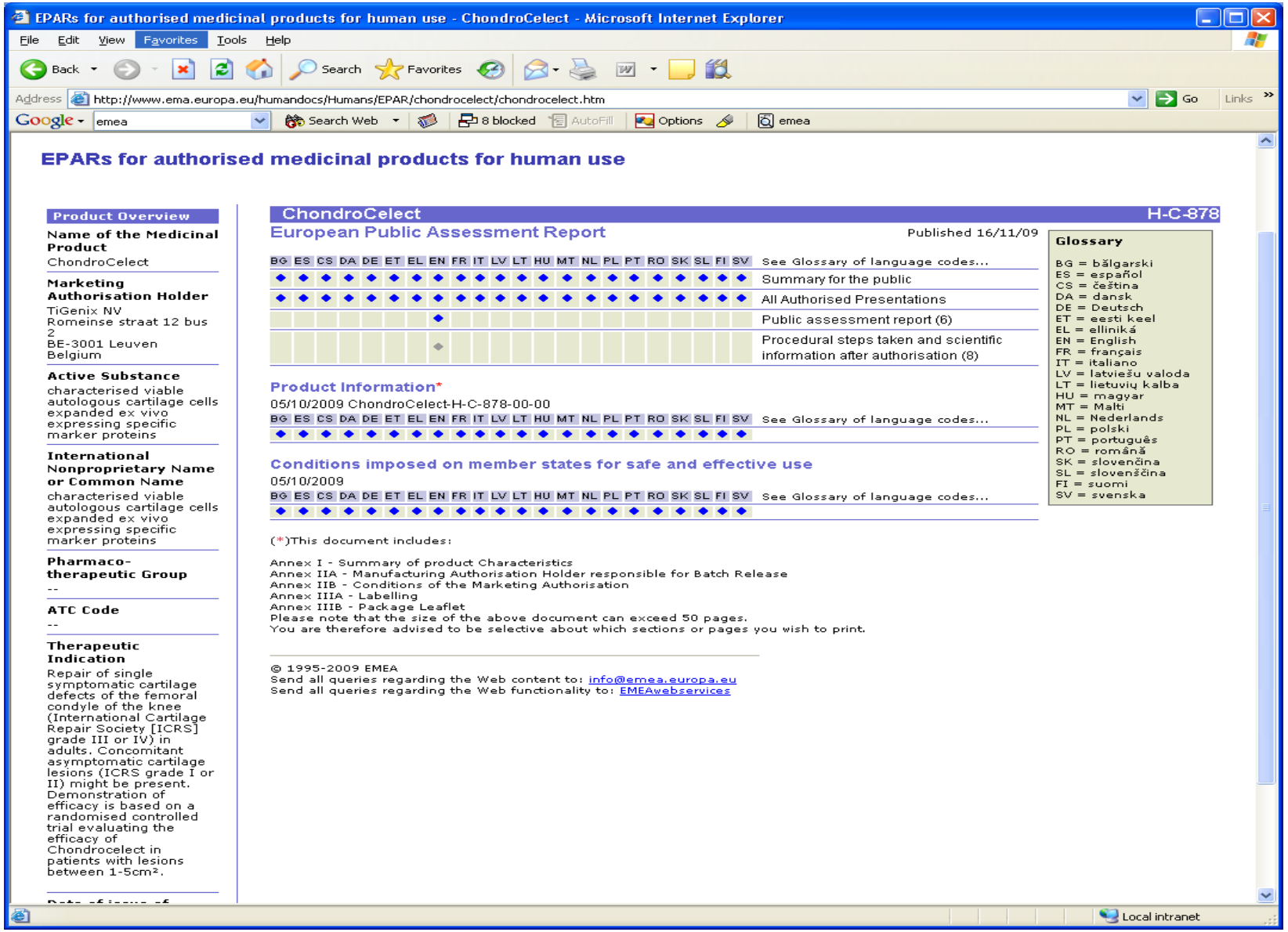
Challenges for cell products

- Autologous product → limited amount of material for testing
- Short shelf-life → limited possibilities for batch release testing
- Difficulties to find a suitable potency test
  → correlation of cell quality to clinical outcome?
- No suitable animal models
  → non-clinical testing cannot be performed; clinical evidence?
- Wide clinical experience already
  → not necessary to conduct non-clinical studies?
- Administration of the cells impacts the final outcome / rare diseases / unmet medical need / proper comparator not available
  → open-label, single arm, non-controlled study with minimal number of patients enough? No clinical trial conducted?

Case study of an approved ATMP

Tissue Engineering - ChondroCelect





EPARs for authorised medicinal products for human use - ChondroCelect - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Search Favorites

Address http://www.ema.europa.eu/humandocs/Humans/EPAR/chondrocelect/chondrocelect.htm Go Links

Google emea Search Web 8 blocked AutoFill Options emea

EPARs for authorised medicinal products for human use

Product Overview

Name of the Medicinal Product
ChondroCelect

Marketing Authorisation Holder
TiGenix NV
Romeinse straat 12 bus 2
BE-3001 Leuven
Belgium

Active Substance
characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins

International Nonproprietary Name or Common Name
characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins

Pharmaco-therapeutic Group
--

ATC Code
--

Therapeutic Indication
Repair of single symptomatic cartilage defects of the femoral condyle of the knee (International Cartilage Repair Society [ICRS] grade III or IV) in adults. Concomitant asymptomatic cartilage lesions (ICRS grade I or II) might be present. Demonstration of efficacy is based on a randomised controlled trial evaluating the efficacy of Chondrocelect in patients with lesions between 1-5cm².

ChondroCelect H-C-878

European Public Assessment Report

Published 16/11/09

BG ES CS DA DE ET EL EN FR IT LV LT HU MT NL PL PT RO SK SL FI SV See Glossary of language codes...

Summary for the public

All Authorised Presentations

Public assessment report (6)

Procedural steps taken and scientific information after authorisation (8)

Glossary

BG = bălgarski
ES = español
CS = čeština
DA = dansk
DE = Deutsch
ET = eesti keel
EL = elliniká
EN = English
FR = français
IT = italiano
LV = latviešu valoda
LT = lietuvių kalba
HU = magyar
MT = Malti
NL = Nederlands
PL = polski
PT = português
RO = română
SK = slovenčina
SL = slovenščina
FI = suomi
SV = svenska

Product Information*

05/10/2009 ChondroCelect-H-C-878-00-00

BG ES CS DA DE ET EL EN FR IT LV LT HU MT NL PL PT RO SK SL FI SV See Glossary of language codes...

Conditions imposed on member states for safe and effective use

05/10/2009

BG ES CS DA DE ET EL EN FR IT LV LT HU MT NL PL PT RO SK SL FI SV See Glossary of language codes...

(*)This document includes:

Annex I - Summary of product Characteristics
Annex IIA - Manufacturing Authorisation Holder responsible for Batch Release
Annex IIB - Conditions of the Marketing Authorisation
Annex IIIA - Labelling
Annex IIIB - Package Leaflet
Please note that the size of the above document can exceed 50 pages.
You are therefore advised to be selective about which sections or pages you wish to print.

Send all queries regarding the Web content to: info@emea.europa.eu
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Local intranet

ChondroCelect

- characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins.

Therapeutic indication

Repair of single symptomatic cartilage defects of the femoral condyle of the knee in adults. Concomitant asymptomatic cartilage lesions (ICRS grade I or II) might be present.

Demonstration of efficacy based on a randomised controlled trial evaluating the efficacy of ChondroCelect in patients with lesions between 1-5 cm^2.

❖CHMP positive opinion: June 2009, Commission decision October 2009

Quality data

- A series of functional tests for cell characterise, validation the manufacturing process

- Cell culture (3D cell culture assay),
- Functional assay in animal models,
- Test of cellular expression patterns of genes relevant for cartilage and chondrocyte biology

- Validation of manufacturing process has been adequately performed.

- Comparability and consistency of lots manufactured were adequate

See EPAR: (http://www.ema.europa.eu/humandocs/PDFs/EPAR/chondrocelect/H-878-en6.pdf)

Preclinical data

- Combined pharmacodynamic / pharmacokinetic (distribution) / toxicological studies were performed in ectopic mouse and in orthotopic models in sheep and goats

➢ studies in goats adequate to demonstrate proof of principle in a clinically relevant setting

See EPAR: Scientific Discussion (http://www.ema.europa.eu/humandocs/PDFs/EPAR/chondrocelect/H-878-en6.pdf)

Clinical efficacy

-Study TIG/ACT/01/2000

- phase III, multicentre, randomized, controlled trial to compare ChondroCelect to microfracture in the repair of symptomatic single cartilaginous lesions of the femoral condyles of the knee
- 4-year extension phase
- Clinical non-inferiority in KOOS (patient-based outcome measure)
- Clinical superiority in a structural endpoint (structural assessments (histology and MRI))

See EPAR: (http://www.ema.europa.eu/humandocs/PDFs/EPAR/chondrocelect/H-878-en6.pdf)

Clinical safety

- total of 463 patients exposed
- Safety profile comparable to Microfracture
- Increased joint swelling related to the open knee surgery
- Cartilage hypertrophy reduced by use of biomembrane
- treatment failure was higher in the microfracture arm requiring subsequent surgical intervention.
- acceptable RMP including proposal for confirmatory randomized controlled trial and observational follow-up study

See EPAR: (http://www.ema.europa.eu/humandocs/PDFs/EPAR/chondrocelect/H-878-en6.pdf)

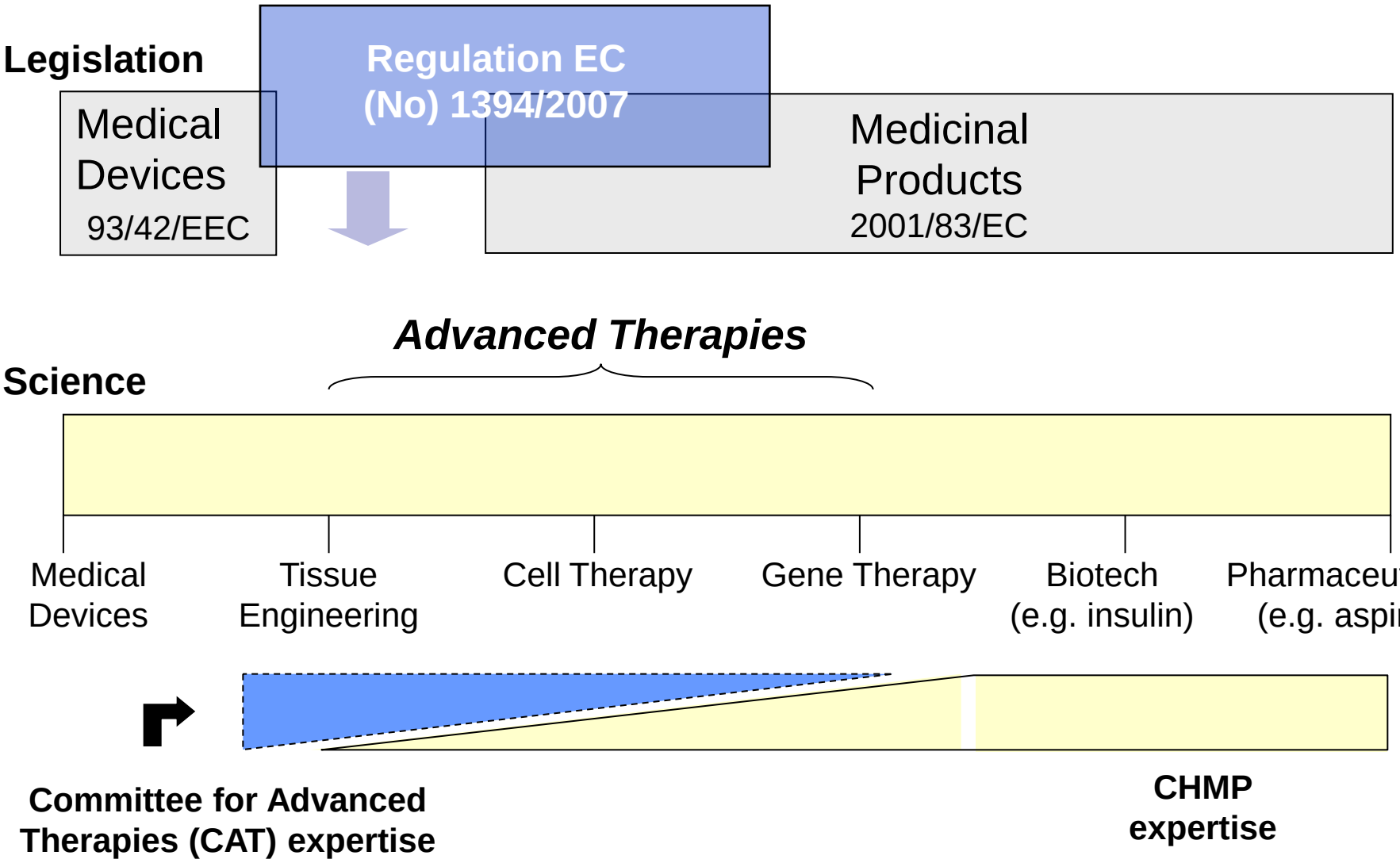
Conclusions

- ATMPs (stem cell products) authorised via centralised procedure involving the CAT
- Scientific Advice!
- 'Mother guideline' Human Cell-based medicinal products (EMEA/CHMP/410869/2006)
- **Quality:** characterisation, consistency, potency and comparability
- **Nonclinical:** adequate animal models, mechanism of action, biodistribution, safety
- **Clinical:** safety, long term efficacy, general endpoints + TEP-specific endpoint, duration of follow-up

EMA Regulatory procedures for ATMPs

EU Regulation for Advanced Therapies

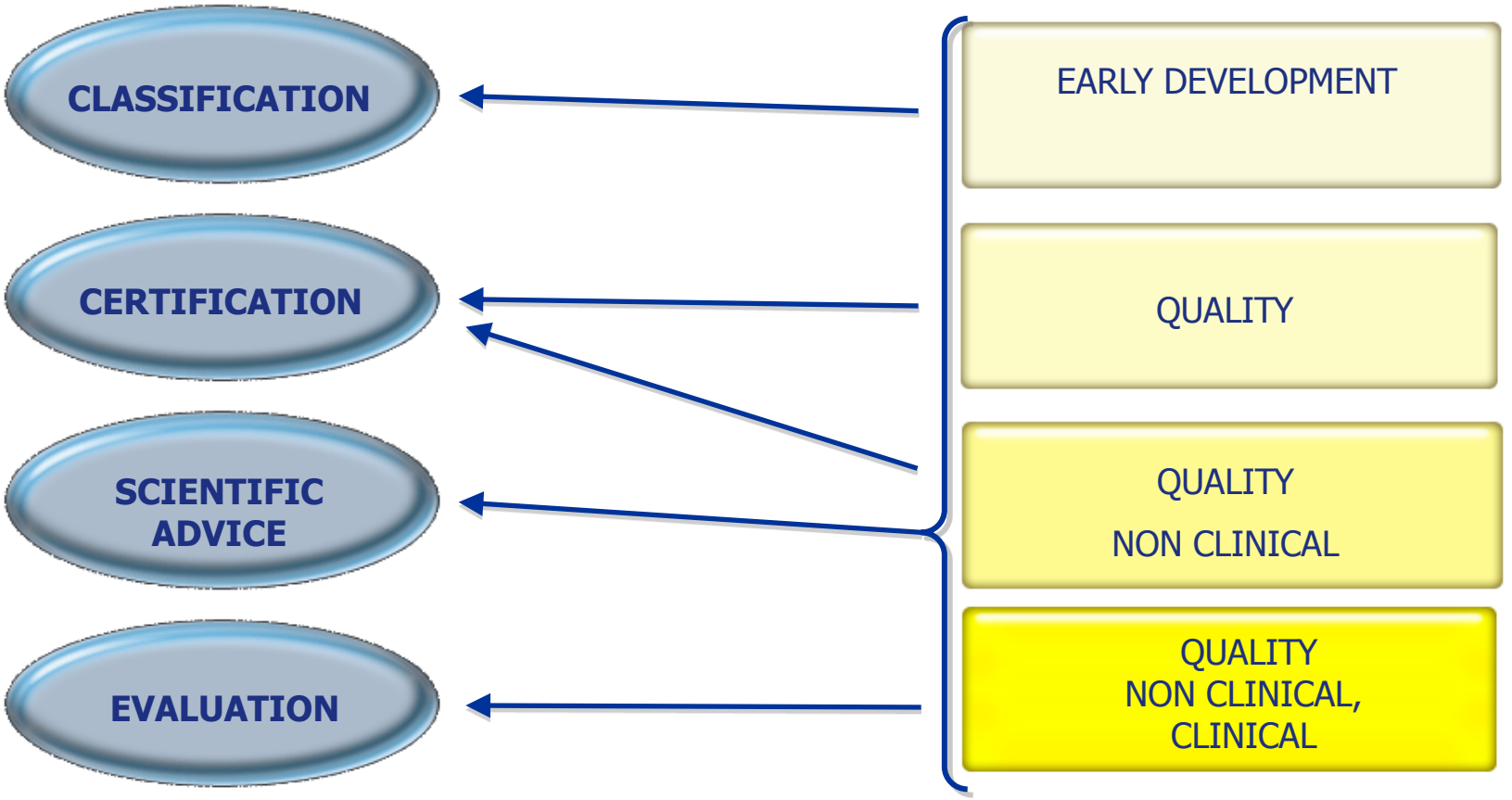
EUROPEAN MEDICINES AGENCY



'Advanced Therapies' Regulation EC (No) 1394/2007

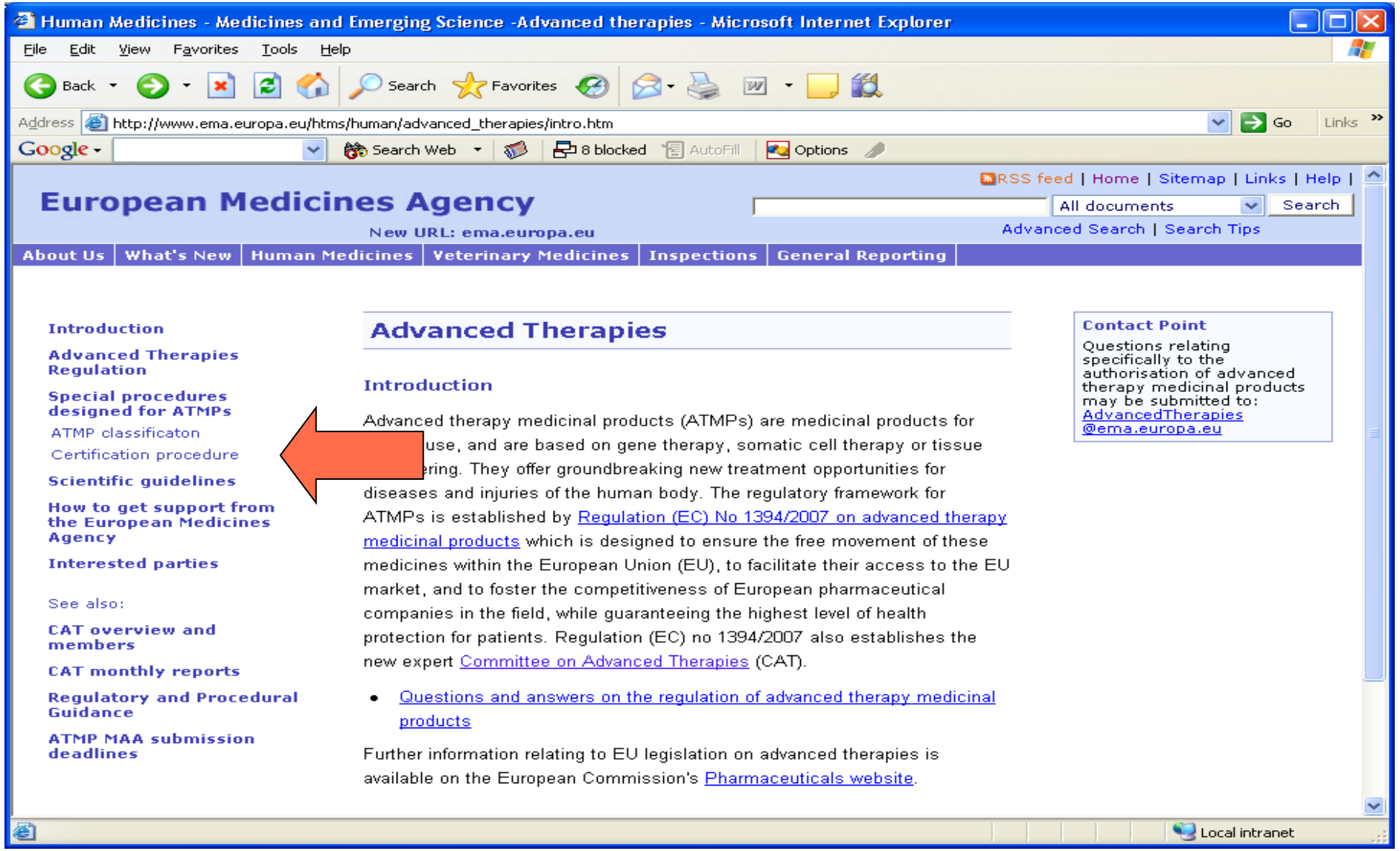
- Definitions for **gene therapy**, **cell therapy** & **tissue engineered products**
- Mandate to EMA/EC to develop guidance
- Combined ATMPs
- Initial Marketing Authorisation Procedure + Requirements for ATMPs
- Post-authorisation requirements including efficacy FU
- Incentives (Scientific Advice, **Certification procedure**, Fee reductions)
- **Committee for Advanced Therapies**
- Transitional period until 2011/2012

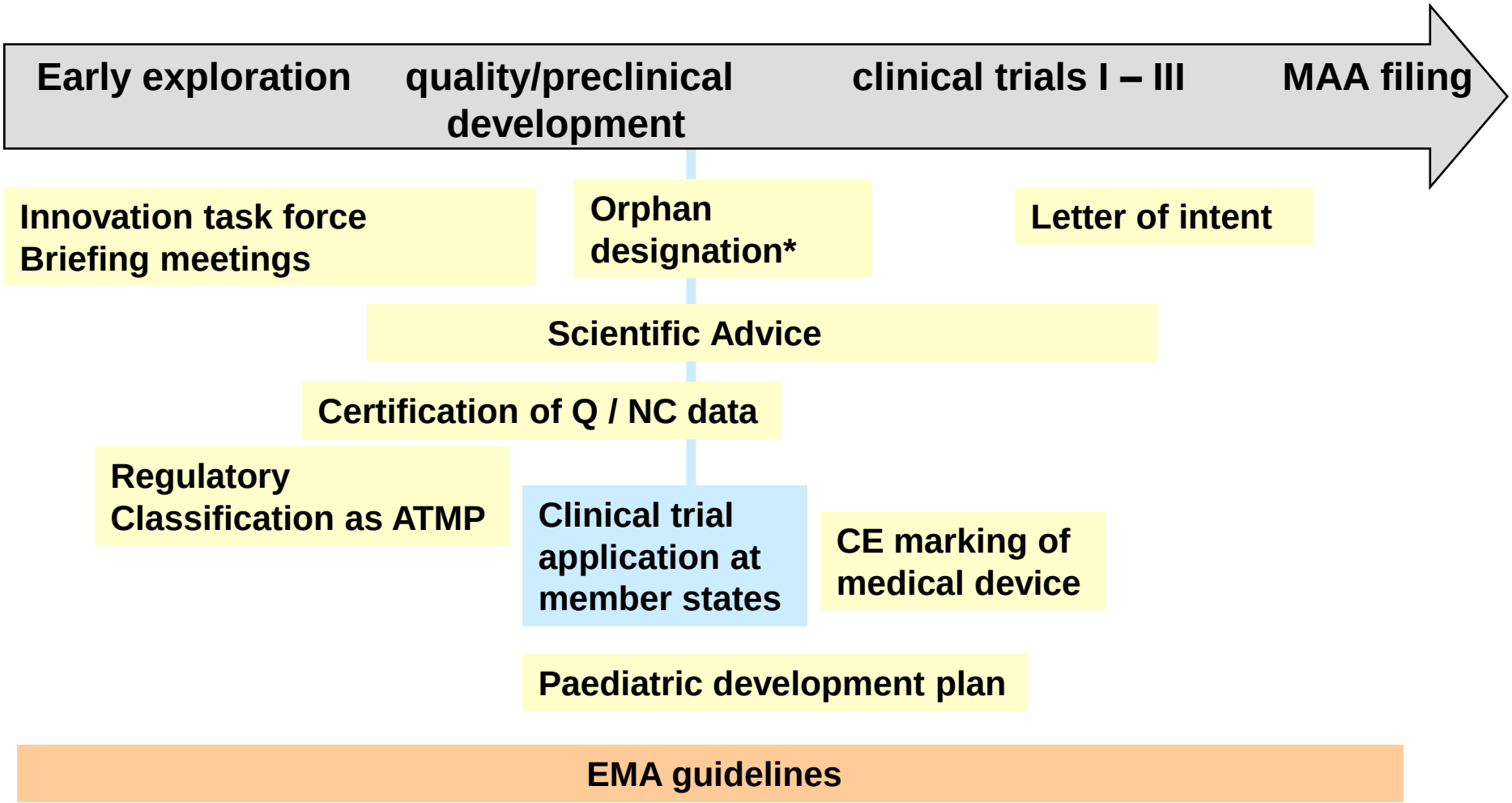
EMA Regulatory procedures for ATMPs



Advanced Therapies Agency Website

EUROPEAN MEDICINES AGENCY





* Orphan designation can be applied for at any time

Is the product an ATMP?

- To define Borderline e.g. with medical device, transplant, cosmetics.
- Incentive for applicants, not legal requirement
- Fast procedure (max 60 days)

Info on EMA website

www.ema.europa.eu -> Home / Regulatory / Human medicines / Advanced therapies / ATMP classification

http://www.ema.europa.eu/htms/human/advanced_therapies/atmp_classification.htm

Procedural advice

Procedural advice on the provision of scientific recommendation on classification of advanced therapy medicinal products

Previous cases

Summaries - Summaries of CAT scientific recommendations on ATMPs classification

How we advice on ATMP development

- Scientific Advice can be given on ANY scientific question: Quality, non-clinical and clinical
- At any time point of the development
  - Pre and Post-marketing advice
- Broad advice, Conditional approval and Exceptional circumstances
- Confidential

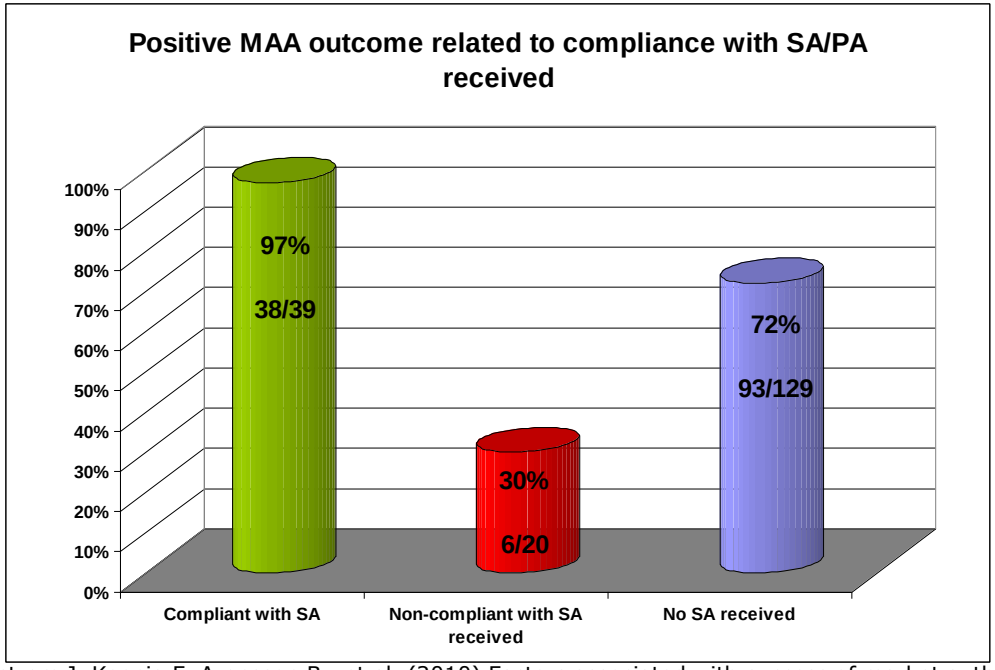
Info on EMA website

www.ema.europa.eu -> Home / Regulatory / Human medicines / Scientific advice and protocol assistance

How to apply
Guidance for companies requesting Scientific advice and protocol assistance

Regulatory strategy: save time

Scientific advice: Complying with SA/PA is significantly associated with positive outcome



Regnstrom J, Koenig F, Aronsson B, et al. (2010) Factors associated with success of market authorisation applications for pharmaceutical drugs submitted to the European Medicines Agency; EJCP 66:39-48

Evaluation of data generated during ATMP development

- Incentive for Small and medium enterprises (SME)
- Assessment of early quality and non-clinical data
- Fast procedure (90 days)
- Certificate may attract investments

Info on EMA website

www.ema.europa.eu -> Home / Regulatory / Human medicines / Advanced therapies / Certification procedure for SMEs

Procedural advice

Procedural advice on the certification on Q, N/C data for SMEs developing ATMPs

Scientific guidance

Guideline on the minimum quality and non clinical data for certification of ATMPs

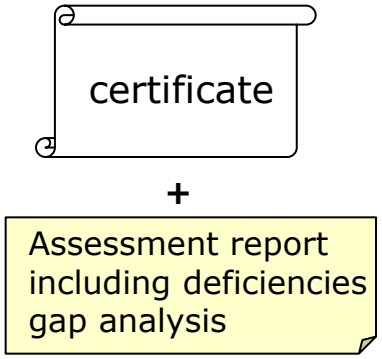
CERTIFICATION

- Scientific evaluation of manufacturing, non clinical data generated during development of an ATMP

  (not on a full Module 3 /4)

What it is

- EMA evaluates compliance with scientific and technical requirements of Annex I Assessment of early quality and non-clinical data
- A CERTIFICATE is issued of those parts / studies that are performed finalised (in line with scientific standards for a MAA)



What it is not

- No assessment of benefit/risk
- No statements on appropriateness to enter into clinical trials
- No prospective statements pertaining to the further development of the product

The product development is completed!

- Principles of existing legislation on medicines apply to advanced therapies
- Centralised procedure mandatory
- A Committee with specific expertise evaluate MAAs
- Special features:
  - Risk based approach
  - Risk management Plan and follow-up of safety and efficacy

Related documents

Procedural advice

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/02/WC500070340.pdf

General Advanced therapies: Regulatory and procedural guidance

European Medicines Agency - Guidance - Advanced therapies: Regulatory and procedural guidance

Where to find information?

EMA website: www.emea.europa.eu

Advanced Therapies: http://www.ema.europa.eu/htms/human/advanced_therapies/intro.htm

Classification: http://www.ema.europa.eu/htms/human/advanced_therapies/atmp_classification.htm

Certification: http://www.ema.europa.eu/htms/human/advanced_therapies/certification.htm

Cell therapy guidelines:

http://www.ema.europa.eu/htms/human/humanguidelines/multidiscipline.htm#celltherapy

Regulatory & Procedural guidance:

http://www.ema.europa.eu/htms/human/raguidelines/advanced_therapies.htm

Who to contact

General Enquiries: info@ema.europa.eu

Advanced Therapies (including certification of ATMPs):

AdvancedTherapies @ema.europa.eu

Informal ITF Briefing meeting: ITFsecretariat@ema.europa.eu

Thank you for your attention

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