



*Making Medicines Affordable*

# **Biogenerics and Legislative Issues GPhA's 2008 Annual Policy Conference**

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# Outlines

- **EU decision procedure**
- **EU framework for biosimilar medicines**
  - Legislative perspective
  - Regulatory perspective
    - Guidelines
    - Nomenclature
    - Approvals and Positive Opinions
    - Risk Management Plans
- **Traceability**
- **Interchangeability**
- **Communication**
- **Biosimilar drugs in the market place**
- **Global development**

# EU27

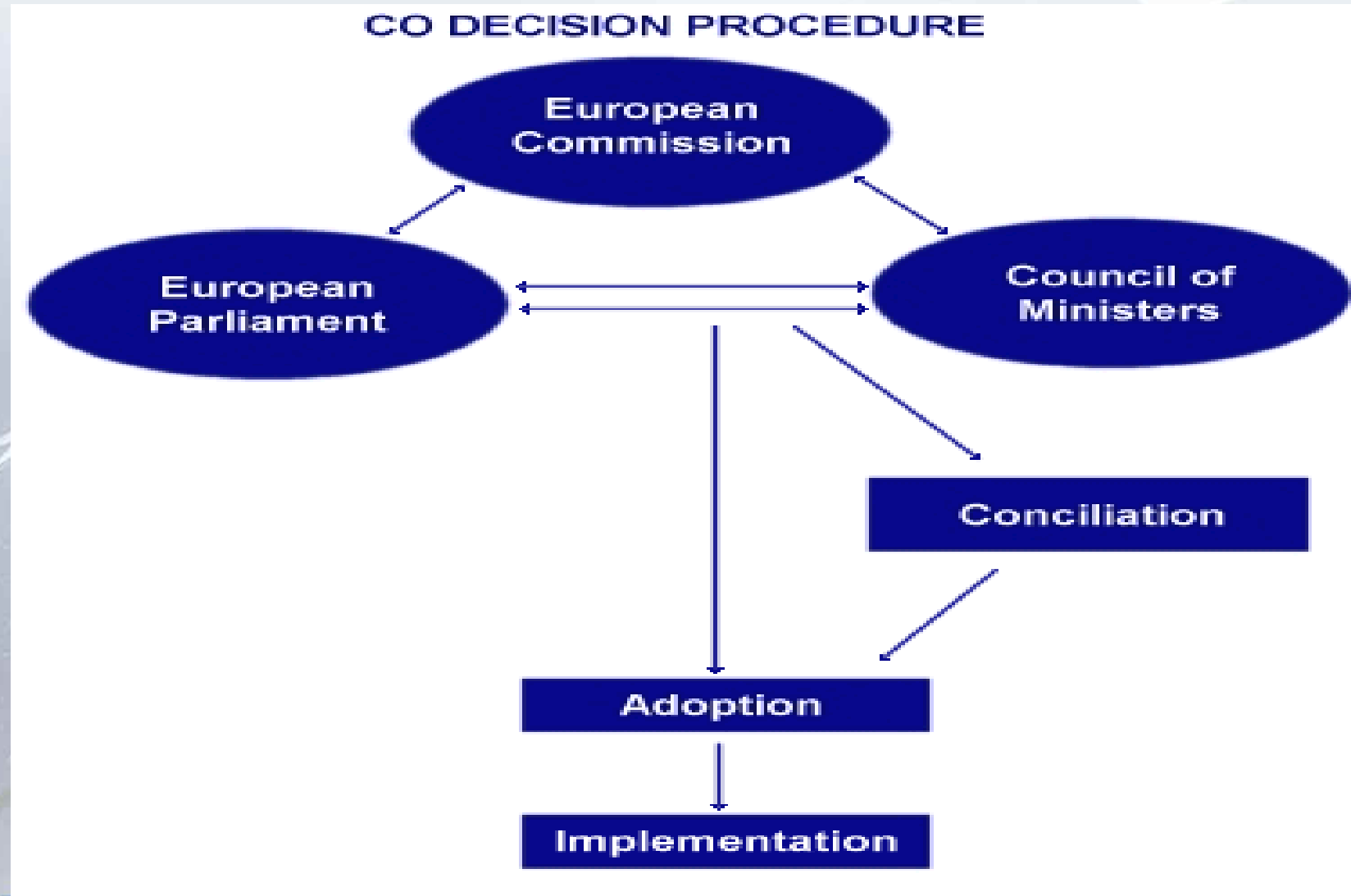
## Diversity, Complexity





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# The Decision-Making Triangle





# EGA: Important Stakeholder in the Process

## ■ Legal framework (adopted by EU15)

- EGA priority issue in 2001
- Negotiated as part of the overall pharmaceutical package (no provision on 'biogenerics' in the initial EC legislative proposal)

## ■ Regulatory framework

- Acceptance of the highest possible scientific standards

# EU Framework Combines

## ■ Legal certainty

- Clear legal basis
- Abbreviated data package

----->key for  
investments

## ■ Flexibility

- Case by case approach
- General and product specific guidelines

-----> adjustments of data  
requirements (science,  
technology, experience)

# Legal Perspective

- Covers the whole spectrum of biologics
- Generic approach is legally not excluded

# Regulatory Perspective

- For the type and quantity of data to be provided, the EU legislative framework refers to detailed guidelines
- **But guidelines are NOT mandatory before submission and approval**
- **Guidance follows science**
  - Guidances are built on experience gained through scientific advice procedures and marketing authorisation applications' assessments
  - Guidelines do not have legal force- a justification for non compliance may be provided

# Omnitrope® Approved Before Somatropin Guidance

■ **Omnitrope Positive  
Scientific Opinion**  
**26 Jan 2006**

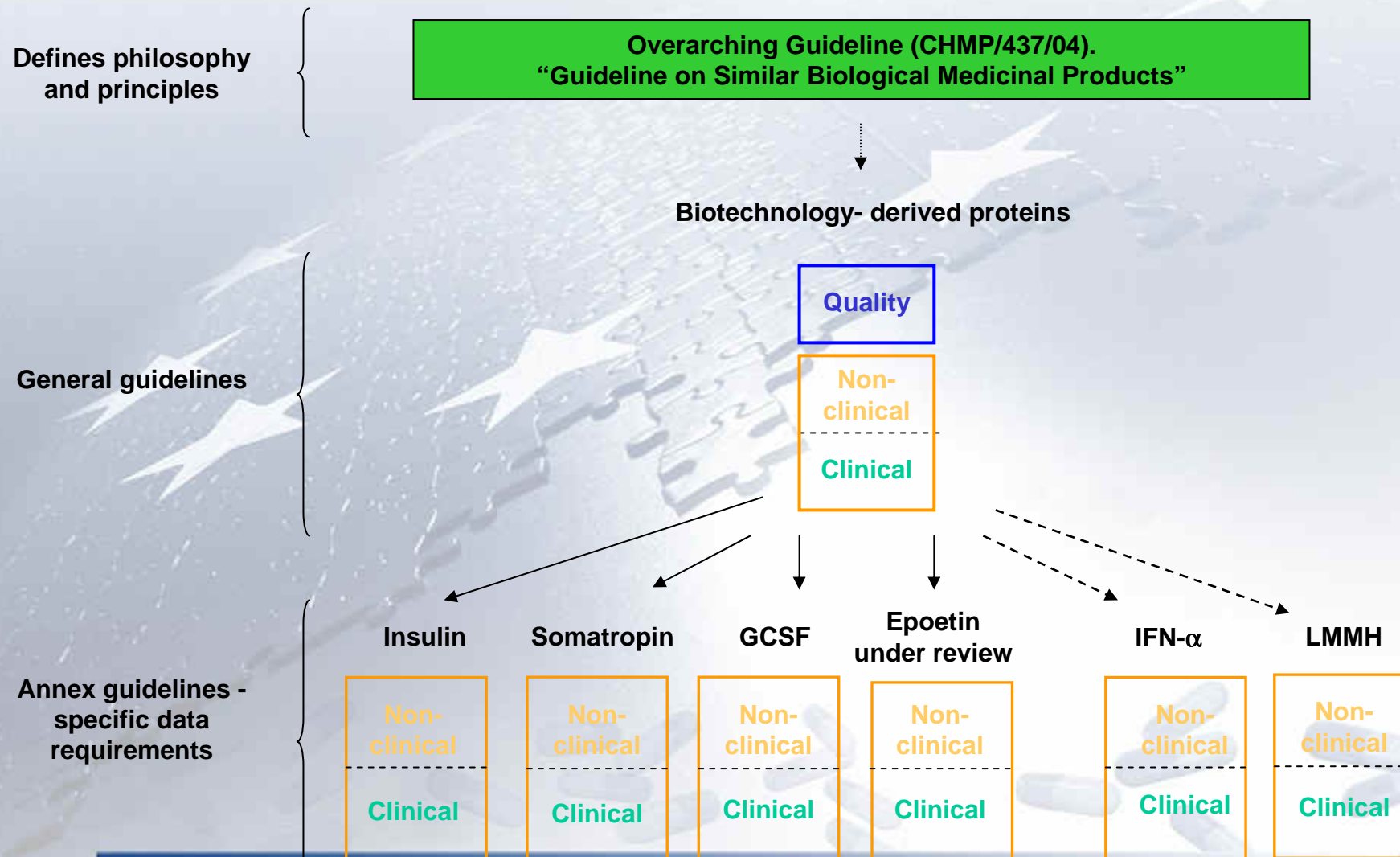
■ **Adoption of  
guideline**  
**22 Feb 2006**

■ **Approval of  
Omnitrope**  
**18 April 2006**

■ **Coming into effect**  
**1 June 2006**

# Current EU Biosimilar Guidelines

<http://www.emea.europa.eu/htms/human/humanguidelines/multidiscipline.htm>

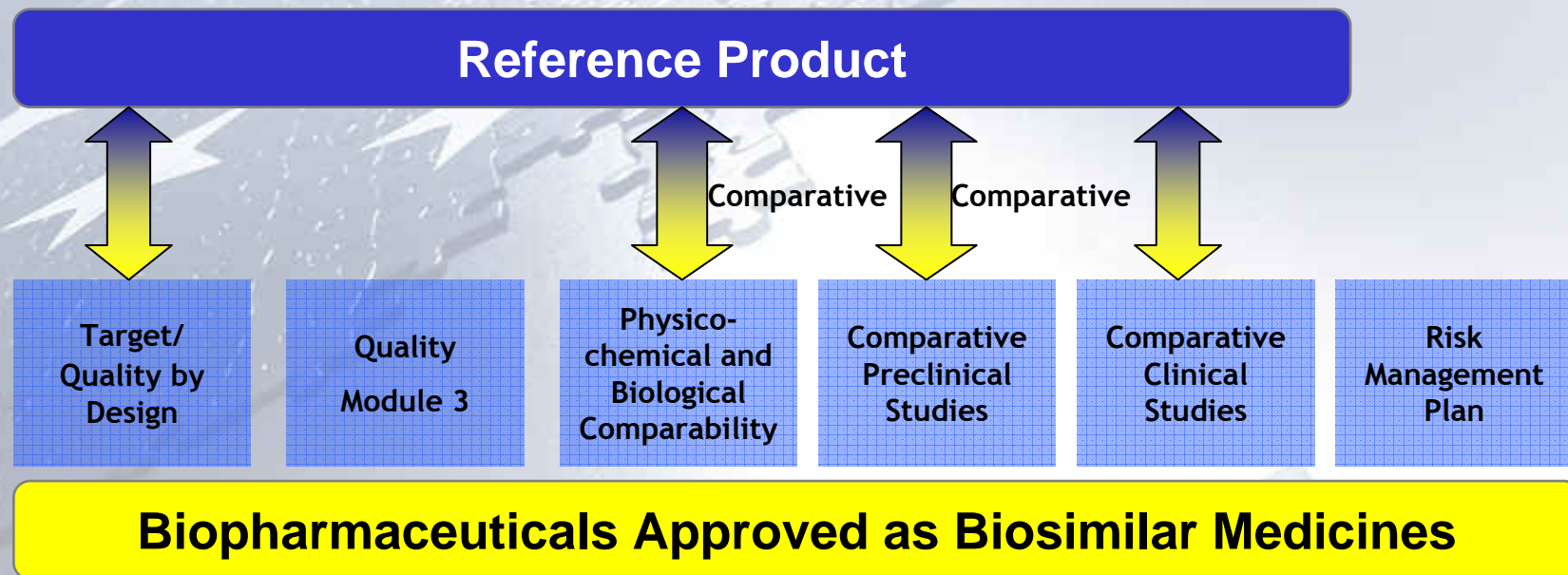


Source: P. Richardson EMEA-EGA 6th symposium on biosimilar medicines

# Scientific Background- **Comparability** (to Establish Similarity)

The development of a biosimilar medicine requires a complete product and process development

**PLUS** comparative testing at all stages of development in order to obtain approval by the European authorities (EMA, CHMP, EC)





## **Nomenclature: Same INN Decision lies with Regulators**

With regard to the nomenclature of biosimilars, we do not endorse the idea that any difference in glycosylation automatically leads to a different INN. We have serious doubts that this stance could be scientifically justified. We are also concerned that the WHO is promoting a double-standard policy on biosimilars.

**G.Lalis/Director General EC -Statement on WHO INN Policy at  
EGA Annual Conference Paris 2 June**

# Purpose of INN

## Is...

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- Identification of drug substance, not drug product
- Nomenclature: means of classifying and cataloguing pharmacological classes

## Is Not ...

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- Identification of a medicinal product or its impurities
- Statement of therapeutic equivalence and/or substitution
- Means of managing the practice of medicine
- Means of establishing traceability or for pharmacovigilance purposes

INN is a nomenclature system for a **drug substance**  
The INN has never been the primary means for clinical decisions by physicians, nor more than one of several components that together make up a robust track-and-trace system for medicinal products



# EU Biosimilar Approvals

Biosimilar	INN	Reference product	Approval date
Omnitrope (Sandoz)	Somatropin	Genotropin (Pfizer)	12 April 2006
Valtropin (Biopartners)	Somatropin	Humatrope (Eli Lilly)	24 April 2006
Binocrit (Sandoz)	Epoetin alfa	Eporex/Erypo (Janssen-Cilag)	28 August 2007
Epoetin alfa Hexal (Hexal)	Epoetin alfa	Eporex/Erypo (Janssen-Cilag)	28 August 2007
Abseamed (Medice)	Epoetin alfa	Eporex/Erypo (Janssen-Cilag)	28 August 2007
Retacrit (Hospira)	Epoetin zeta	Eporex/Erypo (Janssen-Cilag)	18 December 2007
Silapo (Stada)	Epoetin zeta	Eporex/Erypo (Janssen-Cilag)	18 December 2007



## EU Biosimilar Approvals (cont.)

Biosimilar	INN	Reference product	Approval date
Ratiograstim (ratiopharm GmbH)	Filgrastim	Neupogen (Amgen)	15 September 2008
Biograstim (CT Arzneimittel GmbH)	Filgrastim	Neupogen (Amgen)	15 September 2008
Tevagrastim (Teva Generics GmbH)	Filgrastim	Neupogen (Amgen)	15 September 2008
Filgrastim ratiopharm (ratiopharm GmbH)	Filgrastim	Neupogen (Amgen)	15 September 2008

# Status of EU Procedures Status March 2008

1	Omnitrope (somatropin)	Sandoz	Authorised
2	Valtropin (somatropin)	Biopartners	Authorised
3	Alpheon (interferon alfa)	Biopartners	Negative
4	Binocrit (epoetin alfa)	Sandoz	Authorised
5	Epoetin alfa Hexal (epoetin alfa)	Hexal	Authorised
6	Abseamed (epoetin alfa)	Medice	Authorised
7	Silapo (epoetin zeta)	Stada	Authorised
8	Retacrit (epoetin zeta)	Hospira	Authorised
9	Insulin Marvel Short (human insulin)	Marvel Life Sci'	Withdrawn
10	Insulin Marvel Intermediate (human insulin)	Marvel Life Sci'	Withdrawn
11	Insulin Marvel Long (human insulin)	Marvel Life Sci'	Withdrawn
12	Filgrastim Ratiopharm (filgrastim)	Ratiopharm	Positive Opinion
13	Ratiograstim (filgrastim)	Ratiopharm	Positive Opinion
14	Biograstim (filgrastim)	CT Arzneimittel	Positive Opinion
15	Tevagrastim (filgrastim)	Teva	Positive Opinion

# Risk Management Plan for first Biosimilar EPO (EPAR)

Safety issue	Pharmacovigilance activities	Risk minimisation activities
Pure Red Cell Aplasia (PRCA)	<ul style="list-style-type: none"> <li>• <b>Routine pharmacovigilance</b></li> <li>• <b>PASS INJ-14</b></li> <li>• <b>Phase 3 study INJ-17</b></li> </ul>	<ul style="list-style-type: none"> <li>• <b>SPC contraindication, warnings and 4.8</b></li> </ul>
Increased risk of PRCA with off-label subcutaneous administration in renal failure patients	<ul style="list-style-type: none"> <li>■ <b>Routine pharmacovigilance</b></li> <li>■ <b>Phase III study INJ-17</b></li> <li>■ <b>Market survey to monitor potential off-label s.c. use in renal anaemia patients</b></li> </ul>	<ul style="list-style-type: none"> <li>■ <b>SPC advice and warning</b></li> </ul> <p>Additional measures to avoid s.c. use in renal anaemia patients:</p> <ul style="list-style-type: none"> <li>■ <b>Educational leaflet</b></li> <li>■ <b>Cool boxes with visual label</b></li> </ul>
Thrombotic vascular events (TVE)	<ul style="list-style-type: none"> <li>• <b>Routine pharmacovigilance</b></li> <li>• <b>PASS INJ-14</b></li> <li>• <b>Phase 3 study INJ-17</b></li> </ul>	<ul style="list-style-type: none"> <li>• <b>SPC target haemoglobin not exceed 12 g/dl</b></li> </ul>
Tumour Growth Potential	<ul style="list-style-type: none"> <li>• <b>Routine pharmacovigilance</b></li> <li>• <b>PASS INJ-14</b></li> <li>• <b>Phase 3 study INJ-17</b></li> </ul>	<ul style="list-style-type: none"> <li>• <b>SPC - Risk of tumour growth potential</b></li> </ul>

# Traceability of ALL Biologics

All biological drugs need to be monitored

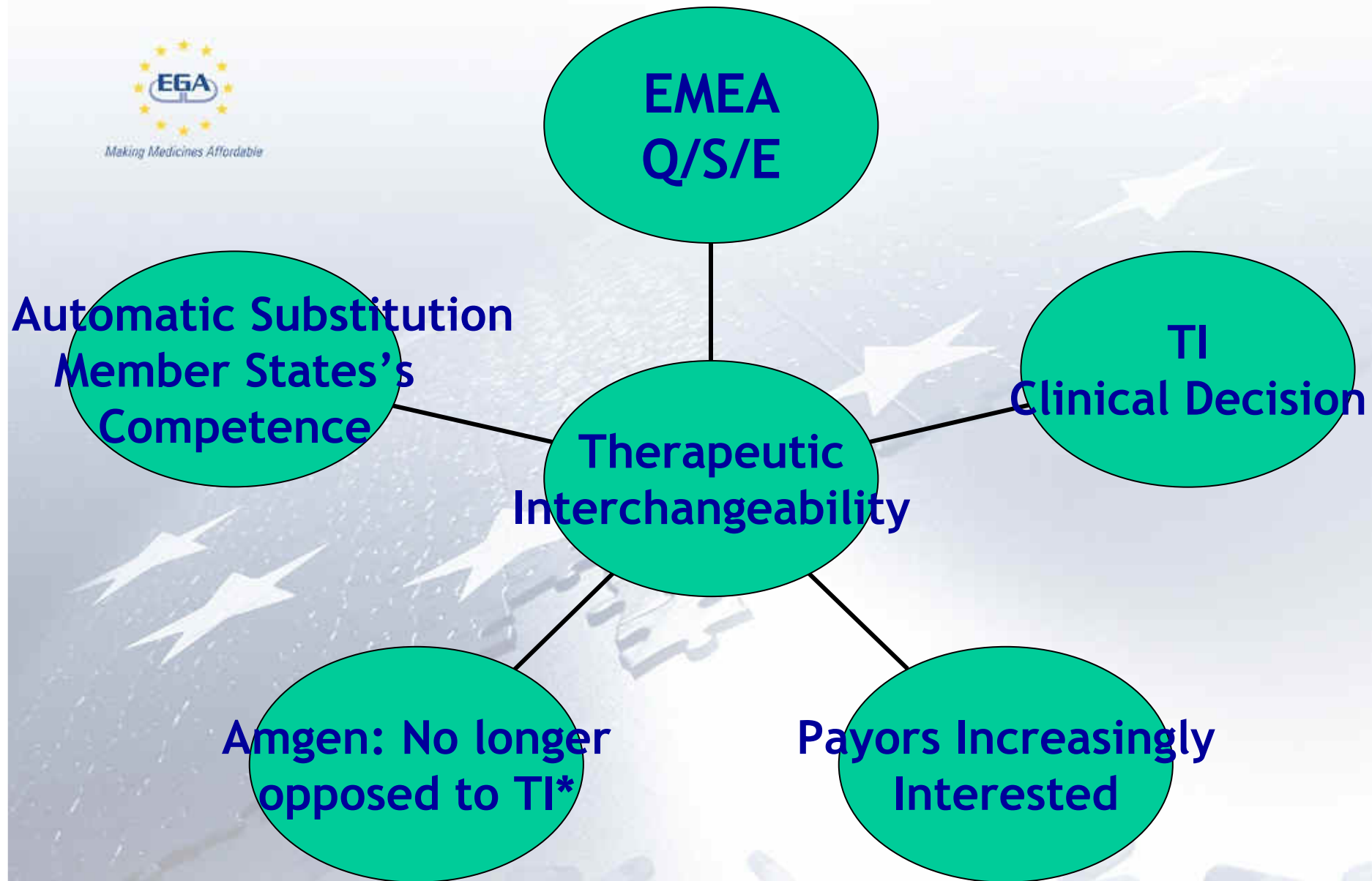
- An adverse reaction report **for any biological drug** should always include
  - full name of the biological drug
  - batch number
- Where information is missing, Member States/MAHs should ensure that reports are followed up for completion

# G.Lalis/Director General EC on Pharmacovigilance for Biosimilars

EGA Annual Conference Paris 6/08

Furthermore we **have written to Member States'** regulatory authorities to take necessary measures to ensure

- a method to link suspected adverse reaction reports to specific products (such as a unique product identifier) and
- to ensure that prescribing doctors know which glycoprotein has been given to their patient.



## Biosimilar Drugs Qualify for Therapeutic Interchangeability

# More Communication Needed

- Lack of education allows regulatory process to be undermined
- Increased communication needed on
  - Availability of Biosimilar medicines
  - Scientific rigour and technical excellence
  - Approval process
  - Risk Management Plans
  - Traceability and ADR reporting
  - Therapeutic interchangeability

# Message from European Commission

..... *'we are confident that if a product goes through all the steps and meets all the requirements and gets at the end an approval through a Commission Decision, it means that this product is as safe and efficacious as any other product authorised by the European Commission in the EU'.*

N. Rossignol at 6th EGA symposium on biosimilar medicines 2008

# Biosimilar Drugs in the EU Market Place

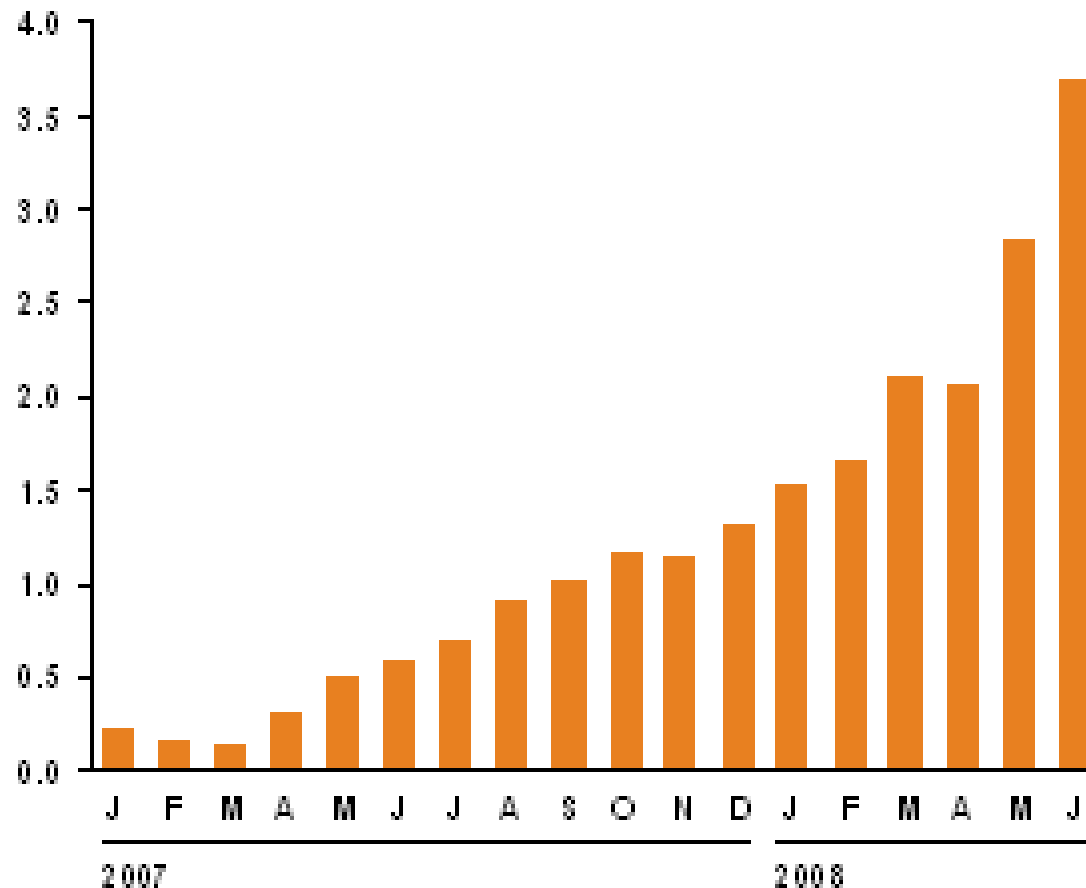
- Pricing approvals and reimbursement have been agreed without any major barriers
- Market in-roads are made
- Patients and healthcare professionals are catching up

by courtesy of Sandoz

as presented to investors on 3rd September

## Rising sales for pathbreaking Omnitrope®

Monthly gross sales<sup>1</sup> of Omnitrope®  
in USD m



**Omnitrope®** 

### Pioneering role

- First approved biosimilar ever
- Geographic rollout underway
- Niche market, but growing patient pool
- Increasing awareness and acceptance for biosimilars

<sup>1</sup> Source: IMS, at constant currency exchange rates

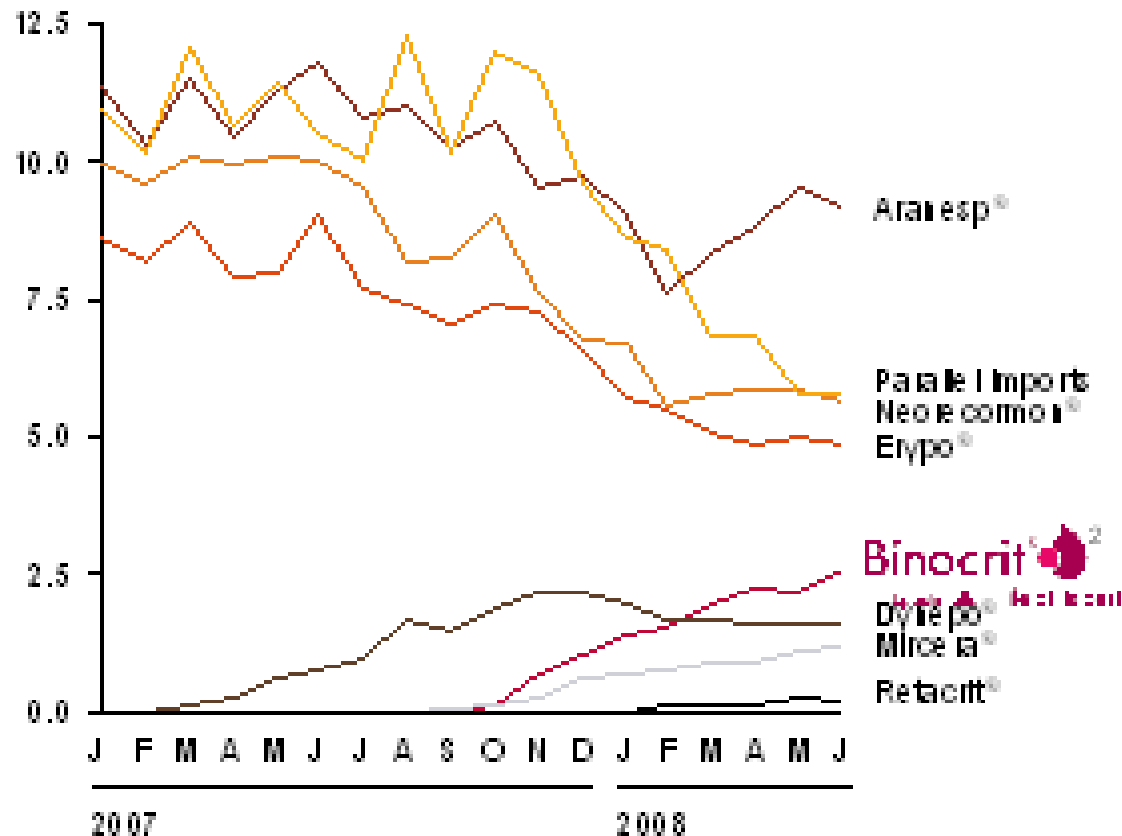
<sup>1</sup> | Sandoz Day | Haines, Texas | September 3, 2008

by courtesy of Sandoz

as presented to investors on 3rd September

## Binocrit® strong EPO launch in Germany

German monthly gross sales development<sup>1</sup>  
in USD m



# Binocrit®

Epoetin alfa life at its best

Complex biosimilar

- Binocrit® as first EPO biosimilar in Germany
- Brands: Binocrit®, Epoetin alfa Hexal® and Abseamed®
- 25% price cuts after biosimilar entry
- Dynepo® taken off the market after biosimilars' entry

<sup>1</sup> Source: IMS, at constant currency exchange rates; <sup>2</sup> including sales of Epoetin alfa Hexal® and Abseamed®

# Vision: Global Development

- **Streamlining the development process**
  - Avoids repetition of unnecessary trials
  - Increases access through affordable medicines
  - Increases competition
    - Market competition from biosimilar drugs will drive the biotechnology industry to do what it does best - discover new drugs that enhance, sustain, and save lives



Making Medicines Affordable

# It's Time!!



America cannot  
afford not to have  
FOBs/'Biogenerics'

Patients are waiting!

*thank you*



*Making Medicines Affordable*

# Acronyms

- EGA European Generic medicines Association
- EU European Union
- EMEA European Medicines Agency
- CHMP Committee for Medicinal Products for Human Use
- EC European Commission
- WHO World Health Organisation
- MS Member State
- MAA Marketing Authorisation Application
- MAH Marketing Authorisation Holder
- DE Data Exclusivity
- ME Market Exclusivity
- INN International Non-Proprietary Name
- ADR Adverse Drug Reaction
- RMP Risk Management Plan
- EPAR European Public Assessment Report