Registration of biological medicinal products in EU

A regulatory perspective

Pavia 11th May 2012

Carla Martino
Quality of Medicines (Biologicals) – European Medicines Agency
Agenda

✓ Introduction to the European Regulatory Network

✓ Overview on biologicals – different level of complexity

✓ Biosimilars – principles and challenges

✓ Marketing Authorization for biologicals in EU

✓ Conclusions
Agenda

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European Medicines Agency (EMA)

A decentralised body of the EU, founded in 1995, based in London, UK

Mission:
- to foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health, serving over 500 million users of medicinal products
- responsible for centralised procedure and co-ordination of EU network
- plays a role in stimulating innovation and research in the pharmaceutical sector
An interface of cooperation and coordination of EU Member States’ activities

- **Single marketing authorisation application**
  valid throughout EU (centralised procedure)

- **EU Network** for scientific advice & expertise constitutes of
  - 27 EU Member states
  - > 40 national competent authorities
  - 4,500 European experts

- **Referral or arbitration procedures** for medicines approved via non-centralised authorisation procedures

- Coordination of activities:
  - **Inspection**
  - **Pharmacovigilance** (new Regulation 2012)
European Regulatory Network

4,500 European experts
European Marketing Authorisation Procedures

Key Principles

- Approval in *n or all* MSs => EU Authorisation system

  3 EU procedures:
  - Centralised Procedure (CP)
  - Mutual Recognition Procedure (MRP)
  - Decentralised Procedure (DCP)

- Approval in *1 MS* =>

  **Route? Choice?**

  National Authorisation Procedure

  Depending on type of product and authorisation history in EU

  + Regulatory & marketing strategy

  Company preferences etc...
Mutual Recognition Procedure

1 Member State (e.g. Italy) performs assessment of application → 1 National MA

Subsequent application to $n$ MSs
Other Member States to “mutually recognise” the Italian assessment (90 days) → $n$ National MAs
Decentralised Procedure

Parallel submissions in $n$ MSs:

- ‘Reference’ MS performs assessment (120 days)
- Peer review by other MSs: ‘Concerned’ MSs (90 days):
  * Assessment report
  * SmPC, leaflet and labelling
- $n$ MSs grant national MA after agreement (in 30 days)
Centralised Procedure

1 Scientific Opinion
1 Commission Decision valid throughout EU
1 Product Information translated into all official EU languages

- Established since Nov 2005 with entry into force of Reg EC no. 726/2004
- Not open to all medicinal products, but dedicated to eligible products as defined in the legislation (Annex to Regulation EC 726/2004)
Centralised Procedure - 210 days

Pre-submission:
- Letter of Intent
- Rap/Co-Rap
- Pre-submission meeting

Primary Evaluation:
- Rap/Co-Rap Day 80 Assessment Reports

Clock Stop:
- LoQ
- Answers

Secondary Evaluation:
- Response Assessment
- CHMP AR EPAR

Opinion/Decision:
- PhVig
- Variations
- Extensions
- Renewal

Post Authorisation:

D.1
D.120
D.121
D.210
Mandatory scope

Art. 3(1) & Annex of Reg (EC) No 726/2004

- Medicines derived from biotechnology and other high-tech processes (e.g. recombinant DNA technology, controlled expression of genes, hybridoma and monoclonal antibody methods), including biosimilars
- Advanced-therapy medicines
- Medicines intended for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and viral diseases
- Designated orphan medicines intended for the treatment of rare diseases.
## Optional Scope

### Art. 3(2) of Regulation (EC) No 726/2004

<table>
<thead>
<tr>
<th>Art. 3(2)(a)</th>
<th>Art. 3(2)(b)</th>
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<tbody>
<tr>
<td>New Active Substances</td>
<td>Significant Innovation</td>
</tr>
<tr>
<td></td>
<td>Therapeutic &amp;/or Scientific &amp;/or Technical</td>
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<tr>
<td></td>
<td>Interest of Patients at Community Level</td>
</tr>
</tbody>
</table>

OR

“known” AS
Committee for Medicinal Products for Human Use

+ Ad hoc working parties
e.g. Biosimilar Medicinal Products Working Party
EMA Committees on Human Medicines

**CHMP**
(Committee for Human Medicinal Products)
Members: 1 per Member State + 1 alternate + 5 co-opted Members
Non voting members: ICE/NO

**COMP**
(Committee for Orphan Medicinal Products)
Members: 1 per Member State + 3 additional Members + 3 Patient Organisations
Non voting Members: ICE/NO

**HMPC**
(Committee for Herbal Medicinal Products)
Members: 1 per Member State + 1 alternate + 5 Co-Opted Members
Non-voting members: ICE/NO

**PDCO**
(Paediatric Committee)
Members: 5 CHMP + 1 per other Member States + 3 HCP + 3 Patient Organisations + 1 alternate per member; Non voting members: ICE/NO

**CAT**
(Committee for Advanced Therapies)
Members: 5 CHMP + 1 per other Member States + 2 Clinicians and 2 Patient Organisations appointed by EC + 1 alternate per member; Non voting members: ICE/NO

**PRAC**
(Pharmacovigilance Risk Assessment Committee ) "chick-off July 2012"
Working parties

Relevant for biological medicinal products:

Biologics working party
- Initially established in 1986
- Face-to-face meetings 11 times per year
- Quality aspects relating to biological and biotechnological medicinal products (including biosimilars)

Working parties’ tasks include:
- Preparation and revision of guidelines
- Provide scientific input to the CHMP and other Committees (e.g. CAT)
- Contributing to international co-operation with other regulatory authorities
- Liaising with interested parties (e.g. briefing meetings with industry)
- Organisation of workshops and trainings (e.g. biosimilar mAbs workshop, immunogenicity workshop, assessor trainings)
EMA is not responsible for:

- Assessment of all medicines in EU
- Control and advertisement of medicines
- R&D of medicines
- Clinical trial approval
- Medical devices
- Price and reimbursement
- European health policies

**Regulation EC No. 726/2004 – Article 1**

“The provisions of this Regulation shall not affect the powers of MS authorities as regards setting the prices of medicinal products or their inclusion in the scope of the national health system or social security schemes on the basis of health, economic and social conditions.

In particular, Member States shall be free to choose from the particulars shown in the marketing authorisation those therapeutic indications and pack sizes which will be covered by their social security bodies.”

Price & reimbursement are responsibility of UE member states.
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✓ Introduction to the European Regulatory Network

✓ **Overview on biologicals – different level of complexity**

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Definition of biological medicinal product
Directive 2011/83/EC - Annex I

“(…) A biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control.”
Heterogeneity – Examples

- **Extracts** from a biological source
- Medicinal products developed by biotechnological processes (e.g. recombinant proteins, monoclonal antibodies)
- **Immunological medicinal product** (e.g. vaccines, toxins, allergen products)
- Human blood and plasma-derived (e.g. albumin, coagulating factors, immunoglobulins)
- **Advanced Therapy (ATMP)**
Different level of complexity

Simple Chemicals
Peptides to 20-30 AA
Proteins, Antibodies
Vaccines
Blood/plasma derived

Gene Therapy
Cell Therapy
Tissue Eng.

Synthetic
rDNA

Aspirin
Insulin

Natural Source

Viable cells

Immunoglobulin
Definition of ATMP
Reg 1347/2007 and Part IV of Annex I Dir 2001/83/EC

Gene therapy medicinal products
Somatic cell therapy medicinal products
Tissue engineering products

adenovirus
mammalian cell
cornea transplant

Combined ATMP + Medical Device
artificial skin
Bridging the gap

Legislation

- Medicinal Products: Dir 2001/83/EC
- Regulation EC (No) 1394/2007
- Medical Devices: Dir 93/42/EEC

Science

- Advanced Therapies
  - Biologicals
    - Pharmaceuticals (e.g. aspirin)
    - Biotech (e.g. insulin)
    - Gene Therapy
    - Cell Therapy
    - Tissue Engineering
    - Medical Devices

Expertise

- CHMP
- CAT
PRODUCTION PROCESS FOR A BIOTECHNOLOGY PRODUCT

Host Cell → Cell Banks → Fermentation → Reagents

Genetic Material

Cell Banks → Harvesting → Drown Stream Processing → Reagents

Fermentation → Drown Stream Processing

Drown Stream Processing → Drug Substance → Storage

Drug Substance → Finished Product → Excipients

Finished Product → Storage
The process defines the product

“One process – one product” paradigm

- Biotechnological medicinal products are ‘individuals’
- Biotechnological medicinal products are more than the drug substance
- Small changes can have a high impact
  - changes in the manufacturing process (e.g. expression system)
  - fluctuations in the manufacturing process (e.g. pH, temperature, culture media)
Control of raw and starting materials

Control of intermediates

Control of drug substance and drug product

Process validation & evaluation

Good manufacturing Practice

QUALITY

Product

Process
Ability to Characterise

- Simple Chemicals
- Peptides to 20-30 AA
- Proteins, Antibodies
- Vaccines
- Blood/plasma derived
- Gene Therapy
- Cell Therapy
- Tissue Eng.

Characterisation:
- Fully Characterised (e.g. HPLC, ID Assay/Purity)
- Characterisation: many methods, including Bioassay
- Physicochemical Characterisation may not be possible
- Defined by Specifications
- Defined by Specifications and Process
- Defined by Process

Increasing requirements for non-clinical and clinical data
Potency Assay

✓ Physicochemical tests alone usually insufficient to permit prediction of the biological activities → Need of appropriate bioassay or potency assay

✓ Potency:
  - **quantitative measure of the biological activity** of the product, based on the attribute of the product and relevant for its efficacy and safety profile in the patients (ICHQ6B)
  - it is a measure of the product activity expressed in terms of the amount required to produce an effect of given intensity
  - It is **linked to the relevant biological properties** of the product
  - The **assay** demonstrating the biological activity should be based on the intended biological effect which should ideally be related to the clinical response (i.e. **predictive of product’s clinical performance**)

PURITY PROFILE

PRODUCT
RELATED
SUBSTANCES

PRODUCT
RELATED
IMPURITIES

IMPURITY PROFILE

desired product

Peptide variants

3D-structure

Post-translational
variants

degradation

PROCESS
RELATED
IMPURITIES
Sources of product variability

**MOLECULAR HETEROGENEITY**
- Variants: conformational / clipped / glycosylation / substitution
- Related substances: disulfide bond / oxidation / deamidation / aggregation

**PROCESS VARIABLES**
- Drug substance: host cells and vectors, fermentation conditions, downstream purification, process impurities (proteins / DNA), reagents / column leachables, analytical techniques, IPC
- Drug products: changes to manufacturing process, excipients, pharmaceutical form, route of administration, analytical techniques and IPC
What we know and What we don’t know

Information provided in the dossier for review

Information and knowledge within the Company → some parts accessible at inspections

Release Tests (Specifications)

Extended Characterization (Process & Product)

Process Control
- Procedures
- Materials
- In-process testing
- Monitoring
- Validation

Unknown
Learned over time – update control strategy

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✓ Introduction to the European Regulatory Network

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✓ **Biosimilars - principles and challenges**

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What is a biosimilar?

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

- Where there are differences, particularly relating to 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**

- The **type and quantity of supplementary data** to be provided must comply with the relevant criteria stated in Annex I and relevant guidelines

- The **results of other tests** and trials from the reference medicinal product’s dossier **shall not be provided**
Biosimilar Process versus originator

1. **Cloning the gene of interest into an expression vector**
   - Usually identical
   - Usually different

2. **Transfer into host cell**
   - Usually similar or different cells

3. **Different cell growth and fermentation conditions**

4. **Formulation and filling**
   - Usually similar or same formulation

5. **Purification**
   - Different purification process

6. **Fermentation**

Source: Niklas Ekman (fimea)
Comparability exercise

- Stepwise **head-to-head comparison** at the levels of **quality, safety and efficacy** to demonstrate that the biosimilar and the reference medicinal product have similar profiles in terms of quality, safety and efficacy.

- Depending on the similarity on the quality profile, **the extent of the non-clinical and clinical testing may be reduced** compared to a stand-alone development.

- Any differences in the **quality attributes** require a satisfactory justification of the potential implications with regard to the safety and efficacy of the product.
Dossier requirements for Biosimilars

CTD Module | Originator | Biosimilar
--- | --- | ---
3 | Quality | Cross reference
4 | Non-Clinical | Cross reference
5 | Clinical | Cross reference

Cross reference – class specific Safety and Efficacy

Integrated Comparability Exercise – product specific
Quality, Safety and Efficacy
Evolution of Biosimilars in the EU

Legislation
- Directive 2001/83/EC
- Directive 2004/27/EC

Overarching guideline
- Quality guideline
  - Non-clinical/Clinical guideline
- Product-class specific guidelines

Guidance

Product evaluation
- First biosimilars authorised – Omnitrope and Valtropin (somatropin)
- First biosimilar epoetins authorised
- First biosimilar filgrastims authorised

First biosimilars authorised – Omnitrope and Valtropin (somatropin)

First biosimilar epoetins authorised

First biosimilar filgrastims authorised
### Biosimilar MAA Procedures

**status March 2012**

<table>
<thead>
<tr>
<th></th>
<th>Product Description</th>
<th>Company</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Omnitrope (somatropin)</td>
<td>Sandoz</td>
<td>Authorised</td>
</tr>
<tr>
<td>2</td>
<td>Valtropin (somatropin)</td>
<td>Biopartners</td>
<td>Authorised</td>
</tr>
<tr>
<td>3</td>
<td>Alpheon (interferon alfa)</td>
<td>Biopartners</td>
<td>Negative</td>
</tr>
<tr>
<td>4</td>
<td>Binocrit (epoetin alfa)</td>
<td>Sandoz</td>
<td>Authorised</td>
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<td>5</td>
<td>Epoetin alfa Hexal (epoetin alfa)</td>
<td>Hexal</td>
<td>Authorised</td>
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<td>6</td>
<td>Abseamed (epoetin alfa)</td>
<td>Medice</td>
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<td>7</td>
<td>Silapo (epoetin zeta)</td>
<td>Stada</td>
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<tr>
<td>8</td>
<td>Retacrit (epoetin zeta)</td>
<td>Hospira</td>
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<tr>
<td>9</td>
<td>Insulin Marvel Short (human insulin)</td>
<td>Marvel Life Sciences</td>
<td>Withdrawn</td>
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<tr>
<td>10</td>
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<td>11</td>
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<td>15</td>
<td>Tevagrastim (filgrastim)</td>
<td>Teva</td>
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<td>16</td>
<td>Filgrastim Hexal (filgrastim)</td>
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<td>Authorised</td>
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<tr>
<td>17</td>
<td>Zarzio (filgrastim)</td>
<td>Sandoz</td>
<td>Authorised</td>
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<tr>
<td>18</td>
<td>Nivestim (filgrastim)</td>
<td>Hospira</td>
<td>Authorised</td>
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<tr>
<td>19</td>
<td>Epostim (epoetin alfa)</td>
<td>Reliance Genemedix</td>
<td>Withdrawn</td>
</tr>
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</table>
Challenges for biosimilars

- Biosimilars currently licensed are "small biologicals"
- In principle, the concept of biosimilar medicinal products applies to any biological
- Can more complex biologicals (e.g. mAb) be biosimilars?
- How far can we go?

How much do we need to know?

How much “similarity” do we need?
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Where to start?

- EMA guidelines
- Innovation Task Force
- Clinical trials
- ATMP Classification
- ATMP Certification Q&NC
- SME status
- Orphan Designation
- Scientific Advice/Protocol Assistance
- Paediatrics
- Marketing Authorisation Application
- Post-authorisation procedures
1. EMA Scientific guidelines

Biologics: Drug product

If you have comments on a document which is open for consultation, please use the Form for submission of comments on scientific guidelines.

Table of contents
- Pharmaceutical Development
- Product Information
- Adventitious Agents Safety Evaluation: Viral Safety
- Transmissible Spongiform Encephalopathies (TSE) (Animal and Human)
- CJD related
- Investigational Medicinal Products
- GMO

Pharmaceutical Development

<table>
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<th>Topic</th>
<th>Documents</th>
<th>Reference number</th>
<th>Publication date</th>
<th>Effective date</th>
<th>Remarks</th>
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Product Information
### Quality of Biotechnological Products Q5A - Q5E

<table>
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<tr>
<th>Code</th>
<th>Document Title</th>
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<tbody>
<tr>
<td>Q5A(R1)</td>
<td>Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin</td>
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<tr>
<td>Q5B</td>
<td>Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products</td>
</tr>
<tr>
<td>Q5C</td>
<td>Stability Testing of Biotechnological/Biological Products</td>
</tr>
<tr>
<td>Q5D</td>
<td>Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products</td>
</tr>
<tr>
<td>Q5E</td>
<td>Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process</td>
</tr>
</tbody>
</table>

### Specifications Q6A - Q6B

### Good Manufacturing Practice Q7
2. SME Status


- Applicants to be designated as ‘SME’ must:
  - be established in the EU Community
  - employ **less than 250 employees** and
  - have an **annual turnover** of **not more than €50 million** or
  - an **annual balance sheet** total of **not more than €43 million**

- **Incentives offered** to ‘SME’ companies:
  - Administrative and procedural **assistance** from the SME Office at EMA
  - **Fee reductions** for scientific advice, inspections
  - Deferral of the fee payable for an application for MA or related inspection
  - Assistance with translations of the product information submitted in MAA

- **SME Office** at EMA: smeoffice@ema.europa.eu
  - Facilitate communication between SMEs and EMA
  - Offers assistance and advise to SMEs
  - Organise workshops and training sessions
3. Innovation Task Force

Briefing Meeting

• EMA multidisciplinary group since 2001

• “Soft landing zone” to establish early dialogue (Briefing Meetings) with sponsors of Emerging Therapies and Technologies (e.g. advanced therapies)

• Involvement of Committees and/or Working parties

• Early dialogue with EMA and experts to present the product and get an understanding on EMA procedures

• Where to find information on EMA website:
  
4. Orphan designation

- **Legal basis** - Reg (EC) No 141/2000
- Committees for Orphan Medicinal Products (COMP)
- **Orphan designation** can be obtained at any stage of development **before** Marketing Authorisation → **no fees** – **90 days procedure**
- **Criteria**:
  - Indication: *life threatening* or debilitating condition
  - Epidemiological: *prevalence* < 5/10.000 *in EU*
  - **No satisfactory methods exist** or *significant benefit* over authorized products/methods
  - Economical: unlikely to generate sufficient **return on investment**
Orphan Drugs - Benefits

- **10 years exclusivity** from the date of marketing authorisation
- Free **Protocol assistance** from the EMA
- Direct access to **Centralised Procedure**
- **Fee reductions** for MA applications and EMA procedures
5. ATMP specific procedures

1. ATMP CLASSIFICATION:
   - **Legal basis:** Art 17 of Reg EC No 1394/2007
   - **Scope:** to determine whether a product based on genes, cells or tissues meets the scientific criteria which define ATMPs
   - Optional, 60 days procedure
   - No fee
   - Only involves CAT (Committee of Advances Therapy)
   - Publication of summaries of recommendation on ATMP classification as:
     - Gene therapy medicinal product
     - Somatic cell therapy medicinal product
     - Tissue engineering products
     - Combined ATMP
2. CERTIFICATION OF Q and NC data for ATMP by SME

- **Legal basis:** Art 18 Reg EC no 1394/2007 and Reg EC No 668/2009
- **Eligibility:** SMEs developing ATMPs

- **What is the aim of certification?**
  - scientific evaluation of *early quality and non-clinical data* generated with the product (Module 3 and 4 only)
  - “snapshot” *in time* of the applicant data with respect to the review standards of an MAA
  - no advice for further development of the product (*not a scientific advice!*)
  - an *incentives to SMEs* who wish to license out their technology or could be used to attract venture capital allowing the SME to further develop their product
6. Scientific Advice / Protocol Assistance

- **Legal basis** – Art 57.1 Reg (EC) No 726/2004

- **Optional/voluntary procedure**, not binding for EMA & Company, but strong commitment from the CHMP is achieved

- Scope: **prospective, no data pre-assessment**, generally product specific advice

- **SAWP – multidisciplinary expert group:**
  - 28 members appointed **by expertise** not by Member State, selected based on complementary scientific competence (pre-clinical, pharmacokinetics, different therapeutic area, statistics)
  - 3 COMP, 1 CAT, 1 PDCO

- **BWP** also involved for the quality part of the advice

- **40/70 days procedure**: written procedure/discussion meeting

- **Fee incentives:**
  - fee waiver (SMEs) or reduction for **orphan products** → Protocol Assistance
  - fee waiver for paediatric-only
  - fee reduction SMEs (10% full fee)
Scientific Advice procedure
FAQs SA: Quality, Non-clinical & Clinical

Does the CHMP agree with...

1. Quality/CMC
   - Proposed potency testing and specifications for characterization and release?
   - Overall approach to show comparability?
   - Proposed stability protocol?

2. Non-clinical and Clinical
   - Relevance of the proposed animal models for a product with human specific targets (animal models mimicking the human disease)
   - Carcinogenicity and reprotoxicity study waivers, etc.
   - Design key features exploratory/pivotal clinical trial?
     - endpoints
     - definition of patient population (inclusion and exclusion criteria)
     - comparator
     - placebo-controlled study design acceptable in this indication?
     - single pivotal study as basis for approval?
     - size of safety database at the time of MAA?
7. Paediatrics

- **Legal basis** – Reg (EC) no. 1091/2006

- Improve the health of children:
  - Avoid the off label use in children of medicines primarily developed for adults
  - Increase availability of authorised medicines for children

- Achieve the above:
  - Without unnecessary studies in children
  - Without delaying authorization for adults
Paediatric Investigation Plan (PIP)

• Basis for development and authorisation of a medicinal product for all paediatric population subsets
• Includes details of the timing and the measures proposed, to demonstrate:
  - Quality
  - Safety
  - Efficacy
• To be agreed upon and/or amended by the PDCO
• **Binding** on company → **compliance check** at the time of validation of Marketing Authorisation Application (MAA)
When is a PIP necessary?

**Required**
- when applying for a **new marketing authorisation**
- in case of an already authorised and “patented” product, when applying for a **new indication / route / dosage form** (but not for new strengths)

**Not required**
- **Off-patent products** already authorised in the EU
- New medicinal products that belong to some specific groups:
  - Herbal medicinal products, Homeopathic products, Generic products, Hybrid products, **biosimilar products**
- **Class-waivers:**
  [Link](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000036.jsp&mid=WC0b01ac05801177cd)
  - for all products in a condition (e.g. treatment of Alzheimer’s disease)
  - for a class of products in a condition (e.g. ‘glitazones’ in the treatment of type II diabetes mellitus)
When should the PIP be requested?

- Non-clin
- Phase 1
- Phase 2
- Phase 3
- Post approval

Paediatric Committee (PDCO)
8. What about Clinical Trials?

Legal basis - Directive 2001/20/EC ‘Clinical Trial Directive’

Not under the responsibility of EMA

Responsibility at National level in competent authorities

European level:

• European Clinical Trial Facilitation Group (Voluntary Harmonisation Procedure (VHP) for assessment of multinational clinical trials)
• National experts at the level of Committees and Working Parties
• Harmonization of scientific requirements at EU and international level (EMA/ICH guidelines)
9. Marketing Authorisation Application

Common Technical Document

Module 1
- Regional Information 1.0
  - Introduction 2.2
  - Quality Overall Summary 2.3
  - Non clinical Overview and Summary 2.4-2.6
  - Clinical Overview and Summary 2.5-2.7

Module 2

Module 3
- Quality 3.0

Module 4
- Non clinical Study Reports 4.0

Module 5
- Clinical Study Reports 5.0
Assessment procedure

Day 180 List of Outstanding Issues (LoOI)*

Day 120 List of Questions (LoQ)

Clock Stop*

Day 120

Day 121

Day 180

Day 181

Day 210

Secondary Evaluation

CHMP Opinion

Day 150 Joint Assessment Report from Rapporteurs

Day 80 Assessment Reports from each Rapporteur

*optional

Pre-submission

Primary Evaluation

Secondary Evaluation

Day 1

Day 120

Day 180

Day 210

Decision Making Process

Commission Decision

CHMP AR

EPAR

Day 1

Day 120

Day 180

Day 181

Day 210

*optional
Product team

- **Rapporteur**
- **Co-Rapporteur**
- **SA/OD**
- **Inspection**
  - **GMP/GLP/GCP**
- **Paediatric**
- **PTM**
  - **Regulatory Affairs**
  - **Quality or Safety/Efficacy**
- **PTL**
- **PTM**
- **Risk management**
- **Administrative Assistant**
- **APPLICANT**
EPAR
European Public Assessment Report

- Summary of Product Characteristics
- Labelling
- Scientific discussion
- Steps taken before authorisation of the product
- Steps taken after granting the Marketing Authorisation (if applicable)

- All readers
- Patients
- Health professionals
- Pharmacists/patients
- Scientific community / health professionals
- Anyone interested

= available in all EU languages
= available in English
• **Overview** of the CHMP discussion

• Concise document which provides the **scientific rationale** on which the CHMP has based its opinion

• Substantiation of the statements made in the different sections in the **SmPC** so that consistency between these two documents is reached

• Description of **key issues** identified during the review / authorisation (e.g. major objections)

• **Deletion of confidential information**: from the CHMP AR to the EPAR
General information to the public

Name, INN, therapeutic area, MAH

SmPC, Labelling, Package leaflet, Presentations, Manufacturers (MAH, AS), Conditions to the MA
Biologics – authorised via CP update March 2011

1995 – 20th March 2012:

168 biologic products approved
- 8 negative opinions
- 20 withdrawal in pre-authorisation
- 28 withdrawals in post-authorisation

16 Insulins & analogues
15 Hormones
14 Growth factor /citokines
8 IFNs
9 Coagulation factors/ fibrinolitics
5 EPOs
8 Other enzymes
10. Post Authorisation Procedures

Legal basis - Variation Regulation EC No. 1234/2008

Changes not requiring any prior approval

- Type IA
- Type IA

Changes requiring prior approval

- Type IB
- Type II
- Extension

Variations

Evaluation Procedure adapted to the level of risk to Quality Safety and Efficacy

- do and tell

RISK
Grouping and Worksharing

If different related variations are affecting the **same product** (MA)

The changes may be combined in **one application**: **GROUPING**

If the **same change** is affecting several products (MAs) of the same MAH

The changes may be combined in **one application**: **WORKSHARING**
Main changes introduced in Variation Classification Guideline - Biologicals

Quality changes - Biologicals

- Downgrade changes where possible (e.g. Type II to IB)
- **Comparability** used as a cut-off for downgrading procedures
- Changes to PMFs/ VAMFs included in the Guideline for the first time
- New concepts (applicable both to CHE and BIO):
  e.g. Post approval **Change Management Protocols**
Agenda

- Introduction to the European Regulatory Network
- Overview on biologicals – different level of complexity
- Biosimilars – principles and challenges
- Marketing Authorization for biologicals in EU
- Conclusions
Drug Development Overview

Discovery → Chemistry → Preclinical Development → Clinical Development
- Phase I
- Phase II
- Phase III

MAA Evaluation → Post marketing

EMA guidelines

SME Status

Briefing Meeting ITF

Orphan Designation

Scientific Advice/Protocol Assistance

ATMP classification

Certification of Q / NC data for ATMP

Clinical trials

PIP Submission

MAA Submission

Post-authorisation
In conclusion

- Early dialogue between developers and regulators
- Find right balance between science development and regulatory requirements
- Risk-based approach
- Benefit/risk of the product
- Long term follow-up on safety & efficacy
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