Biopharmaceuticals in the EU

1st Drug Evaluation Forum
Pharmaceutical Society of Japan
10th August 2007
John Purves, Peter Richardson, Patrick Celis
EMEA

Overview of Presentation

- **Introduction and background – John Purves**
  - » European Union
  - » Review of the Legislation
  - » Science – Activities of the Committee on Human Medicinal Products (CHMP) and its Working Parties
- **Ongoing Activities – Peter Richardson and Patrick Celis**
  - » Biosimilar medicinal products
  - » Regulatory procedures in the event of an influenza pandemic
  - » Advanced Therapy Medicinal Products
- **Summary and conclusions – John Purves**

Introduction and Background

- **European Union**
- **Review of the Legislation**
- **Science - activities of the:**
  - » Committee for medicinal products for human use - CHMP
  - » Biotechnology Working Party - BWP
  - » Vaccine Working Party - VWP
  - » Other Working Parties: Gene Therapy, Cell Therapy, etc.
  - » CHMP Scientific Opinions on collaboration with the W.H.O.

EU Enlargement

- **10 new member states joined the Community on the 1st of May 2004**
  - » Estonia
  - » Latvia
  - » Lithuania
  - » Poland
  - » Czech republic
  - » Slovakia
  - » Hungary
  - » Slovenia
  - » Cyprus
  - » Malta

EMEA, It's "Euro-partners" and International Network

- **European Commission (DG Enterprise, DG Research and DG Sanco)**
- **European Parliament**
- **National competent authorities (human and veterinary)**
- **~4,000 European experts**
- **European Pharmacopoeia (Council of Europe)**
- **Medicines Control Laboratories Network**
- **F.D.A. and Japan – I.C.H.**

40 Years of Harmonisation

- 1965 - First Directive set out basic principles
- 1975 - Experience consolidated and old CPMP created
- 1981 - Specific veterinary legislation and old CVMP created
- 1985 - "1992 Single Market" project started
- 1987 – Directive 87/22/EEC, Concertation Procedure (rDNA)
- 1989 – First Directives on vaccines and products derived from blood and plasma
- 1993 - Council Regulation (EEC) No 2309 / 93 adopted
- 1995 - EMEA officially opened
- 2001 - Review of the legislation
- 2001 - Directive 2001/20/EC – Clinical Trials
- 2003 - Commission Directive 2003/63/EC amends 2001/83/EC
- 2004 - New Regulation (EC) No 726/2004, Replaces 2309/93/EC

'Review 2001'

- **Many of changes to the centralised procedure / EMEA are not specific for biologicals / biotech. products, for example:**
  - » Validity of marketing authorisations
    - – No need for 5-year-renewals (initial proposal);
    - – 1 renewal, thereafter valid for unlimited duration (modified proposal)
    - – Product to be placed on the market within a certain time
  - » Conditional approvals
    - – Authorisation valid for 1 year, renewable
  - » Accelerated review
    - – Products with major public health interest / therapeutic innovation
    - – 150 days instead of 210 days

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'Review 2001'

- » Compassionate use
  - – For products of major interest for public health, eligible for Community marketing authorisation
  - – CHMP may adopt recommendations on conditions for use, distribution and patients envisaged
- » Small Medium Enterprises (SME)
  - – Dedicated office at EMEA
- » Scientific opinions to WHO
  - – For medicinal products for human use not intended for EU
  - – On request of WHO
- » Similar biological medicinal products
- » Advanced therapy medicinal products

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Main Elements Within Legislation

- **Major proposals for biological products**
  - » Definition of a medicinal product and scope
  - » Scope of the centralised procedure
  - » Plasma Master Files and Vaccine Antigen Master Files
  - » Data protection and generics
  - » Influenza pandemic
  - » Procedures timeframe
  - » Biosimilar medicinal products
  - » Renewal and sunset clause
  - » Provision of scientific opinions - W.H.O.
  - » EMEA responsibilities
  - » Advanced therapy medicinal products
  - » Pharmacovigilance

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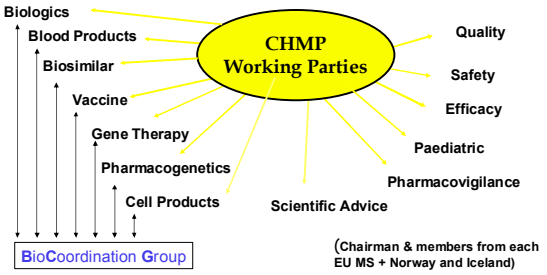
Scientific Input



+ Specific ad-hoc working groups or subgroup meetings when needed

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Biotechnology Working Party

- **Evaluation of the quality and safety of biological & biotechnology derived medicinal products.**
  - » e.g. TSE / BSE, Plasma derived medicinal products, Viral safety
- **Provision of scientific advice**
  - » product specific
- **Preparation of guidance documents**
  - » e.g. Biosimilars, Gene transfer, Cell and Xenogeneic cell therapy, Transgenic plants

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Vaccine Working Party

- **Main tasks: evaluation of the quality, safety and efficacy of vaccine products**
  - » Advice to CHMP on multidisciplinary product (vaccine) related issues
- **Provision of scientific advice – product specific**
- **Preparation of guidance documents (multidisciplinary) e.g.**
  - – Guidance on requirements for evaluation of new immunological adjuvants in vaccines
  - – Guidance on influenza pandemic plans
  - – Provision of CHMP scientific opinions for vaccines

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Provision of CHMP Scientific Opinion to WHO

- **Proposal to amend the Council Regulation (EEC) No 2309/93 including Article 58**:
  - » **EU Co-operation with the World Health Organization**
  - » **Medicinal products (human use) exclusively for markets outside the Community**
  - » **CHMP / EMEA gives scientific opinion**
  - » **No marketing authorisation granted in Europe (No Commission Decision)**

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Provision of CHMP Scientific Opinion to WHO

- **Key philosophy – assist developing countries**
- **Same data requirements, procedure and overall benefit / risk ratio as for EU medicines**
- **The CHMP shall establish specific procedural rules for the implementation of paragraph 1, as well as for the provision of scientific advice."**
- **Guidance for the procedural aspects for the implementation of Article 58 - mirrors the centralised procedure for initial assessment of the dossier**

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Ongoing Activities

Peter Richardson

- **Similar biological medicinal products - comparability of biotechnological products**

Patrick Celis

- **Influenza pandemic**
- **Advanced therapy medicinal products**
  - » Gene therapy
  - » Cell therapy
  - » Tissue-engineered products

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Similar Biological Medicinal Products

(SBMP) / Biosimilars

EMEA/EU Regulatory Direction

Peter Richardson
European Medicines Agency (EMEA)

Overview of presentation

- **Rationale / Introduction**
- **EMEA Guidelines**
- **Vision**
- **Goals / Conclusion**

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Biosimilars - Centralised Procedure

- **Omnitrope (somatropin)**
  - » Authorised April 2006 (MAH: Sandoz)
- **Valtropin (somatropin)**
  - » Authorised April 2006 (MAH: Biopartners)
- **Alpheon (interferon alfa-21)**
  - » Negative opinion June 2006
- **Binocrit (epoetin alfa), Hexal, Abseamed**
  - » Positive opinion June 2007

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Rationale - biosimilar evolution

- **New Pharmaceutical Legislation**
  - » (Directive 2001/83/EC, as amended: Article 10.4)
- **"additional data, in particular, the toxicological and clinical profile shall be provided."**
- **Development of comparability concept**
  - » History of changes to various products

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Rationale for Guidelines

- **Guidelines need to address:**
  - » Types of Product / Classes Applicable
  - » Quality / Safety / Efficacy / Pharmacovigilance
  - » Sufficient detail with flexibility
  - » Balance of "case-by-case" v recipe

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Introduction

- **Regulatory perspective - What is a SBMP ?**
  - » Previous Generic Definition - NOT sufficient
  - » * "The provisions of Article 10(1)(a)(iii) [i.e. for generic medicinal products] may not be sufficient in the case of biological medicinal products. If the information required in the case of essentially similar products (generics) does not permit the demonstration of the similar nature of two biological medicinal products, additional data, in particular, the toxicological and clinical profile shall be provided."

    * Section 4, Part II, Annex 1 (Dir. 2001/83/EC)

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Introduction

- **Regulatory perspective – "Biogeneric" ??**
  - » Can SBMP be a generic ?
  - » In THEORY – YES
  - » In PRACTICE – may be possible where molecule is fully characterised (depends on complexity).
  - » RESULT – SBMP (Similar Biological Medicinal Product). *Informally: "biosimilar"*

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Biosimilar Legislation

- **New legislation* refines legal base for SBMP:**
  - » Where there are differences (particularly) in raw materials or manufacturing processes of biosimilar and reference product, then results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided.

* Article 10(4) of Directive 2001/83/EC, as amended

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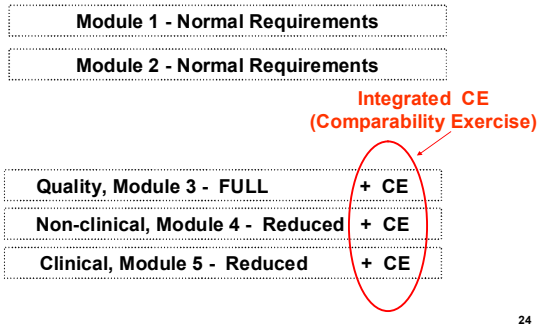
Dossier requirements for biosimilars



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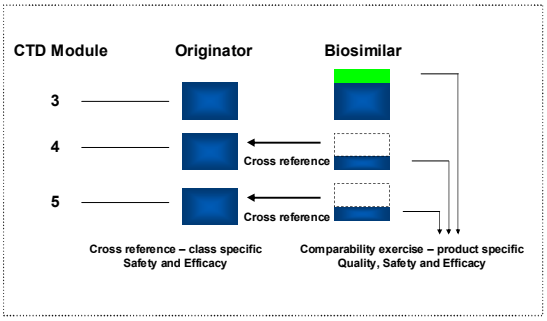
Dossier requirements for biosimilars



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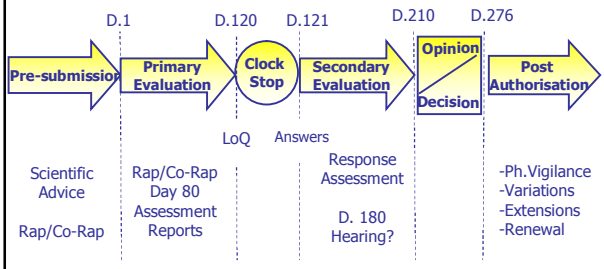
Overview of Centralised Procedure - Biosimilar Timetable (Full MAA)



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- Vision
- Goals / Conclusion

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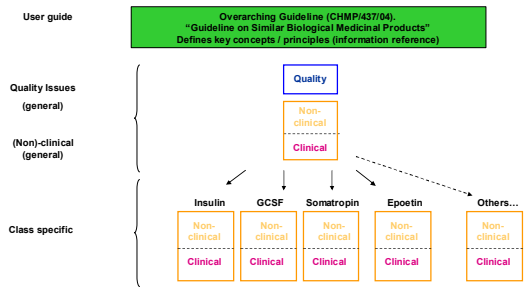
Biosimilar Guidelines – Summary Overview



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SBMPs – Guidelines

- **Overarching guideline on SBMP**
- **Quality guideline on SBMP**
- **(non)-clinical guideline on SBMP**
- **Product-class specific guidelines on SBMP - (non)-clinical**

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Overarching Guideline

- **Guideline on Similar Biological Medicinal Products. CHMP/437/04 (CHMP Adopted).**
- **Main points:**
  - » Outline concepts and basic principles
    - – Biological, Biotech. (rDNA), Immunological & Blood / plasma derived products
  - » Considerations: analytical methods, processes, clinical and regulatory experience.
  - » Choice of Reference Product
    (EU Reference for comparability exercise)

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Quality guideline

- **Specific for rDNA derived proteins**
- **Main issues**
  - » state-of-art analytical methods to characterise both similar and reference products
  - » Manufacturing process should be well developed
  - » Avoid changes, i.e. additional Comparability Exercises during development

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(Non)-Clinical Guideline

- **Guideline on general principles**
  - » Clinical equivalence
  - » Safety studies
  - » Immunogenicity
  - » (Pharmacovigilance)

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(Non)-Clinical Guideline – Annexes:

- **Product Class specific annexes**
  - » Insulin
  - » Granulocyte Colony Stimulating Factor
  - » Somatropin
  - » Epoetin
  - » Others ? – interferon-alfa, LMMH
- **Annexes provide specific (non)clinical data requirements**

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Current applicability - Biosimilars

- **Biotechnology-derived: recombinant proteins**
  - » Product complexity – major factor
  - » Data requirements not always the same
  - » Case-by-case approach partly applicable
- **Applications to other biologicals**
  - » Not ruled out
  - » Ability to characterise becomes critical

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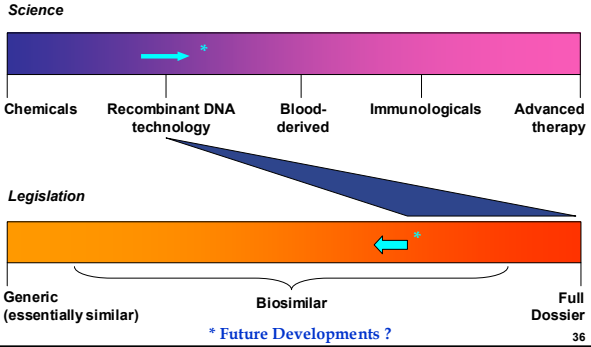
Spectrum of Complexity



* Future Developments ?

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Goals – Guideline Development

- **Stimulate scientific and regulatory debate**
- **Gain further experience**
- **Update guidelines as new information becomes available**
  - » based on requirements (INF-α, LMMH), experience

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Conclusions

- **Constructive guideline consultation phase**
  - » Regulators / Industry Workshop (Paris 2005)
- **Promote early meetings with EMEA**
  - » Legal / Regulatory
- **Scientific Advice**
  - » Complexity / Study Design
- **Continued growth in interest in biosimilars**
  - » USA – legislative proposals
  - » WHO guidance being considered

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- **General information:**
  - » EMEA Website: http://www.emea.europa.eu
- **Biosimilars:**
  http://www.emea.europa.eu/htms/human/humanguidelines/multidiscipline.htm
  - » peter.richardson@emea.europa.eu

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Pandemic influenza

EMEA/EU Regulatory Direction

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Pandemic influenza

- **Two Guidelines on pandemic influenza vaccines - adopted in March 2004**
  - » Note for guidance on dossier structure and content of marketing authorisation for pandemic influenza vaccines: Scientific guidance
  - » Guideline on submission of marketing authorisation applications for pandemic influenza vaccines via the centralised procedure: Procedural guidance
- **Guideline on influenza vaccines prepared from viruses with pandemic potential ("avian influenza" vaccines / "pre-pandemic" vaccines): adopted in January 2007**

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Core-dossier / "Mock-Up" Pandemic Vaccine approach

- **Aim of core dossier**
  - » Fast track authorisation of pandemic influenza vaccines
- **Most scientific aspects can be considered before a pandemic:**
  - » Manufacturing and quality data
  - » Clinical experience gained with a pandemic-like (mock-up) vaccines in naïve population
  - » Evaluation of novel concepts prior to a pandemic e.g. use of adjuvants with the objective of increasing available doses

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Pandemic influenza vaccines: Scientific Guidance

- **Core pandemic dossier**
  - » Quality, Safety and Efficacy data for "mock-up" vaccine to be provided
  - » Authorised during interpandemic period
- **Pandemic variation**
  - » Only quality data related to the pandemic influenza strain
  - » Commitment to gather clinical information during pandemic
  - » Fast track approval (Art. 8 of Regulation (EC) 1085/2003)

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Pandemic influena vaccines: Procedural Guidance

This guidance describes:

- Setting up of specific Task force Groups involved in the evaluation of pandemic influenza vaccines
- Evaluation procedure of the core dossier in the prepandemic period
- Fast track evaluation of the pandemic strain change variation during pandemic

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Pandemic influena vaccines: Procedural Guidance

Setting up of Task Force Groups

- **Joint EMEA – Industry Task Force**
  - » Regular (yearly) meetings in inter-pandemic period
  - » General, advisory role
- **EMEA Task Force**
  - » Advice to Authorities and manufacturers before submission of pandemic variation application
  - » Discussion of safety/efficacy obtained during pandemic
- **Evaluation Project Team**
  - » Product specific
  - » Evaluation of pandemic variation

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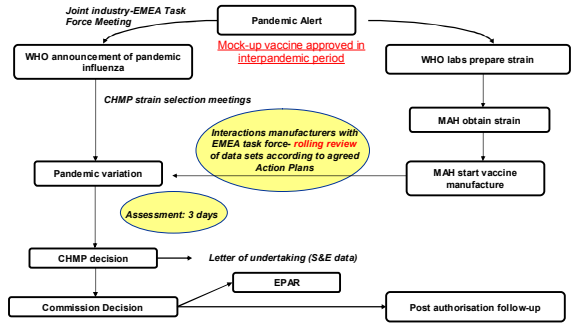
Core dossier: approved Mock-up vaccine



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Guideline on influenza vaccines prepared from viruses with pandemic potential

- **This guideline addresses quality, non-clinical and clinical requirements for dossiers for marketing authorisation applications**
- **Inactivated influenza vaccines prepared from viruses with the potential to cause a pandemic**
  - ➢E.g. avian H5N1 strain
- **Possible uses: stockpiling, prime-boost strategies, use in early stages of pandemic**

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Advanced Therapy Medicinal Products

EMEA/EU Regulatory Direction

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Regulation on Advanced Therapy Medicinal Products

What are Advanced therapy medicinal products?

- **Gene therapy MP**
  - » E.g. GT product for treating Skid children
- **Somatic cell therapy MP**
  - » E.g. Dendritic cell loaded with cancer antigens
- **Tissue engineered products**
  - » E.g. Artificial Skin, Neo-organs

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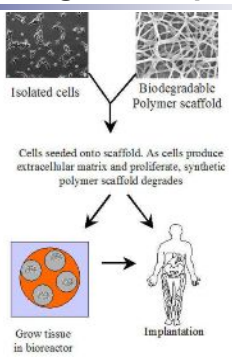
Tissue engineered products



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Definition of a tissue engineered product

- **Tissue engineered products**
  - » Contain engineered cells/tissues
  - » Regeneration, repair, replacement of human tissue

→ Engineered cells/tissues mean:

- » Substantial manipulation to change biological/ physiological/structural characteristics or
- » Not for same function(s) in recipient & donor

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Why is a new legislation needed?

- **Gene therapy MP and Somatic cell therapy MP are already covered by the existing pharmaceutical legislation**
  - » Annex I, Chapter 4
- **Tissue engineered products: not explicitly covered by the pharmaceutical legislation and not covered by the Medical device legislation**
  - » Legal uncertainty in Europe
  - » Negative impact on development & availability for patients

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Advanced Therapy Regulation

- **Submitted by Commission for EP/Council Discussion on 16 November 2005**
- **Adopted by EP: 25 April 2007**
- **Adopted by Council: 31 May 2007**
  http://ec.europa.eu/enterprise/pharmaceuticals/advtherapies/docs/st09756_en.pdf
- **Publication in OJ expected in 4Q 2007: entry into force 20 day following publication**
- **Entry into application: 1 year after entry into force (4Q 2008)**

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Advanced Therapy Regulation

- **Some highlights from this new legislation:**
  - » Donation, procurement & testing: in accordance with Directive 2004/23
  - » Post-authorisation follow-up of efficacy and adverse events & risk management
  - » Recommendation of the EMEA whether the product falls, on scientific grounds, within the definition of an advanced therapy medicinal product
  - » For SMEs: possibility to certify quality & non-clinical part

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Advanced Therapy Regulation

- » Traceability
  - – MAH: from raw/starting materials to individual products
    - For 30 years
    - In case of bankruptcy: data to EMEA
  - – Hospital/institutions/private practices: from ATMP to patients
  - – Compatibility of both systems (tracing back/ forward from donation to patient & vice versa)

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Committee for Advanced therapies

- **New committee (Committee for Advanced therapies – CAT) will prepare an opinion on ATMP application. CHMP adopts this opinion.**
- **Composition:**
  - » 5 members or co-opted members from CHMP
  - » 1 members + alternate per member state
  - » 2 members + alternates representing clinicians
  - » 2 members + alternates representing patients

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Committee for Advanced therapies

- **Expertise to covers the scientific areas relevant to advanced therapies, i.e.**
  - » medical devices (min. 2 members),
  - » tissue-engineering,
  - » gene therapy,
  - » cell therapy,
  - » biotechnology,
  - » surgery,
  - » pharmacovigilance, risk management
  - » ethics

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Implementing guidance to be developed

- Guidelines on GMP/GCP specific for ATMP
- Guidelines on post-marketing follow-up (efficacy/PhVig) + RMP
- Guidelines on traceability
- Update of Annex I to Dir 2001/83/EC
  - » Technical requirements for TEP (new)
  - » Technical requirements for GT and CT (update)?

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New procedures to be developed

- CAT: Rules of procedure (including how CAT will interact with CHMP)
- Consultation of notified bodies for combined Advanced Therapy products (cells + med dev)
- Certification of Q/N-Clinical data
- Scientific recommendaton on ATMP classification
- 'Grand fathering' procedure (bringing products already on the market in the centralised procedure)

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Working party on cell-based products (CPWP)

- **Guidelines under development:**
  - » Guideline on human cell-based medicinal products
    - – External consultation until July; Workshop on 18-19 October 2007
  - » Guideline on Xenogeneic cell based products
    - – Revision of PTC; Concept paper published
  - » Guideline on post-marketing surveillance for cell-based products
    - – Initial discussion at June CPWP

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Summary and Conclusions

- **Ongoing activities:**
  - » CHMP / BWP and VWP continuing activities
  - » Biosimilar medicinal products
  - » Influenza pandemic issues
  - » Advanced Therapy Medicinal Products

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Scientific Innovation: a moving target

- **Need to keep up to date with scientific progress and its potential benefit for public health**
- **Knowledge management: how to handle the corpus of scientific knowledge and how to find and keep the experts needed for scientific review**
- **Flexibility needed to integrate different disciplines and regulatory frameworks**

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Regulatory challenges: rules cannot stand still

- **Regulatory requirements must reflect scientific progress not define scientific pathways**
- **New ways of ensuring compliance in a changing environment (pre- and post-licensing)**
- **Greater regulatory transparency, with more complex risk communication issues**
- **International cooperation to establish common rules that take into account different interests**

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Resources

- **Scientific guidance documents from BWP and Ad-hoc groups are published on the EMEA Website:**

  http://www.emea.europa.eu
- **Pharmaceutical legislation and regulatory guidance to applicants (Eudralex) can be found on the Website of the European Commission:**

  http://pharmacos.eudra.org/F2/home.html

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Thank you for your attention !

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