Symposium

Raw Materials for the Production of Cell-based and Gene Therapy Products

3 April 2013

Strasbourg, France

Welcome Address

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Welcome introduction European Medicines Agency

Presented by: Dr Alexis Nolte
Head of Sector - Quality of Medicines, European Medicines Agency

An agency of the European Union

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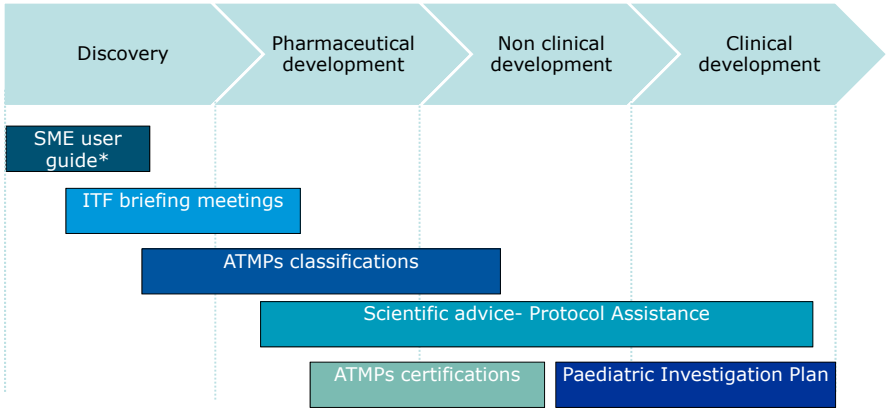
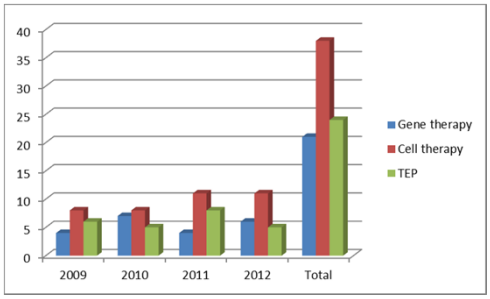
EMA support to ATMPs developers



*Link to SME user guide:
http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004134.pdf

EMA support to ATMPs developers – SA/PA

Number of SA/PA given from 2009 to 2012



EMA support to ATMPs developers –SA/PA

SA recurrent quality questions asked:	MAA Major quality objections asked:
Definition of active substance vs. finished product;	Active substance vs.. Finished product have not been defined appropriately;
Acceptability of the **raw materials** used;	Impact of **raw materials** used in the ATMP manufacture;
Acceptability of characterisation of the AS and FP;	Insufficient characterisation of the AS and FP;
Acceptability of markers;	Potency assay not sufficiently correlated to biological activity;
Acceptability of the potency assay;	No correlation between markers and clinical outcome
Acceptability of the comparability data;	Lack of comparability data;
Acceptability of purity and identity tests, etc…	Purity and identity tests not adequate, etc..

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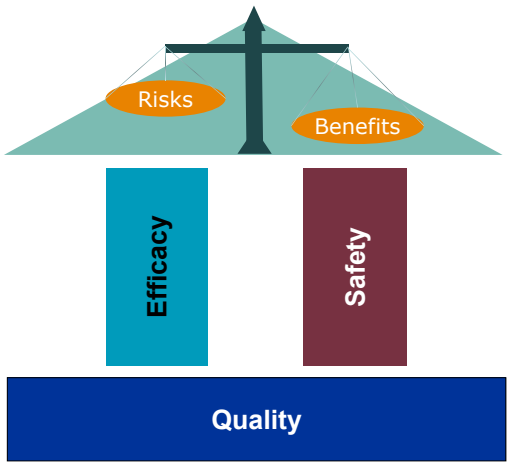
Quality is key for ATMP development



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EMA/EDQM Working together

Session 1

EDQM, EMA & The RCG Working Party

Background to the Council of Europe, European Directorate for the Quality of Medicines and HealthCare (EDQM) and the European Pharmacopoeia

SYMPOSIUM

RAW MATERIALS FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY PRODUCTS

Emmanuelle Charton, PhD

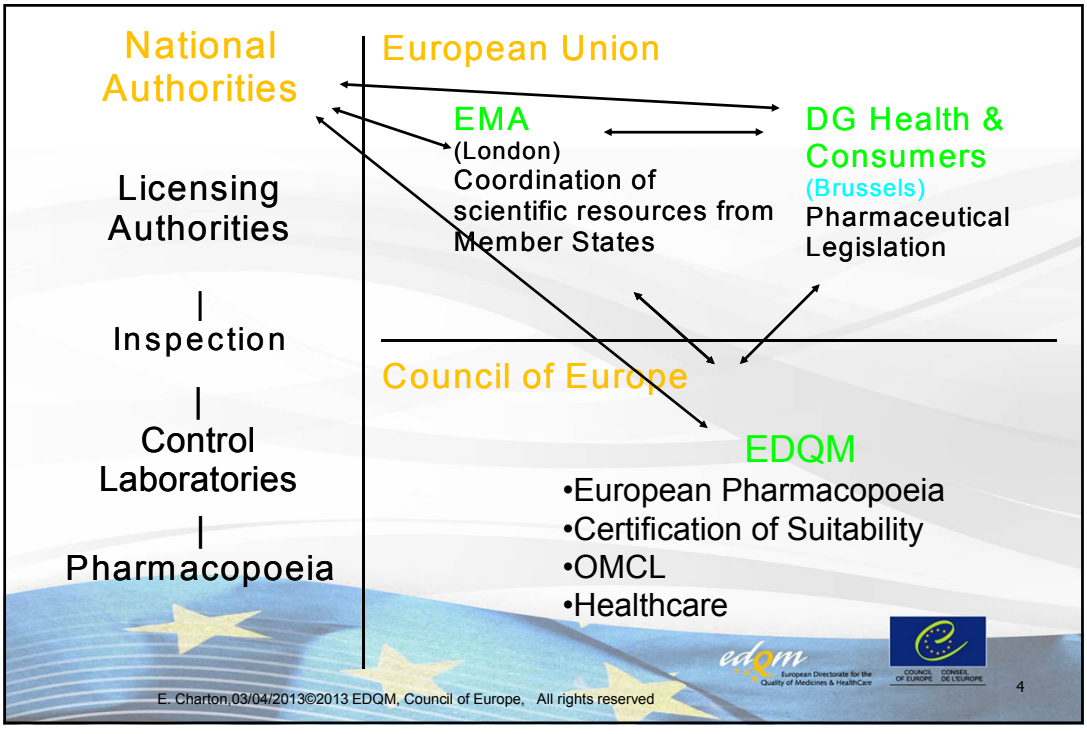
Deputy Head, European Pharmacopoeia Department

The Council of Europe

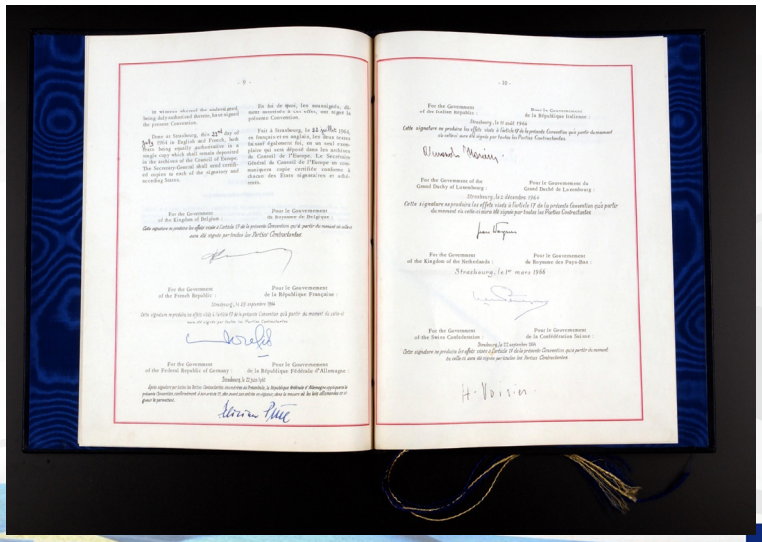
- Founded in 1949
- Development of European common and democratic principles
- 47 member countries
- Headquarters in Strasbourg
- Core values :
  - protection of human rights
  - pluralist democracy & the rule of law

European Directorate for the Quality of Medicines & HealthCare (EDQM)

- A Council of Europe Directorate, based on the Convention on the Elaboration of a European Pharmacopoeia (PA, 1964)
- Mission: to contribute to a basic human right: access to good quality medicines and healthcare



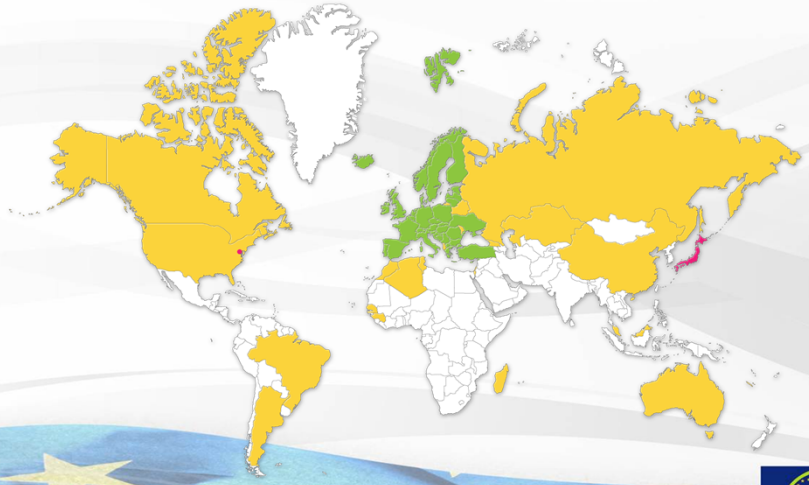
European Pharmacopoeia Convention



The European Pharmacopoeia

- 1964: Convention on the elaboration of a European Pharmacopoeia
- Today:
  - 37 member states + the European Union
  - 25 observers
    - 9 European countries
    - 16 non-European countries
    - World Health Organization (WHO)

Members & Observers



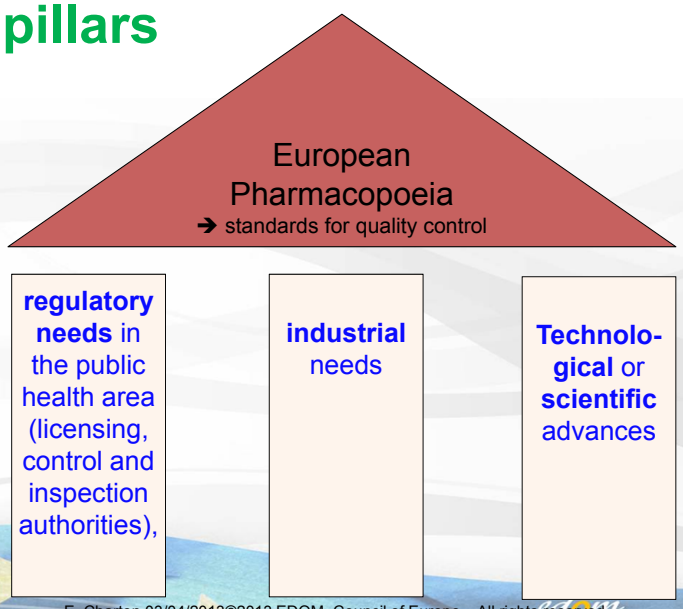
European Pharmacopoeia & its legal status

- Lays down common, compulsory quality standards for all medicinal products in Europe, i.e. raw materials, preparations, dosage forms, containers
- Mandatory at the same date in 37 states (CoE) and the EU
- National pharmacopoeias to cover subjects of solely national interest
- 1975: Mandatory status reinforced in the EU pharmaceutical legislation for the EU/EEA member states

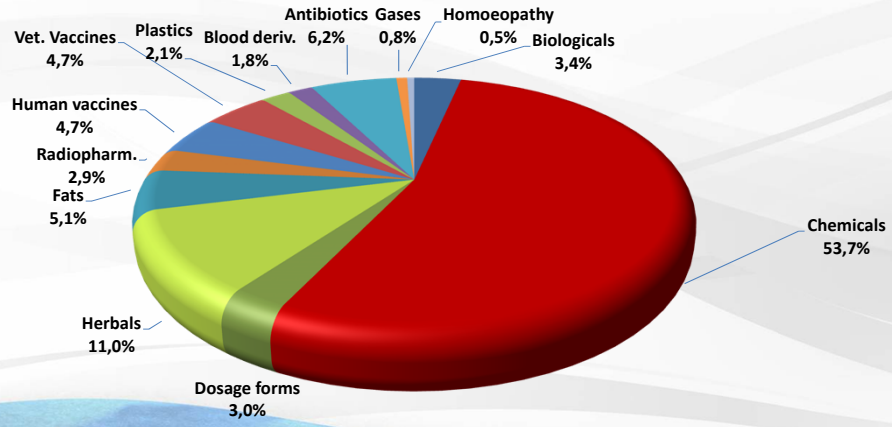
Its purposes (II. Introduction to Ph. Eur.)

- To promote public health by the provision of recognised common standards. Such standards are to be appropriate as a basis for the safe use of medicines by patients and consumers.
- Their existence:
  - facilitates the free movement of medicinal products in Europe;
  - ensures the quality of medicinal products and their components imported into or exported from Europe.

The pillars



Contents of the European Pharmacopoeia:
Nearly 2200 Monographs and more than 330 General chapters



EDQM Workshop on the Future of monographs on biologicals (2011)

- Opinion of assessors gathered
- Key raw materials are high risk biologicals (growth factors, cytokines, mAbs): need for harmonised quality criteria
- For some of these raw materials, only ´research use´-grade materials available;
- Raw material manufacturers have difficulties in delivering confidential quality information to all their customers to be further delivered for assessment by authorities
- The same quality data e.g. for clinical trials have to be evaluated by multiple national authorities (overlapping work)

Current Ph. Eur. texts of interest

- Human haematopoietic stem cells (2323)
- Chapter 5.14 Gene transfer medicinal products for human use

*« **Substances used in production**. The raw materials used during the manufacturing process, including viral seed lot and cell bank establishment, where applicable, are qualified. Unless otherwise justified, all substances used are produced within a recognised quality management system using suitable production facilities. Suitable specifications are established to control notably their identity, potency (where applicable), purity and safety in terms of microbiological quality and bacterial endotoxin contamination. (…). Where bovine serum is used, it complies with the monograph Bovine serum (2262). The use of antibiotics is avoided wherever possible during production. »*

Current Ph. Eur. texts of interest

- Products of fermentation (1468)
- Products of rDNA technology (0784)
- Products with risk of TSE (1483), implementing chapter 5.2.8
- Viral safety (5.1.7)
- TSE note for guidance (5.2.8)

Current Ph. Eur. texts of interest

- Insulins (0838, 1637, 1638)
- G-CSF (2206)
- GM-CSF (1641)
- Erythropoietin (1316)
- Interferon gamma (1440)
- Bovine serum (2262)
- Trypsin (0694)

These requirements for substances used as APIs might not be adapted to raw materials

Ph. Eur. Commission: Nov. 2011

- Recognition of the need to set up quality requirements for these raw materials
- Strong support from delegations to create a respective Working Party
- Certification system is not in the scope
- Collaboration with CTP, GTP (at Ph. Eur.), CAT and BWP (at EMA) is essential
- Creation of a new Working Party « RCG »
  - Elaborate a text on Raw Materials for the Production of cellular products and gene transfer products
  - Scope: antibodies, basal media (for cell culture), serum/serum replacements, growth factors and cytokines


Thank you for your attention !
E. Charton,03/04/2013©2013 EDQM, Council of Europe. All rights reserved.

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The European Medicines Agency's views on raw materials for gene and cell therapy products

Presented by: Jean-Hugues Trouvin
Chairman of the BWP (Biological Working Party) at the European Medicines Agency
CAT member from January 2009 to September 2013

An agency of the European Union

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To Jean-Marc Spieser

Head of the Department for Biological Standardisation, OMCL Network and HealthCare

EDQM, council of Europe, Strasbourg

In memoriam

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Agenda

- ✓ Introduction - Definition
- ✓ The ATMP regulation context for raw materials
  - EU regulation
  - EU requirements
- ✓ Raw materials in the EMA guidance for ATMPs
- ✓ Need for quality standards for raw materials used in the ATMPs manufacture

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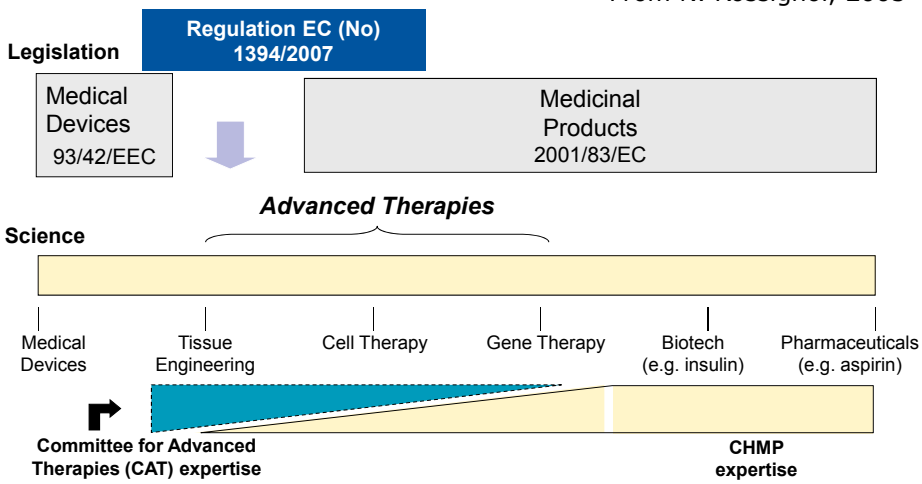
EU Regulation for Advanced Therapies

ATMPs are classified as medicinal products

From N. Rossignol, 2005



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EU Regulation for Advanced Therapies

- ✓ Definitions given for gene therapy, cell therapy & tissue engineered products
- ✓ New class of "combined ATMPs" (medicinal product + medical device)
- ✓ Marketing Authorisation Procedure + specific requirements for ATMPs (part IV of annex I, Dir. 2001/83, as amended by Dir. 2009/120)
- ✓ Post-authorisation requirements including long term follow up for efficacy and safety
- ✓ Risk-based approach (Dir. 2001/83/EC, Annex I, Part IV)
- ✓ Incentives (Scientific Advice, Certification procedure, Fee reductions)
- ✓ Committee for Advanced Therapies
- ✓ Hospital exemption

Clinical trial approval
at member state level
National decision on all aspects, including quality

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EU Regulation for Advanced Therapies Definitions

- ✓ Gene therapy medicinal product:
  - ➢ recombinant nucleic acid → to regulating, replacing, adding or deleting a genetic
- ✓ Somatic cell therapy medicinal
  - ➢ substantially manipulated, prevent or diagnose a disease (pharmacological, metabolic action)
- ✓ Tissue engineered
  - ➢ substance/tissue → to regenerate repair or replace
- ✓ Combined
  - ➢ Incorporate an integral part of the product one or + MD or AIMD (Dir. 93/42/EEC or Dir. 90/385/EC)

For preparation of these products, need for
- starting material
- reagents and other raw materials
- a well established production process

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From EU regulation 1394/2007

Article 15

Traceability

1. The holder of a marketing authorisation for an advanced therapy medicinal product shall establish and maintain a system ensuring that the individual product and its starting and raw materials, including all substances coming into contact with the cells or tissues it may contain, can be traced through the sourcing, manufacturing, packaging, storage, transport and delivery to the hospital, institution or private practice where the product is used.

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Technical requirements, from EU regulation
(Annex I, part IV amended by Dir. 2009/120)

3. SPECIFIC REQUIREMENTS REGARDING MODULE 3

3.1. **Specific requirements for all advanced therapy medicinal products**

A description of the traceability system that the marketing authorisation holder intends to establish and maintain to ensure that the individual product and its starting and raw materials, including all substances coming into contact with the cells or tissues it may contain, can be traced through the sourcing, manufacturing, packaging, storage, transport and delivery to the hospital, institution or private practice where the product is used, shall be provided.

3.2. **Content: basic principles and requirements**

(3) This Module shall in addition supply detailed information on the starting and raw materials used during the manufacturing operations of the active substance(s) and on the excipients incorporated in the formulation of the finished medicinal product.

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Technical requirements, from EU regulation
(Annex I, part IV amended by Dir. 2009/120

3.3. **Specific requirements for somatic cell therapy medicinal products and tissue engineered products**

3.3.1. *Introduction: finished product, active substance and starting materials*

The finished medicinal product shall consist of the active substance formulated in its immediate container for the intended medical use, and in its final combination for combined advanced therapy medicinal products.

The active substance shall be composed of the engineered cells and/or tissues.

Additional substances (e.g. scaffolds, matrices, devices, biomaterials, biomolecules and/or other components) which are combined with manipulated cells of which they form an integral part shall be considered as starting materials, even if not of biological origin.

Materials used during the manufacture of the active substance (e.g. culture media, growth factors) and that are not intended to form part of the active substance shall be considered as raw materials.

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From the CTD (annex I)

3. MODULE 3: CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL INFORMATION FOR MEDICINAL PRODUCTS CONTAINING CHEMICAL AND/OR BIOLOGICAL ACTIVE SUBSTANCES

3.2. **Content: basic principles and requirements**

(3) This Module shall in addition supply detailed information on the starting and raw materials used during the manufacturing operations of the active substance(s) and on the excipients incorporated in the formulation of the finished medicinal product.

3.2.1. *Active substance(s)*

3.2.1.1. General information and information related to the starting and raw materials

Any other substances used for manufacturing or extracting the active substance(s) but from which this active substance is not directly derived, such as reagents, culture media, foetal calf serum, additives, and buffers involved in chromatography, etc. are known as raw materials.

3.2.1.2. Manufacturing process of the active substance(s)

Raw materials shall be listed and their quality and controls shall also be documented.

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From GMP annex 2

- ✓ 10.3 → Control measures for the pharmaceutical raw materials at establishments such as abattoirs should include appropriate elements of Quality Management System to assure a satisfactory level of operator training, materials traceability, control and consistency.
- ✓ 10.5 → Regular audits of the raw material supplier should be undertaken ……. Issues must be investigated to a depth appropriate to their significance, …….. Systems should also be in place to ensure that effective corrective and preventive actions are taken.

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From GMP annex 2

- ✓ 4.3 →Where human cell or tissue donors are used, full traceability is required from starting and raw materials, including all substances coming into contact with the cells or tissues through to confirmation of the receipt of the products at the point of use
- ✓ 6.1→ The source, origin and suitability of biological starting and raw materials (e.g. cryoprotectants, feeder cells, reagents, culture media, buffers, serum, enzymes, cytokines, and growth factors) should be clearly defined.

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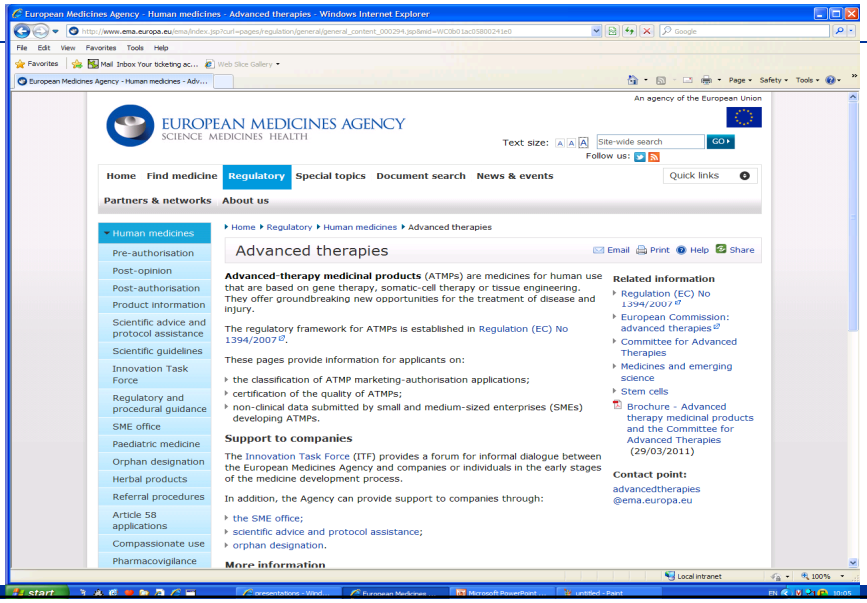
EMA guidance available for ATMPs



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EMA guidance available for ATMPs: Gene Therapy

Parental Guideline
Guidance on Qual, Pre- Clin. and Clin. aspects of gene transfer products (2001, under revision)

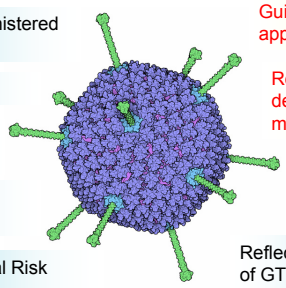
Guideline on follow up of patients administered with gene therapy (2010)

Q&A on Gene therapy (2009)

Qual., Non Clin. & Clin. issues of adeno-associated viral vectors (2009)

ICH considerations – Oncolytic viruses (2009)

Scientific requirements for Environmental Risk Assessment (2008)



Guideline on risk based approach (Feb 2013)

Reflection paper on clinical risks deriving from insertional mutagenesis (drafting)

Guideline on MPs containing genetically modified cells (2012)

Reflection paper on design modifications of GTMPs during development (2012)

Non-clinical studies required before first clinical use (2008)

Non clinical testing of inadvertent of gene transfer vectors (2007)

Guideline on Development and manufacture of lentiviral vectors (2005)

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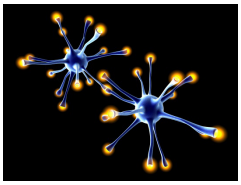
EMA guidance available for ATMPs: Cell Based medicinal products

Guideline on Risk Based Approach (Feb 2013)

Reflection paper on stem-cell based MPs (2010)



Clinical aspects to tissue engineered products (drafting)

Guideline on MPs containing genetically modified cells (2012)

Potency testing of cell-based immunotherapy MPs for treatment of cancer (2007)

Guideline on Xenogeneic CBMPs (2009)

Guideline on Safety & Efficacy Follow-up – Risk Management of ATMPs (2008)

Reflection paper on Chondrocyte containing MPs for cartilage repair (2009)

Position Statement on CJD aspects (2011)

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EMA guidance available for ATMPs Gene Therapy

Gene Therapy parental guideline:

- Gene addition/expression for therapeutic purposes
- DNA vaccination
- DNA/RNA transfer to modify gene function/expression

  - Quality + manufacturing aspects
  - Nonclinical development
  - Clinical development

The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 24 April 2001
CPMP/BWP/3088/99

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

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

DISCUSSION IN THE BIOTECHNOLOGY WORKING PARTY (BWP)	June – December 1999
DISCUSSION IN THE SAFETY WORKING PARTY (SWP)	June 1999
DISCUSSION IN THE EFFICACY WORKING PARTY	July – November 1999
TRANSMISSION TO CPMP	December 1999

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NfG on gene transfer medicinal products ("mother guideline")

- ✓ All raw materials used in production and purification have to be described, including quality controls.
- ✓ Raw materials of biological origin should be selected which have been thoroughly tested and manufactured by a process validated for the removal of adventitious and endogenous viruses

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Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells

5.1.2. Other materials, reagents and excipients

Materials and reagents used for the transduction process and subsequent steps should be of appropriate quality, including testing for sterility, absence of adventitious agents and endotoxin among other controls, in order not to compromise the quality, safety and efficacy of the final product. Viral safety as well as measures taken to minimise the risk of transmitting agents causing TSE of any reagent or material of animal origin should be demonstrated. Recombinant proteins such as enzymes, antibodies, cytokines, growth or adhesion factors should be characterised and controlled, where appropriate and relevant, in accordance with the principles described in the Agency guidelines on

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EMA guidance available for ATMPs: Cell Based medicinal products

Guideline on human cell based medicinal products ("mother guideline")

- Quality + manufacturing aspects
- Nonclinical development
- Clinical development

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

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GUIDELINE ON HUMAN CELL-BASED MEDICINAL PRODUCTS

4.2.1 Starting and raw materials

The manufacturing process of CBMP usually does not include terminal sterilisation, purification steps, viral removal and/or inactivation steps. Therefore, stringent sourcing requirements and acceptance criteria for all materials derived from human or animal origin should be adequately defined according to their intended use.

When the raw materials, reagents and/or excipients have a marketing authorisation or mentioned in a Pharmacopoeia, appropriate references may be given.

Adventitious agents

A critical aspect is to establish that CBMP are free from adventitious microbial agents (viruses, mycoplasma, bacteria, fungi). The contamination could originate from the starting or raw materials (see above), or adventitiously introduced during the manufacturing process. A risk assessment should be performed to evaluate the possibility of reactivation of cryptic (integrated, quiescent) forms of adventitious agents. A thorough testing for the absence of bacteria, fungi and mycoplasma shall be performed at the level of finished product. These tests should be performed with the current methodologies described in the European pharmacopoeia for cell based products [28]. In cases where the short shelf life of the CBMP is prohibitive for the testing of absence of bacteria under the Eur Ph. requirements, alternative validated testing methods may be acceptable, if justified.

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GUIDELINE ON HUMAN CELL-BASED MEDICINAL PRODUCTS

✓ The quality of biologically active additives in culture media such as growth factors, cytokines and antibodies, should be documented with respect to identity, purity, sterility and biological activity and absence of adventitious agents …..

The quality of biologically active additives in culture media such as growth factors, cytokines and antibodies, should be documented with respect to identity, purity, sterility and biological activity and absence of adventitious agents. It is recommended to keep the use of such materials to a minimal and to avoid the use of reagents with sensitisation potential e.g. β-lactam antibiotics.

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Reflection paper on stem cell-based medicinal products

2.2. Starting materials

The history of the cell line derivation and cell banking, including the raw material used during production, needs to be carefully documented. This is particularly important for hESC's in cases where cell lines, established before the requirements of Dir. 2004/23/EC came into force, are the only source material and results from donor testing are not available.

Viral and TSE safety of the cells and raw materials should be addressed during cell bank and/or starting material qualification or early in the production process to minimize the risk of contamination.

The origin and procurement of the starting material to isolate the stem cells is considered critical for the yield and identity/purity of the final cell population. The selection of appropriate markers is fundamental to the standardisation of isolation conditions and to control cell populations, heterogeneity and yield.

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CHMP/CAT position statement on Creutzfeldt-Jakob disease and advanced therapy medicinal products

In the European regulation advanced therapy medicinal products (ATMP) include those based on gene therapy, cell therapy and tissue engineering. Although they are considered biological medicinal products as described in the directive 2001/83/EC, specific legislation has also been developed (*Regulation (EC) no 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products*).[1a,1b] The composition of ATMPs may include components of human origin (either as active ingredient, excipients, or raw materials used in their manufacture) and, therefore, the risk of transmitting CJD or vCJD agents has to be considered.

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- ✓ Need for quality standards for raw materials used in the ATMPs manufacture
  - ➢ Scientific advice reports
  - ➢ Marketing authorisation dossier

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Issues raised during scientific advice procedures -1-

- ✓ Certificates of Origin / Certificates of Analysis should be supplied for representative batches and as much information as possible should be included for each raw material to demonstrate appropriate control….
- ✓ The risk : benefit evaluation of a product during a MAA procedure incorporates an evaluation of the risks and risk mitigation associated with materials used during manufacture. This requires a thorough understanding of the biological nature of the materials to which the active substance / product has been exposed.
- ✓ A systematic risk analysis is an approach that the applicant is highly recommended to adopt / develop further in order to assist in identifying areas of potential concern such as process reagents (raw materials) or excipients of biological origin and establishing the mitigating strategies ……Risk analysis should be extended to raw materials

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Issues raised during scientific advice procedures -2-

- ✓ Foetal Calf Serum is known to show considerable variability in growth promoting activity, making it necessary to qualify each new batch. It is recommended to put in place procedures defining criteria for control of consistent performance of the final product at the end of the cell culturing steps.
- ✓ The Company should note that release of raw materials for use in production should not be limited to tests for adventitious agents nor limited to tests performed by the supplier (please refer to the guideline on cell-based medicinal products)
- ✓ The Company should carefully consider the testing regime for each of the raw materials ……. The Company should justify the proposed tests on raw materials at the time of a MAA

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Issues raised during scientific advice or dossier assessment -3-

- Fibronectin, rh-EGF, or bFGF are all biologically active reagents used in production. The currently declared materials are not intended for human use and their actual use in production of a medicinal product may not be acceptable, unless the materials are qualified for the intended use. The applicant is requested to qualify these materials for the intended use by providing quality and manufacturing details of the raw materials. In addition, the applicant should fully describe the procedure for qualifying the functionality and safety of these reagents……
- Composition of xxyy and yyzz media should be provided including the origin of each component. If some biological products are used, they should be mentioned and viral safety information has to be provided in the dossier including information on raw material (species, country of origin for the animal, tissues procured/used…) as well as main elements of the process and viral safety controls (if any).

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Recurrent major objections raised during the evaluation of ATMP

- Quantitative and qualitative information of the raw materials composition should be provided
- Raw materials of "research" or "*in-vitro* grades" not acceptable
- Impact and effect of raw materials used on the ATMP final qulaity profile …

Think about contractual agreement between raw materials manufacturers and ATMPs developers!

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Conclusions -1/2-

- ✓ Raw materials are
  - known as possible source of concerns!
    - Microbial, viral
    - Consistency of the quality profile
    - Availability of the documentation
  - key in the production system and resulting quality of the final products…
  - Not a trivial, nor a simple, issue
- ✓ Consistency is needed
  - Qualification and monitoring of the vendor

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Conclusions -2/2-

- ✓ They should be handled with attention both by the manufacturers and the users…
- ✓ Recommendation is made in guidelines on their production and quality system
  - Need for proper identification, traceability,
  - Need for auditing the vendors …
- ✓ But, little is said in the various texts on
  - How to proceed,
  - The right balance between trusting anything or controlling every nanogram of product

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Joint initiative EDQM/EMA

Quality standards for raw materials should be developed

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Thank you for your attention

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Where to find information

✓EMA website: www.ema.europa.eu

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

✓Innovation Task Force: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000334.jsp&mid=WC0b01ac05800ba1d9

✓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

✓Gene and Cell therapy guidelines: http://www.ema.europa.eu/htms/human/humanguidelines/multidiscipline.htm

✓Regulatory & Procedural guidance: http://www.ema.europa.eu/htms/human/raguidelines/advanced_therapies.htm

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Lääkealan turvallisuus- ja kehittämiskeskus | Säkerhets- och utvecklingscentret för läkemedelsområdet | Finnish Medicines Agency

Role and Proposals of the RCG Working Party

Jaana Vesterinen
Raw Materials Symposium
Strasbourg 3. April 2013

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Biological raw materials and quality

- In the production of cell based and gene therapy medicinal products, a wide variety of biological raw materials are used
- Many of these raw materials are available in research grade only
  → quality, safety, consistency may be difficult to assess
  → data for full traceability and exact composition may not be available
- The manufacturer of cell based and gene therapy products faces a challenge to fulfill the requirement to provide adequate and reliable information on the raw materials used. Alternatively, if clinical grade raw materials exist, they may be expensive.
- The producer of the raw materials may not be familiar with the needs and wishes of the user in the absence of standard quality requirements
- The regulatory authorities need to use a case by case approach

→ There is a need for harmonising quality standards for raw materials

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Creation of RCG WP

- In order to respond to the needs within the field, the secretariat of EDQM suggested the creation of a Ph. Eur. Working Party to elaborate on a text concerning the quality aspects of *raw materials for the production of cellular and gene transfer products* (RCG WP) in November 2011
- Ph. Eur. Commission decided to establishing RCG WP in June 2012

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RCG WP Members

• Åkerblom Lennart	Sweden, EMA/CAT
• Bisset Louise	UK, EMA/CPWP
• Charton Emmanuelle	EDQM
• Haunerove Ivana	Czech Repblic, EMA/CAT
• Hinz Thomas	Germany, EMA/CPWP
• Hirvonen Marjatta	Finland (FRC Blood Service tissue establishment)
• Horn Lohrens Ottmar	Swizerland, PhEur/CTP
• Jorritsima-Smit Annelies	The Netherlands,
• Kopf Mireille	EDQM
• Menezes Ferreira Margarida	Portugal, EMA/CAT, BWP
• Ruiz Sol	Spain, EMA/BWP (vice chair), CAT,CHMP,TSE
• Saarela Sirkku	Finland, EMA/BWP
• Salmikangas Paula	Finland, EMA/CAT (vice chair)
• Trouvin Jean Hugues	France, EMA/BWP (chair), CAT
• Vesterinen Jaana	Finland (chair)
• Vielle Cathy	EDQM
• Voltz-Girolt Caroline	EMA
• Wicks Stephen	EDQM

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Aims of RCG WP

To deliver an overarching text covering the quality requirements of raw materials used for the production of cell based and gene therapy products.

- the status of the text has not been decided
- the purpose of the text is to harmonise the variable practices
- to help stakeholders to identify the critical quality attributes of the raw materials
- to help users to manage batch to batch variation and change in raw materials
- the purpose is **not** to increase regulation

To engage stakeholders into a dialogue about the quality standards

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The text will focus on biologically active raw materials

The scope of the text includes:

- Biologically active raw materials of biological origin: *Raw materials in this context are defined as biologically active substances used for manufacturing or extracting the active substance(s) but from which the active substance is not directly derived*
- For example serum, growth factors, cytokines, antibodies and enzymes, either alone or in a mixture

The scope does not include:

- More complex raw materials such as feeder cells, but they could be included in the future.
- Acellular matrices (such as decellularised bone)
- Plastics, buffers
- A certification system for raw materials
- Manufacturing requirements under GMP

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Quality attributes to be considered

General quality

- Origin, traceability, composition and viral safety

Critical quality attributes

- Identity
- Protein content
- Product related variance
- Impurities
- Biological activity
- Microbiological purity
- Storage/Stability

Existing monographs in Ph Eur

- Bovine serum (2262); Insulins (838, 1637, 1638); G-CSF (Filgrastim, 2206); GM-CSF (Molgramostim, 1641); Erythropoietin (1316); Interferon gamma-1b (1440); Trypsin (694)

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Survey on the quality of raw materials

•In order to start the dialogue with stakeholders EDQM / RCG WP conducted a survey

•The survey was sent to representatives of raw material manufacturers and users as well as academics and regulatory authorities

•The vast majority agreed that there is a need to harmonising the quality requirements of raw materials and that this could be done via the European Pharmacopoeia

•The survey addressed:

- the type of raw materials that are considered to be the most critical from a quality perspective
- the most important quality attributes of raw materials

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Welcome on behalf of the RCG WP!