



Amgen's Views on Biosimilars

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FOPI/EFA-Symposium on biosimilars, Vienna

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Amgen Is Delivering on the Promise of Biotech in Europe and Around the Globe



Founded in 1980

9 innovative medicines

> 12 million patients helped

Nearly 20,000 staff
in 35 countries



2006 financial highlights:

Total revenue: \$14B

R&D investment: \$3B

More than 45 molecules and
programs in development



Amgen's Interest In Biosimilars Is Based On Three Principles

Ensure patient safety

- Patients have a right to safe and effective medicines

Safeguard reputation of biotech industry

- Healthcare biotech has strong reputation due to serving unmet medical needs with excellent safety record
- Reputation should not be risked by premature approval and usage biotech products

Share experience in biotech manufacturing

- Amgen has long, successful history in biotechnology manufacturing since 1980s
- Sharing knowledge allows regulators to develop robust, science based standards

Amgen Europe Biosimilars Corporate Statement

- Biotechnology medicines, developed from living cells, are some of the newest and most effective treatments for tackling serious diseases such as cancer and kidney disease. Today, patients have access to more than 150 biotechnology medicines, which have transformed the lives of over 325 million patients worldwide. Amgen is a pioneer in developing medicines to treat serious illnesses and strives to serve patients by transforming the promise of science and biotechnology into therapies that have the power to restore health or even save lives. As Amgen is dedicated to ensuring patient safety and innovation, **we believe that patients should have access to the safest and most effective medicines.**
- **Amgen supports Europe’s biosimilar approval process that state that biosimilars “by definition” are not generics, and that the generic approach “is scientifically not appropriate” for these products.** As biosimilars are similar and not identical to the original biotechnology product that they copy, **national healthcare systems should ensure that: 1) patients and physicians are informed of the nature of the clinical data to make informed decisions for clinical practice and; 2) because no two biotech medicines are identical, these medicines should not be substituted at the pharmacy level, without the prior consent of the treating physician.**
- Amgen believes that biosimilars will play a limited role in patient care because in many cases newer innovative biotechnology medicines are available that offer advantages over the older biotechnology medicines that biosimilars attempt to imitate. **We believe patients and medical professionals have the right to access the most appropriate medicines and should not be forced to use biosimilars based purely on economic grounds as newer innovations may offer better care.**

Impact of small differences among biotech products on efficacy and safety is unpredictable

- Safety and efficacy can differ significantly with small changes in
 - protein biophysical characteristics or
 - formulation of the drug product
- Long term safety profile of biosimilars has yet to be established
- Prescribers and patients should be aware of this to ensure appropriate introduction into clinical practice

Need to recognize safety and efficacy issue in both approval process and introduction into clinical practice of biosimilars

The Stage Is Set For The Entry Of Biosimilars In The European Market ...

EU have established a pathway for biosimilars approval ...

- EU has recognized that biosimilars are different from "generics"
 - Not identical to original product
 - Need to undergo evaluation trials prior to approval
- and has developed product specific regulatory approval guidelines
 - Erythropoietin
 - G-CSF
 - Somatropin
 - Insulin

...which should open the way for biosimilars entering the market

- Expect to see several biosimilars for each of the original products in next years, e.g.
 - G-CSF (Teva, BioGeneriX, Biopartners, Pliva, Mayne, DRL, others)
 - Somatropin (Teva, Sandoz, Biopartners, Cangene, others)
 - Erythropoietin (Sandoz, Teva, Stada, Biopartners, others)
 - Insulin (Biopartners, others)

Expect to see many biosimilars on the market in 5-years

... However The Market Entry Of Biosimilars Poses Some Unique Challenges

Biosimilars will be similar but not identical to the reference products

Automatic/Generic Substitution Rules

- Should rules designed for small molecules apply to biotech/biosimilar products?

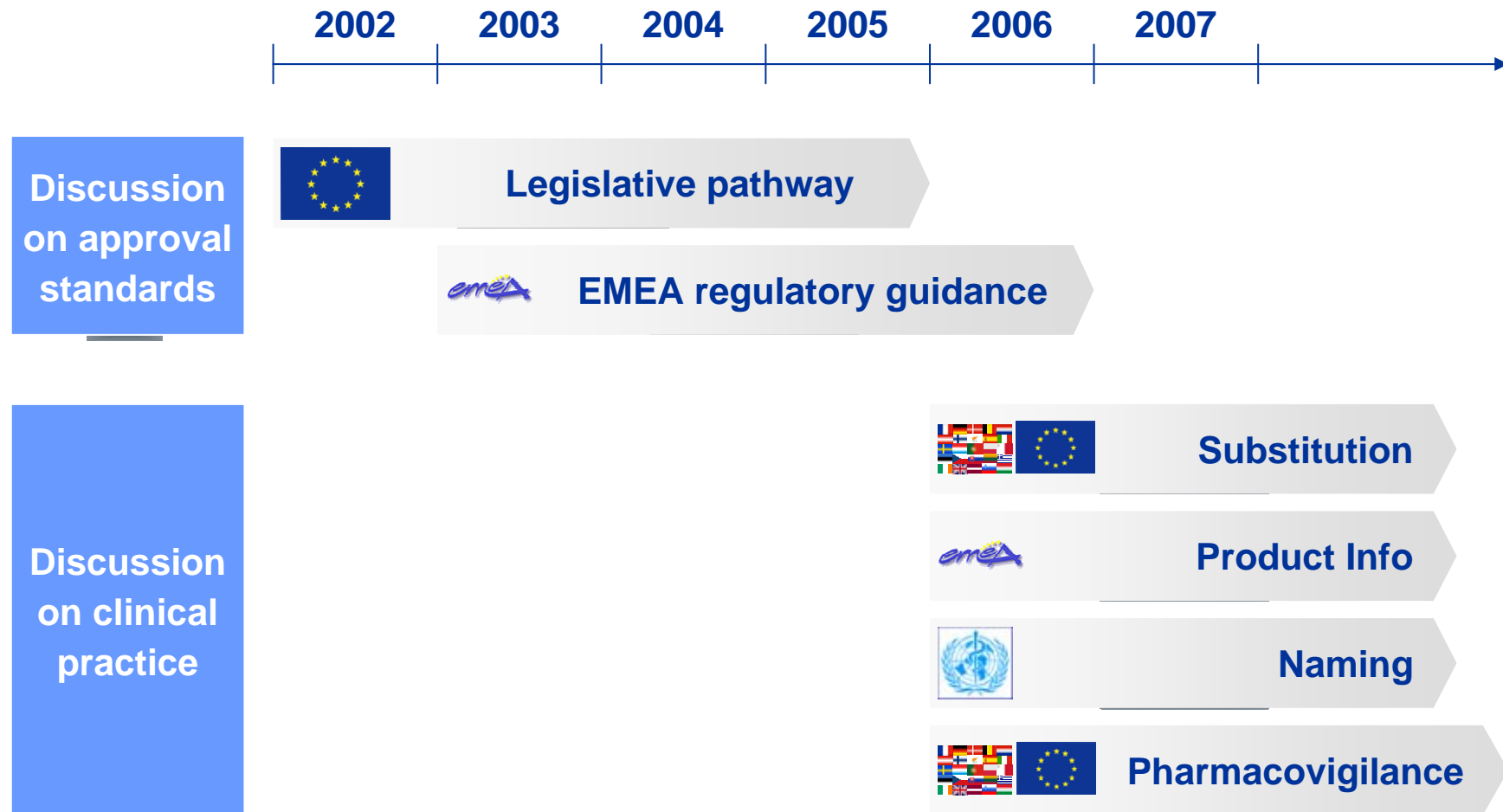
Clear Identification for Healthcare Providers

- How will physicians and pharmacists distinguish one biotech product from another?
- How will they be provided with the approval data and post-approval data?

Accurate Pharmacovigilance

- Will existing Pharmacovigilance systems cope?
- Are any changes needed?

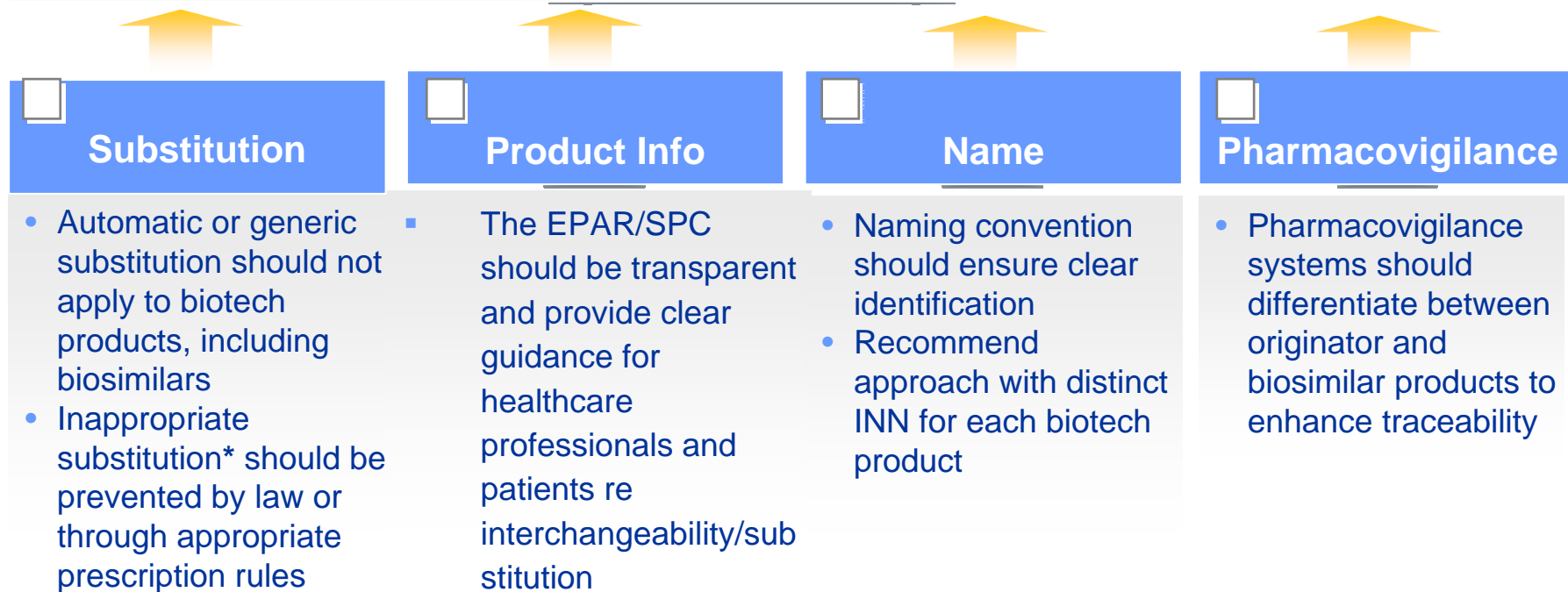
Biosimilar Debate In Europe Is Advancing In Phases And Involves Different Authorities



Four Open Issues Need Clarification To Ensure Patient Safety In Clinical Practice

Legal and regulatory framework established and applied successfully

Ensure appropriate introduction into clinical practice: prevent inappropriate substitution* and facilitate pharmacovigilance



Issues apply not only to biosimilars, but to all biotech medicines

*Inappropriate substitution = the physician is not involved in the decision-making process

Aim is to prevent inappropriate substitution and to facilitate correct attribution of adverse events

Biosimilars are *similar* but not identical to original product



Patients may respond differently to a similar but not identical product
(eg. immunogenic response)



- Inappropriate substitution might have severe clinical consequences
- Repeated switching will confound accurate pharmacovigilance



- Automatic or generic substitution should not apply to biotech medicines

- At approval, limited clinical experience



- Accurate pharmacovigilance and correct attribution of adverse events is vital

Inappropriate Substitution Can Be Controlled Through Independent But Complementary Initiatives

	Prevent substitution	Brand name dispensing(1)	Distinct INN
Description	<ul style="list-style-type: none"> ▪ Include biotech in non-substitutable lists (eg. list in Spain) ▪ No biotech on substitutable lists (eg. Nordics) ▪ Law to prevent biotech substitution (eg. France) 	<ul style="list-style-type: none"> ▪ Require that physicians prescribe and pharmacists dispense by brand name 	<ul style="list-style-type: none"> ▪ Every biotech to have a distinct INN ▪ Stem to be maintained from "original" ▪ Find appropriate "differentiating" suffix (eg. epoetin zeta)(1)
Influencing authority	Member States, but EMEA could refer to lack of interchangeability in the label and at approval		<ul style="list-style-type: none"> ▪ European Commission, EMEA and WHO
Issues	<ul style="list-style-type: none"> ▪ New laws/concept for most countries ▪ Requires change in European law⁽²⁾ 		<ul style="list-style-type: none"> ▪ Requires changes to the current WHO INN system
	1. Ensure that substitution, does not take place without physician consent	2. Ensure proper dispensing	3. Ensure clear identification

Process is slow due to lack of clarity and different levels of responsibility

(1) Examples already exist: Stada obtained a distinct INN ("epoetina zeta") for their biosimilar product.
 (2) Obligation to prescribe and dispense only with the brand/ manufacturers name could be done at national level

Prescription/dispensing Policies Are A National Competency, But EMEA Has Also Issued Advice

National authorities regulate drug substitution



- Law on non-substitutability of biotech medicines**
 - 
French Parliament legislation bans automatic substitution based on precautionary principle
- Non-substitutable lists**
 - 
 In Spain, biotech drugs maybe included in non-substitutable list

- Both will prevent a pharmacist to overturn the decision of the physician to prescribe a specific biotech product**



London, 19 April 2007
Doc. Ref. EMEA/74562/2006

Questions and Answers on biosimilar medicines (similar biological medicinal products)

What is a biosimilar medicine?

A biosimilar medicine is a medicine which is similar to a biological medicine that has already been authorised (the 'biological reference medicine'). The active substance of a biosimilar medicine is similar to the one of the biological reference medicine. Biosimilar and biological reference medicines are used in general at the same dose to treat the same disease. Since biosimilar and biological reference medicines are similar but not identical, the decision to treat a patient with a reference or a biosimilar medicine should be taken following the opinion of a qualified healthcare professional.

The name, appearance and packaging of a biosimilar medicine differ to those of the biological reference medicine.

- Attached to individual biosimilar medicine's European Public Assessment Reports (EPARs)
- Sent to all Regulatory Agencies
- On EMEA website

Product Info Of Biosimilar Products Should Be Transparent And Clear

Physicians, pharmacists and patients should be aware of the data available to support a medicine

- EPAR, SmPC, PIL should be transparent and include the following:
 - Advice on interchangeability, i.e. approval does not mean that product interchangeability is acceptable
 - Unique clinical data for biosimilar product
 - Exact identification of the reference product
 - Description of the basis for approval and relevant issues for safe use of the biosimilar product
 - A statement defining those indications (if any) that are extrapolated

“Label” should contain summary of differences to reference product

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Naming Convention Should Consider Existing Guidance From WHO On Clear Identification

„The aim of the INN has been to provide health professionals with a unique and universally available designated name to identify each pharmaceutical substance. The existence...of INNs, is important for **clear identification, safe prescription and dispensing of medicines to patients**, and for **communication and exchange of information** among health professionals and scientists worldwide.“⁽¹⁾

Guidelines on the use of INNs for pharmaceutical substances

Clear identification

- Designed for chemically derived medicines
- No two biotech products are identical
- Minor differences can have clinical consequences

Safe prescription and dispensing

- Prescribing by INN strongly encouraged in many countries
- INN often used as signal for substitution
- Similar biotech medicines are not interchangeable

Communication and exchange of information

- INN is crucial in adverse event reporting
- “...to support pharmacovigilance monitoring, the specific medicinal product given to the patient should be clearly identified.”⁽²⁾

Additionally, brand name not mandatory in EU law for any type of medicine

(1) WHO Publication WHO/PHARM S/NOM 1570, 1997

(2) Guideline on Similar Biological Medicinal Products, 30 Oct 2005

Proposal: A Distinct INN For All Biotech Medicines

A common stem and unique qualifier

Approach

- New products = new name
- Identical products = identical name
- Similar products = similar name

Medicine type

New chemical or biological entities
Small molecule generics
Biosimilars

- **Guarantees clear identification**
- **Ensures safe prescription and dispensing of medicines to patients**
 - INN is not misused as a signal for substitution
- **Ensures consistency with WHO principle – different medicine = different name**

Each biotechnology-derived drug produced by a different manufacturer should be given a name composed of a common stem with a unique qualifier

Pharmacovigilance Will Be A Challenge..

- No brand name required...
 - ...And we have the first biosimilar without brand already:
Epoetin Alfa Hexal...
- In 2007 already 8 ESAs on the market in Europe (and still two to come)
 - Various INNs for EPOs
 - EPO Delta
 - EPO Beta
 - EPO Alfa - originator
 - 3 EPO Alfa – biosimilar
 - 2 EPO Alfa biosimilar to come – EPO Zeta
- Increasing number of countries ‘encourage’ INN prescription

European Commission Recognizes Need For Action



EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL
Consumer goods

Brussels, 31 JUL 2007
DG ENTR/F2/NR/DN D25244 (2007)

Subject: Adverse reaction reporting and traceability of glycoproteins

Dear Heads of Agencies,
Dear Members of the Pharmaceutical Committee,

At the meeting of 18-21 June 2007, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has adopted three positive opinions for the following medicinal products: Binocrit (Epoetin alfa), from Sandoz GmbH, Epoetin alfa Hexal (Epoetin alfa), from Hexal Biotech Forschungs GmbH, and Abseamed (Epoetin alfa), from Medice Arzneimittel Pütter GMBH & Co¹. All three products are claimed to be similar to the reference product Eprex/Erypo (Epoetin alfa), from Johnson&Johnson. All these four products are erythropoietins and have the same International Non-proprietary Name (Epoetin alfa). The procedure for the adoption of the decision on the granting of marketing authorisation for the three 'biosimilar' medicinal products (Binocrit, Epoetin alfa Hexal and Abseamed) is still ongoing.

Glycoproteins in general and erythropoietins in particular are complex biological substances which bear inherent variability at the molecular level, especially as regards glycosylation. Seemingly minor changes in the manufacturing process can affect the safety/efficacy profile of medicinal products containing glycoproteins as an active substance. The cases of Pure Red Cell Aplasia (PRCA) with Eprex highlight the importance of a pharmacovigilance system that enables regulatory authorities to know which specific medicinal product has been given to which patient, and when.

The Commission has already announced its commitment to improve and strengthen the Community pharmacovigilance system, with a legal proposal foreseen in 2008². It is intended that this initiative will address the specific issue of pharmacovigilance in relation to biological medicinal products such as erythropoietins.

¹ <http://www.emea.europa.eu/pdfs/human/press/pr/26755607en.pdf>

² http://ec.europa.eu/enterprise/pharmaceuticals/pharmacovigilance_act/index.htm

Heads of Medicines Agencies (Human) – by e-mail
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“The cases of [...] PRCA [...] highlight the importance of a pharmacovigilance system that enables regulatory authorities to know which specific medicinal product has been given to which patient, and when.”

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“It is intended that this initiative will address the specific issue of pharmacovigilance in relation to biological medicinal products such as erythropoietins.”

“Member States regulatory authorities to take any necessary measures to ensure that the reporting and pharmacovigilance system [...] :

- *includes, in the case of glycoproteins, a method to link suspected adverse reaction reports to specific products (such as a **unique product identifier**);*
- *ensures that prescribing doctors know which glycoprotein has been given to their patient in cases where reporting relies on prescribing doctors, and taking into account that substitution may occur in some systems at the level of pharmacies.*

Pharmacovigilance Systems Should Differentiate Between Different Biotech Products

Ensure traceability

Company and regulatory agency AE reporting systems should distinguish one manufacturers product from another

- Complex, if biosimilars have same INN as innovator
- AE reports are often incomplete eg. lot number missing
- Peel-off labels, “blood-product” tracing system

Prevent repeated, uncontrolled switching

Repeated, uncontrolled product switching will confound accurate pharmacovigilance

- Occasional changes are inevitable or necessary in chronic therapy
- Local practice should prevent repeated, uncontrolled changes for biotechnology medicines

Need To Address Open Issues To Ensure Patient Safety In Clinical Practice

No automatic substitution

Physician should always be involved in decision to dispense

- Generic substitution rules should not apply to biotech medicines, including biosimilars
- Explicit prior consent of the physician to substitute
- Impact on pharmacovigilance

Transparent Product Info

Biosimilar EPA/SmPC/PIL should provide clear and transparent information

- Advice on interchangeability (ie.under strict medical supervision)
- Unique clinical data (safety and efficacy)
- Identify reference product

Distinct naming (INN)

All biotech/derived therapeutic proteins should have distinct INNs

- If no distinct INN for biotech products, different identification and subscription rules need to be designed

Ensure accurate pharmacovigilance

EU pharmacovigilance systems should cope with biosimilar introduction

- Traceability should be ensured
- Repeated, uncontrolled switching should be prevented