Special populations: paediatric and orphan medicines

2nd International Awareness Session - The EU medicines regulatory system and the European Medicines Agency

Presented by Enrica Alteri MD on 9 March 2018
Human Medicines Research & Development Support Division
General introduction to EMA activities related to paediatric and orphan medicines:

EU Paediatric Regulation
- Paediatric Investigation Plan
- Procedures
- Incentives for Paediatric Medicines
- Achievements

EU Orphan Regulation
- Orphan Designation
- Significant Benefit, clinically relevant advantage, major contribution to patient care
- Incentives for Orphan Medicines
- Specific MAA requirements: confirmation of orphan designation criteria, similarity
- Achievements

1 Special populations: paediatric and orphan medicines
Paediatric Regulation in the EU

  • Committee for Paediatric Medicines (PDCO)
  • Paediatric Investigation Plan
  • Procedures
  • Incentives

• EC Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies (2014/C 338/01)
Objectives of the EU Paediatric Regulation

Improve the health of children:
- Increase high quality, ethical research into medicines for children
- Increase availability of authorised medicines for children
- Increase information on medicines

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
  (but modifications possible, at the company’s request)
When is a PIP/Waiver necessary?

- New marketing authorisation
- Already authorised product:
  - New indications
  - New routes of administration
  - New formulations (but not for new strengths)
When is a PIP/Waiver not needed?

- Authorised products that do not have a valid Supplementary Protection Certificate (SPC) or a valid patent that qualifies for it (i.e. off-patent products already authorised in the EU) – PUMA exception
- New medicinal products that belong to:
  - Herbal medicinal products, Homeopathic products
  - Generic products, Hybrid products, Biosimilar products
- **Class-waivers:** European Medicines Agency decision CW-0001-2015 of 23 July 2015 on class waivers in accordance with Regulation EC No 1901-2006 of the European Parliament and of the Council (23/07/2015)

6 Special populations: paediatric and orphan medicines
When should the PIP be requested?

Paediatric Investigation Plan

(PIP Amendments)

Compliance check

Paediatric Committee (PDCO)

Non-clin Phase 1 Phase 2 Phase 3 Post approval
Incentives for Paediatric medicines

- Reward is given to completed PIPs
  - if development is compliant with agreed PIP *(compliance statement in MA)*
  - if results of studies *(positive or negative)* included in SmPC + patient’s leaflet
  - if product is authorised in all MSs (except for PUMA)
- Non-orphan products: 6-month extension of SPC (patent protection)
- Orphan medicinal products: + 2 additional years of market exclusivity
- PUMA: 8 + 2 years of data + market protection
  - *Product-specific or class waiver does NOT trigger the reward*
  - *Inconclusive studies in PIP do NOT trigger the reward*
Achievements of the EU Paediatric Regulation

Positive impact on paediatric drug development *:

• More medicines for children (from 2007 until 2016, 267 new medicines for use in children and 43 new pharmaceutical forms appropriate for children were authorised in the EU), better and more information for prescribers and patients (by the end of 2015, approximately 140 updates of the product information);

• Better paediatric research and development;

• More regulatory support for paediatric matters;

• Paediatrics now being an integral part of medicine development.

Useful links – Paediatric medicines

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000023.jsp&mid=WC0b01ac0580b18c75
Orphan Regulation in the EU

  • Criteria for designation
  • Committee for Orphan Medicinal Products (COMP)
  • Procedure
  • Incentives (market exclusivity)
  – laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and
  – definitions of the concepts ‘similar medicinal product’ and ‘clinical superiority’
• Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products
Main characteristics orphan designation

- For medicinal products for human use
- Procedure free of charge
- Can be requested at any stage of development
- Sponsor can be either company or individual
  - Established in the Community (EU, Ice, Liech, Nor)
- COMP assessment, 90 days procedure
- European Commission Decision gives access to incentives
Designation criteria

RARITY (prevalence) / RETURN OF INVESTMENT (Art 3.1 (a) of 141/2000)

- Medical condition affecting not more than 5 in 10,000 in the Community (around 250,000 people)
- Without incentives it is unlikely that the marketing of the product would generate sufficient return to justify the necessary investment

SERIOUSNESS

- Life –threatening or chronically debilitating

ALTERNATIVE METHODS AUTHORISED (Art 3.1(b)of 141/2000)

- If satisfactory method exist the sponsor should establish that the product will be of significant benefit

EXCLUSIVE for EU

Special populations: paediatric and orphan medicines
Significant benefit

- Unique to the European Orphan Regulation
- Defined as:
  - a clinically relevant advantage
  - a major contribution to patient care
- showing significant benefit may facilitate the work of the HTAs and reimbursement bodies.
Clinically relevant advantage

- Legal definition: “clinically relevant advantage” translated into operational definition:

- “A relevant clinical benefit (in relation to all methods authorised for the condition) where there is a reasonable probability that the patient will actually experience this benefit”

Fregonese L

Special populations: paediatric and orphan medicines
Major contribution to patient care

Theoretical examples

- Pills vs. injection (but not 3 pills a day vs 1 injection per month)
- Ready to inject vs need to reconstitute (sterile)
- Easy to carry (e.g. not requiring storage in the fridge)
Incentives for Orphan medicines

- Fee reduction / exemptions
  - Extended incentives for SMEs
- 10-year market exclusivity (+ 2 if paediatric)
  - Protection against similar products (structure, mechanism of action, same indication)
  - Three derogations: Sponsor’s consent, Lack of supply, Clinical superiority
- Product development
  - Protocol assistance, reduced fee
- Community marketing authorisation
- National incentives (EC inventory)
Authorisation of an orphan drug

- Based on same standards as for non orphan products (quality / safety / efficacy)
- Authorisation only via centralised procedure, CHMP responsible for assessment
- The sponsor is requested to submit a report on the maintenance of ODD criteria: COMP re-evaluation in parallel with the MA assessment
- Authorisation within designated condition
- More than one designation possible per product (independent incentives)
Specific requirements MAA

Assessment of similarity by the CHMP

- If other orphan medicines authorised for same designated condition
  - Unless any derogation applies

- Similarity assessment by CHMP, during MAA:
  - Same molecular features?
  - Same mechanism of action?
  - Same therapeutic indication?
Achievements of the EU Orphan Regulation

- Stimulated sponsors to develop medicinal products for rare diseases
- From 2000 to 2016, over 1,805 orphan designations have been issued by the European Commission, of which 128 have resulted in authorised medicinal products
- The orphan designations cover a wide variety of rare diseases, including genetic diseases and rare cancers, for which there are limited treatment options, a large number of these diseases also affect children
- 143 Protocol Assistance (including follow-up) in 2016
Useful links – Orphan medicines

Any questions?

Further information

Dr Emilie Desfontaine
Paediatric Coordinator, Product Development Scientific Support Development

European Medicines Agency
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 Facsimile +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Follow us on @EMA_News
Back-up slides
Procedures evaluated by the PDCO

- PIP application: 120-day procedure, clock-stop at D60 (Request for Modification)
  Deferrals for initiation and/or completion of some measures are possible
- PIP modification: 60-day procedure, no clock-stop
  → PDCO Opinion, EMA Decision (partially published on EMA website)
- PIP Compliance check: 60-day procedure, no clock-stop
  → PDCO Opinion (outcome published on EMA website)
- Confirmation of class waiver
- Inclusion of an indication within an agreed condition
Paediatric Article 45 and 46

- Article 45: all existing paediatric studies to be communicated to EMA/NCAs (deadline 26/1/2008)
- Article 46: results of all new paediatric studies, sponsored by applicant, to be submitted to EMA/NCA within 6 months of completion (LPLV), whether part of a PIP or not
- Mandatory inclusion of paediatric information in SmPC
ODD Similarity assessment

- Same molecular features?
- Same mechanism of action?
- Same therapeutic indication?

If yes to all questions, then SIMILAR PRODUCT

- Accept another MAA
- Grant a MA
- Accept application to extend existing MA (variation/Line extension)

* Unless any derogation applies
Similarity assessment derogations

- Consent
- Unable to supply sufficient quantities
- Clinically superiority

➢ If one of derogations applies => then 2\textsuperscript{nd} product can be authorised.

**SHARING the MARKET**
Generic, biosimilars and herbal medicines

2nd International Awareness Session - The EU medicines regulatory system and the European Medicines Agency

Presented by Enrica Alteri MD
9 March 2018
General approach to regulation of Generic and Biosimilar medicines at EMA

• Generic and Biosimilars have their own framework under EU legislation (Article 10(1) and Article 10(4) of Directive 2001/83/EC, as amended)

• General Guidelines and products specific guideline have been developed throughout the years to support the development of this categories of medicinal products

• CHMP committee and working parties are the bodies involved in the regulation of Generic and Biosimilars
**Definition**

A **generic medicinal** product is a product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the **reference medicinal product**, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.

A **biosimilar** is a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (**reference medicinal product**) in the EEA.
Generic

Biosimilar

Increase complexity

SMALL MOLECULE DRUG

Aspirin
21 atoms

SMALL BIOLOGIC

Human Growth Hormone
~ 3000 atoms

LARGE BIOLOGIC

Monoclonal antibody
~ 25,000 atoms

Reference Product

Reference Product

Reference Product
Principle to follow for the development of a generic and a biosimilar: Bridging studies

- Generic and Biosimilar do not need to follow the classic development of a new medicinal product but they need to show bioequivalence and biosimilarity to the reference medicine authorized in Europe.
- The development aims of demonstrating equivalence and comparable safety and efficacy.
- The reference’s medicine entire clinical development programme does not need to be repeated
- Their approval builds on existing knowledge on safety and efficacy of the reference medicine gained during its clinical use therefore fewer clinical data are needed.
Generic: Key Criteria for Demonstration of Bioequivalence

• Two medicinal products containing the same active substance are considered bioequivalent if they are **pharmaceutically equivalent** or pharmaceutical alternatives and their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits.

• The purpose of establishing bioequivalence is to demonstrate **equivalence in biopharmaceutics quality** between the generic medicinal product and a reference medicinal product in order to allow **bridging of preclinical tests and of clinical trials** associated with the reference medicinal product.

• Selected pharmacokinetic parameters and **pre-set acceptance limits** allow the final decision on bioequivalence of the tested products.
Increase complexity

Generic
- SMALL MOLECULE DRUG
  - Aspirin
    - 21 atoms

Biosimilar
- SMALL BIOLOGIC
  - Human Growth Hormone
    - ~3000 atoms
- LARGE BIOLOGIC
  - Monoclonal antibody
    - ~25,000 atoms

Reference Product
- Reference Product
- Reference Product
- Reference Product
Principle to follow for the development of a biosimilar: Bridging studies
Quality – the foundation of biosimilars: highly structured development

- Define Target Profile
- State of art analytical tools
- Structured development: QbD
- Critical Quality Attributes – systematically Controlled
- Non-critical attributes – greater tolerance

Sensitivity to differences

Lower

Higher

Quality

Clinical

PK/PD

Preclinical

Biological characterization

Physicochemical characterization
Biosimilars

- Because biosimilars are made in living organisms there may be some minor differences from the reference medicine. These minor differences are not clinically meaningful (i.e. no differences are expected in safety and efficacy). Natural variability is inherent to all biological medicines and strict controls are always in place to ensure that it does not affect the way the medicine works or its safety.

- Biosimilars are approved according to the same standards of pharmaceutical quality, safety and efficacy that apply to all biological medicines approved in the EU.
Biosimilar guidelines: evolution in EU

- **Initially**: conservative on clinical (e.g. epoetin: 2 studies required in titration and maintenance) + emphasis on animal studies.

- **Now**: use of PD markers for clinical, relevant non-clinical in-vivo study + increased value from detailed quality (characterisation).
Evolution of Biosimilars in the EU

**Legislation**
- Directive 2001/83/EC
- Directive 2004/27/EC
- Directive 2003/63/EC
- Overarching guideline
- Directive 2004/27/EC
- Quality guideline
- Non-clinical/Clinical guideline

**Product evaluation**
- First biosimilars authorised – Omnitrope and Valtropin
- First biosimilar epoetins authorised
- First biosimilar filgrastims authorised
- First biosimilar mAbs authorised

**Guidance**
- Guideline Revision / Update
Biosimilar Product Review (January 2018) *

74 MAAs submitted

59 MAAs post-review

15 MAAs under review

2 Negative
Interferon alfa
Insulin

13 Withdrawn (pre-approval)
Insulin (6)
Bevacizumab (1)
Epoetin (1)
Pegfilgrastim (4)
Trastuzumab (1)

13 Withdrawn (post-approval)
Filgrastim (2)
Somatropin (1)

44 Positive opinions

39 Valid MAs
Somatropin (1)
Epoetin (5)
Filgrastim (7)
Infliximab (3)
Follitropin alfa (2)
Etanercept (2)
Bevacizumab (1)
Insulin glargine (2)
Enoxaparin (2)
Teriparatide (2)
Rituximab (6)
Adalimumab (4)
Insulin lispro (1)
Trastuzumab (1)

2 Awaiting EC decision
Trastuzumab (1)
Insulin glargine (1)

* Information on EMA website
Biosimilars in the EU

- The EU is the global leader in the area of biosimilars, with the highest number of biosimilar medicines approved, extensive experience of their use and safety;
- The EU’s legal framework on biosimilars has been in place since 2004 and is used by other international regulators;
- Over the last 10 years, the EU monitoring system for safety concerns has not identified any relevant difference in the nature, severity or frequency of adverse effects between biosimilar medicines and their reference medicines.
Herbal Medicines
Legal framework - what are we trying to achieve

Directive 2004/24/EC amending Dir. 2001/83/EC introduced:
• Definitions for herbal MP and traditional herbal MP
• Committee on Herbal MP (HMPC) at EMA
• EU harmonised authorisation/registration and scientific/regulatory standards

Objective:
• public access to safe & high quality MPs containing herbal ingredients
• provide access to medicines of choice, including herbal medicines of long tradition (when their medicinal use is not substantiated by clinical efficacy data)
• harmonised provisions to allow trade without distortion of competition
### Regulatory pathways for Herbal Medicines

<table>
<thead>
<tr>
<th>Traditional use registration (Art. 16a(1) of Dir. 2001/83/EC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No clinical testing</td>
</tr>
<tr>
<td>• Bibliographical information</td>
</tr>
<tr>
<td>• &gt; 30 y use / 15 y in EU</td>
</tr>
<tr>
<td>• Use without MD supervision/not by injection</td>
</tr>
<tr>
<td>National procedures</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Well-established use marketing authorisation (Art. 10a of Dir. 2001/83/EC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Scientific documentation of well-established use</td>
</tr>
<tr>
<td>• Bibliographical information</td>
</tr>
<tr>
<td>• &gt; 10 years in use</td>
</tr>
<tr>
<td>National &amp; centralised procedures</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Standalone/mixed marketing authorisation (Art. 8(3) of Dir. 2001/83/EC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Safety/Efficacy data</td>
</tr>
<tr>
<td>• Combination with bibliographical data</td>
</tr>
<tr>
<td>National &amp; centralised procedures</td>
</tr>
</tbody>
</table>

While some derogations are made as regards required safety/efficacy documentation for TU and WEU products, a **full quality dossier** is required in all cases.
How does the European System work?

**Standards**

**EMA**
HMPC EU monographs on Safety + efficacy/plausibility Guidelines

**European Pharmacopoeia**
Eur. Ph. Monographs on Quality

**National authorities**
Product applications Assessment Licensing
Active substances originating from Herbal starting materials

GACP
Good Agricultural & Collection Practice

Plant source

Starting material

GMP
Good Manufacturing Practice

Active substance

Herbal substance/preparation

Chemical substance

Biological substance

chemicals active substance (i.e. ICH & CHMP)

biological active substance (i.e. ICH & CHMP)

Specific Herbal guidance

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000497.jsp&mid=WC0b01ac0580033a9b#Quality
**Examples**

**Chemically defined substance**

Taxotere EMEA/H/C/000073/

Docetaxel prepared by semisynthesis from a substance (extracted from needles of *Taxus baccata* L.)


**Biological substance**

Nexobrid (previously Debrase)

EMEA/H/C/002246/

Bromelain enriched proteolytic enzyme preparation from *Ananas comosus* (L.) Merr.


**Herbal substance/preparation**

Episalvan (EMEA/H/C/003938)

Dry extract from Birch bark (*Betula* spp.) formulated as a sterile gel for treatment of partial thickness wounds.

Herbal Products – borderline with other product categories

In the EU, there is a clear distinction between medicines and other product categories such as food, cosmetics and other etc.

**EMA’s scope is medicinal products** (not e.g. food/dietary supplements)

Ingredients from the same plant can be found in different product categories, however, according to purpose, effect and presentation their requirements differ.

Definitions according to Dir. 2001/83/EC:
- Medicinal product:...
- Herbal Medicinal Product:...
- Traditional Herbal Medicinal Product:...
What have we delivered so far

**EMA/HMPC output:**

EU herbal monographs: **157**
EU List Entries: **13**
Monograph revisions: **30**
Public statements: (assessment but no monograph outcome): **20**

National registrations / authorisations in EU MS 2004-2016

TU: **1719**
WEU: **859**


Guidance documents: > **30**


How can you benefit from the information developed?

Herbal medicinal products

The Committee on Herbal Medicinal Products (HMPC) issues scientific opinions on herbal substances and preparations, along with information on recommended uses and safe conditions, on behalf of the European Medicines Agency (EMA). This gives companies and national competent authorities a clear reference point when preparing or assessing an application for marketing authorisation or registration of herbal medicinal products in European Union (EU) Member States.

In this section

- Bringing herbal medicinal products to market within the EU
- Establishing EU standards for national procedures

- Scientific guidelines
- Regulatory and scientific support
- Questions and answers

Bringing herbal medicinal products to market within the EU

Companies seeking to bring herbal medicinal products to the market in EU Member States should follow the national procedures overseen by national competent authorities.

There are three main regulatory pathways for bringing a herbal medicinal product to market in EU Member States:

<table>
<thead>
<tr>
<th>Regulatory pathway</th>
<th>Main requirements on safety and efficacy</th>
<th>Where to apply</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional use registration (Article 10a of Directive 2001/83/EC)</td>
<td>No clinical tests and trials on safety and efficacy are required as long as sufficient safety data and plausible efficacy are demonstrated.</td>
<td>National competent authority of a Member State for national, mutual recognition and decentralised procedures.</td>
</tr>
<tr>
<td>Well-established use marketing authorisation (Article 10a of Directive 2001/83/EC)</td>
<td>Scientific literature establishing that the active substances of the medicinal products have been in well-established medicinal use within the EU for at least ten years, with recognised efficacy and an acceptable level of safety.</td>
<td>National competent authority of a Member State for national, mutual recognition and decentralised procedures.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regulatory pathway</th>
<th>Main requirements on safety and efficacy</th>
<th>Where to apply</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scientific guidelines</td>
<td>EU monographs and list entries</td>
<td>National competent authority of a Member State for national, mutual recognition and decentralised procedures.</td>
</tr>
<tr>
<td>Regulatory and scientific support</td>
<td>Procedures for monograph and list establishment (including calls for scientific data and public consultations)</td>
<td>National competent authority of a Member State for national, mutual recognition and decentralised procedures.</td>
</tr>
<tr>
<td>Questions and answers</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Any questions?

Further information

EMAIInternational@ema.europa.eu

European Medicines Agency
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 Facsimile +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Follow us on @EMA_News