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**Biogeneric  
Drug Development  
- A European Perspective -**

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# Overview

- **Introduction & company profile**
- Market potential for Bx
- Definition of "biogenerics"
- Legal situation in the EU
- Targets: The first & second wave
- Practical aspects in development
- Entrance barriers and risks
- Conclusions

# Introduction

## - Company Profile BGX-



- Under 100% ownership of ratiopharm (rtp)
- Founded in June 2000
- Located in the Bioregion Rhine-Neckar
- Currently 35 employees
- Own biotech laboratories
- Development and licensing of biotech drugs
- Access to knowledge and network of rtp
- Covers all steps of product development

- **Molecular biology**
- **Cell biology**
- **Process development**
- **Protein chemistry**

- **Preclinical/clinical development**
- **Regulatory affairs**
- **Patent affairs**
- **Business development**

## Company Profile rtp

**Founded 1974 in Germany, 1st generic Company**  
**Headquarter in Ulm, Germany**  
**Market leader in generics in Europe (up to recently)**  
**No. 3 in generics world wide**  
**Present in 24 different countries**  
**Biggest pharmaceutical manufacturer in Germany**  
**3,170 different products**  
**322 million packs a year**  
**1.1 billion Euro turnover in 2003**

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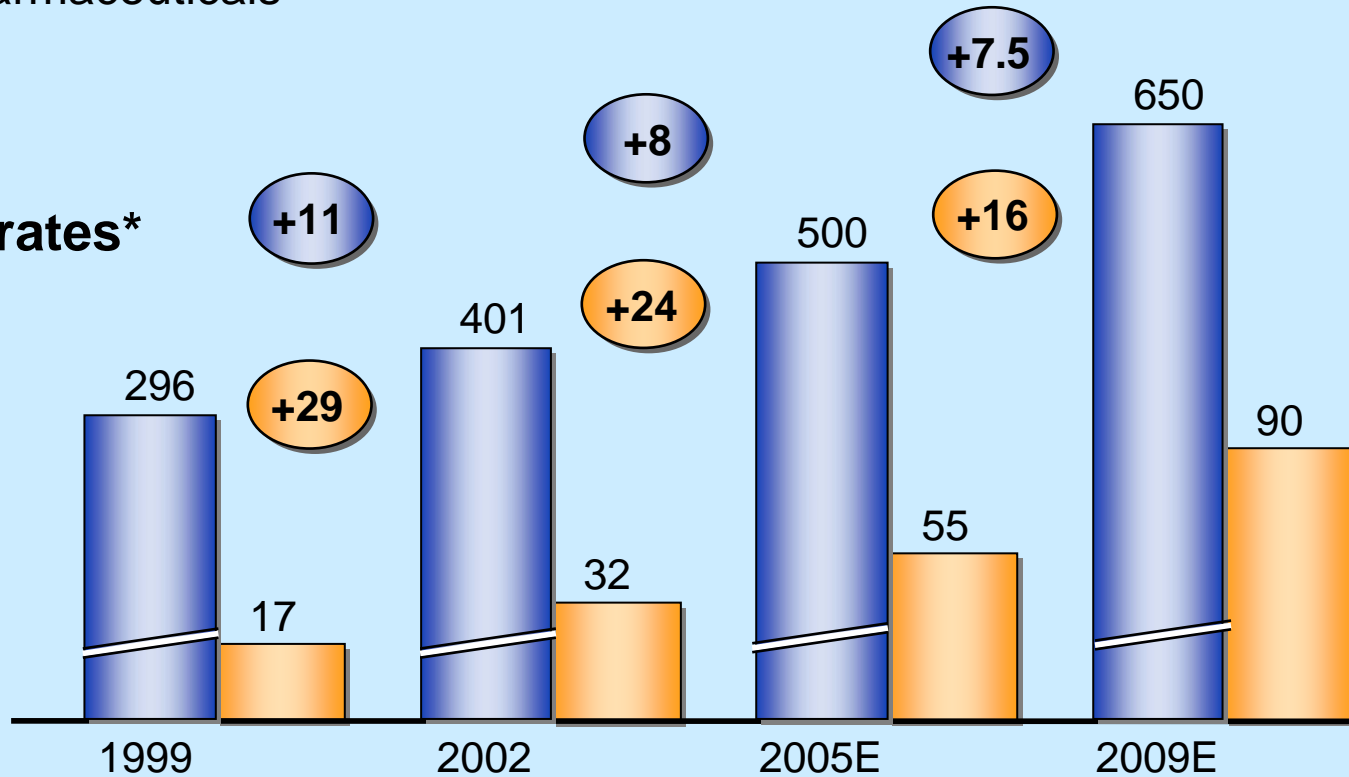
# Market Potential of Biopharmaceuticals

## The Global Pharma Market

■ Total Market  
■ Biopharmaceuticals

Annual  
growth rates\*

Sales\*  
in billion  
US\$

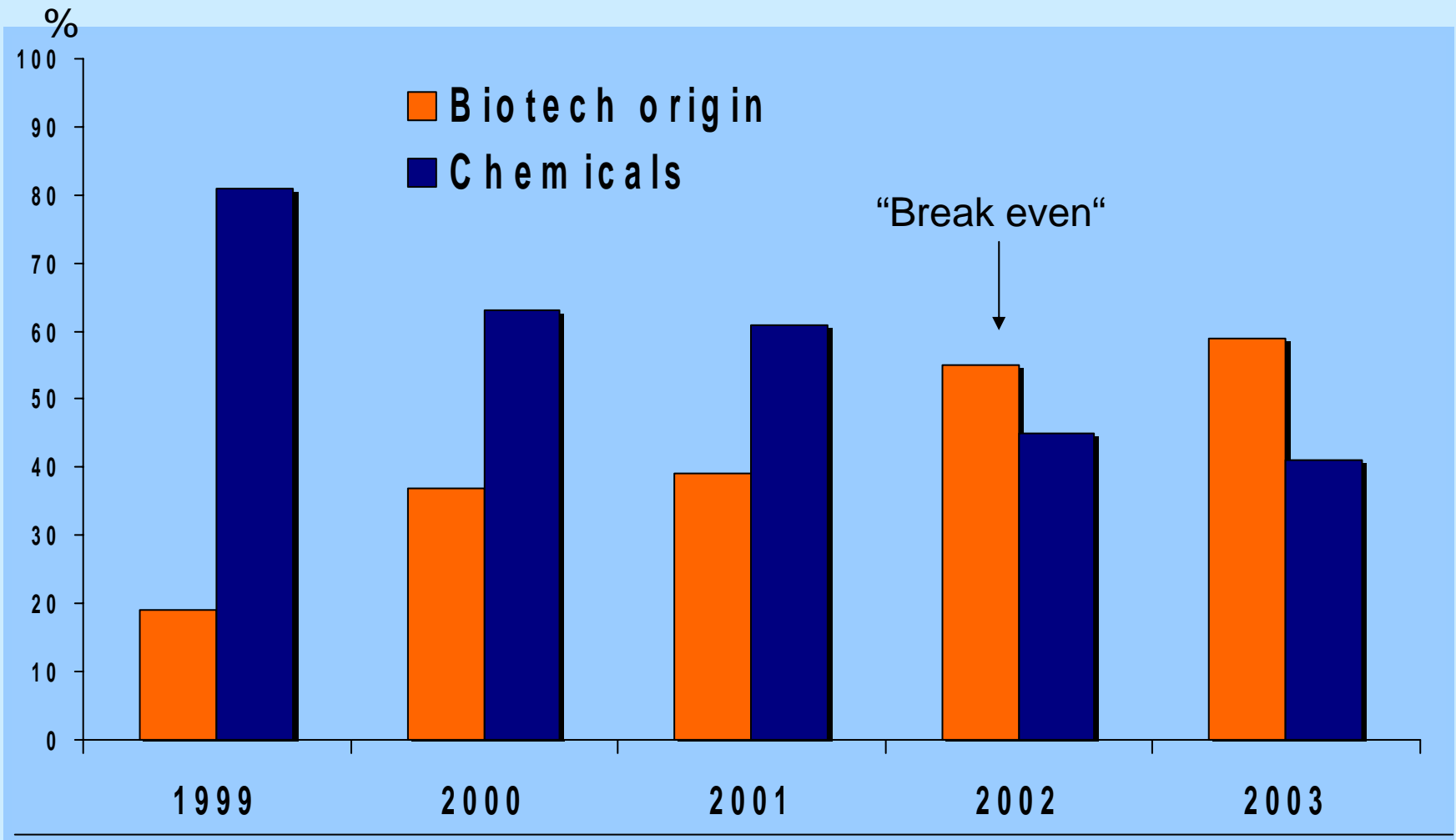


**In 2005 appr. 50% of new approved drugs will be of biotech origin**

\* Rx; Source: IMS Health, Frost&Sullivan

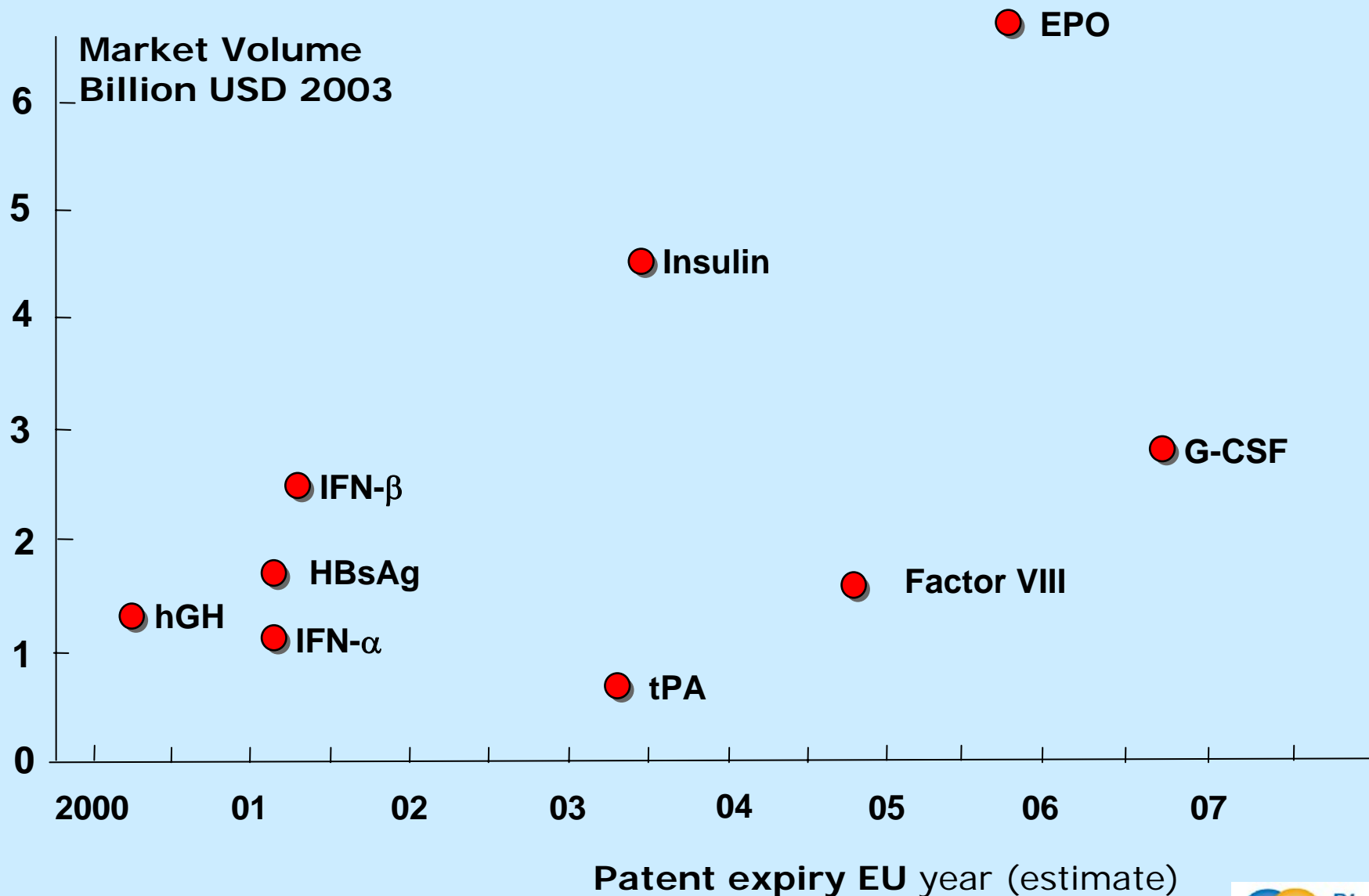


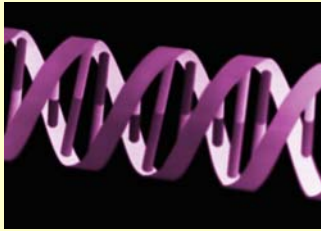
# Approvals of New Pharmaceuticals Percentage of Biotech Products (US)



Source: ChemManager 21/2004

# Biotech Products: Patent Expiries until 2007



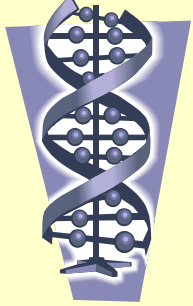


# Market Potential Summary

- In 2003 appr. 50 recombinant protein drugs are approved in the EU, some are blockbusters
- These drugs gain more than 10% of the total pharmaceutical market
- The biopharmaceuticals represent a fast growing market segment
- In this year more than 50% of newly approved drugs will be derived from biotechnology
- The first wave of therapeutic proteins runs off patent protection within this decade
- Therefore, the protein drugs are highly attractive for generic manufacturers
- The strong competition between generic companies extends to biogenerics

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# Definition

## Term "Biogenerics"

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The commonly used term **"biogenerics"** is not appropriate in the eyes of regulatory authorities.

The actual wordings according to recent guidelines are:

- **"similar biological medicinal products"** or
- **"biological medicinal products claimed to be similar"** or abbreviated
- **"biosimilar products"**



# Definition

## Classical Generics (Regulatory)

### Revised EU-Directive 2001/83/EC:

Art. 10.2.b: **Generic medicinal product** shall mean a medicinal 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. (...continues)

Source: Official Journal of the European Union C297 (9.12.2003)



# Definition

## Classical Generics (Cx) vs. Biogenerics (Bx)

Definitions (commercial)	Cx	Bx
Launched after patent expiry	yes	yes
Offered with a lower price	yes	yes <sup>1)</sup>
Sold under the generic name (INN) <sup>2)</sup>	yes <sup>3)</sup>	yes/no <sup>3)</sup>
No (little) product-specific promotion	yes	no

1) Bx: Moderate price reduction only

2) INN = International non-proprietary name = generic name

3) Cx: Branded generics are exceptions; Bx: Brands are more likely

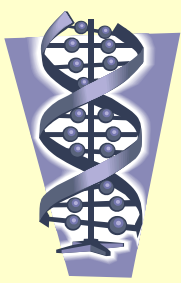


# Definition

## Classical Generics (Cx) vs. Biogenerics (Bx)

Definitions (regulatory)	Cx	Bx
Essential similarity of the API	yes	no <sup>1)</sup>
Approved without independent proof of efficacy and safety (bioequivalence only)	yes	no <sup>2)</sup>
Approval procedure is facultative	yes	no <sup>3)</sup>
Abridged application dossier	yes	no <sup>4)</sup>

- 1) Bx: biosimilarity instead of essential similarity, to be confirmed by preclinical/clinical studies
- 2) Efficacy and safety to be proven by clinical studies
- 3) Centralised procedure is mandatory for biological products
- 4) Cx: Reference to the originator's dossier; Bx: Full dossier required, however not all safety and efficacy studies are required



# Definition of Bx Summary

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## **"Biogenerics" are ...**

- ...copies of therapeutic proteins
- ...launched after patent expiry of the API
- ...moderately cheaper than the original products

## **The EMEA approval requires ...**

- ...the centralised procedure
- ...a complete dossier (all modules)
- ...significant clinical studies (efficacy and safety)

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# Legal Situation (EU)

## Legal Frameworks

Several legal frameworks rule or affect the development of biological medicines:

-  **ICH-guidelines (ICH Tripartite Documents)**
-  **EC Directives (+ Annexes)**
-  **CPMP/CHMP Guidelines**
-  **National Medicinal Laws**
-  **European Patent Convention (EPC)**
-  **National Laws on Intellectual Property**



# Legal Situation (EU) "Comparability Guideline"

- 📄 EMEA/CPMP/BWP/3207/00/Rev1 (quality)
- 📄 EMEA/CPMP/3097/02 (non-clinical/clinical)

**Guideline on comparability of medicinal products containing biotechnology-derived proteins as active substance**

**Comparability exercise for...**

- (1)...a change introduced in the manufacturing process**
- (2)...a product claimed to be similar to another one already authorised**



# Legal Situation (EU) "Pharma Review"

## Revised EU-Directive 2001/83/EC:

Art. 10.4: Where a biological medicinal product which is similar to a reference biological product does not meet certain conditions in the definition of generic medicinal products, owing to, in particular, **differences in manufacturing process** of the biological medicinal product and the reference biological medicinal product, the results of appropriate **pre-clinical tests or clinical trials** relating to these conditions must be provided. The results of other tests and trials from the reference medicinal product's dossier shall not be provided.

Source: Official Journal of the European Union C297 (9.12.2003)



# Legal Situation (EU) "Annex I"

## Commision Directive 2003/63/EC = Annex I to Directive 2001/83/EC:

Part II.4: Similar biological medicinal products: ... Information to be supplied shall not be limited to Modules 1, 2 and 3 (pharmaceutical, chemical and biological data), supplemented with bio-equivalence and bio-availability data. The type and amount of additional data (i.e. **toxicological and other non-clinical and appropriate clinical data**) shall be determined on a **case by case** basis in accordance with relevant scientific guidelines.

Source: Official Journal of the European Union L159 (27.6.2003)



# Legal Situation (EU) "Draft Guidelines"



**EMEA/CHMP/437/04/16.11.04**

## **Draft Guideline on similar biological medicinal**

- **Reiteration of the biosimilar approach**
- **Closed for comments on February 2005**
- **Accompanied by four concept papers:**
  - (1) Recombinant human growth hormone
  - (2) Recombinant human insulin
  - (3) Recombinant human erythropoietin
  - (4) Recombinant human G-CSF



# Legal Situation (EU) Comparability for Bx?

There are severe hurdles for a generic approach or a pure comparability exercise:

- Bx will be produced with different methods and processes compared to the reference product
  - Bx will possess modified formulations (patent reasons)
  - Bx developers have neither access on data nor on material from intermediate steps of the originator's process
- ➔ The CHMP authorities may regard each Bx as unique and handle the approval case by case
- ➔ Substantially abbreviated clinical programmes for Bx seem currently not realistic. Preclinical and clinical trials demonstrating efficacy and safety are mandatory (modules 4 and 5)



# Legal Situation (EU) Approval of Biologics

The quality of a biological medicinal product is based on...

- (1)...the product specifications and...
- (2)...the manufacturing process, including...
- (3)...the production site (facility)

**These three parts build an inseparable package for the approval!**

→ Change of the process or transfer to another production site require the comparability exercise and a revised approval (variation)

→ This strongly influences the development strategy of Bx



# Legal Situation (EU)

## Approval of Bx: Summary

- Several legal frameworks have been revised recently and mention for the first time "similar biological medicinal products" (biogenerics)
- Bx will not be regarded and treated as "essentially similar products" (generics) by the authorities
- Bx require independent preclinical and clinical studies, i.e. all modules of the dossier
- A comparability exercise seems possible, however this would not overcome the requirement of preclinical and clinical studies
- The degree of abbreviations in the non-clinical and clinical programme is uncertain as the authorities will treat the Bx "case by case"



# Legal Situation (EU) Biotech Patents

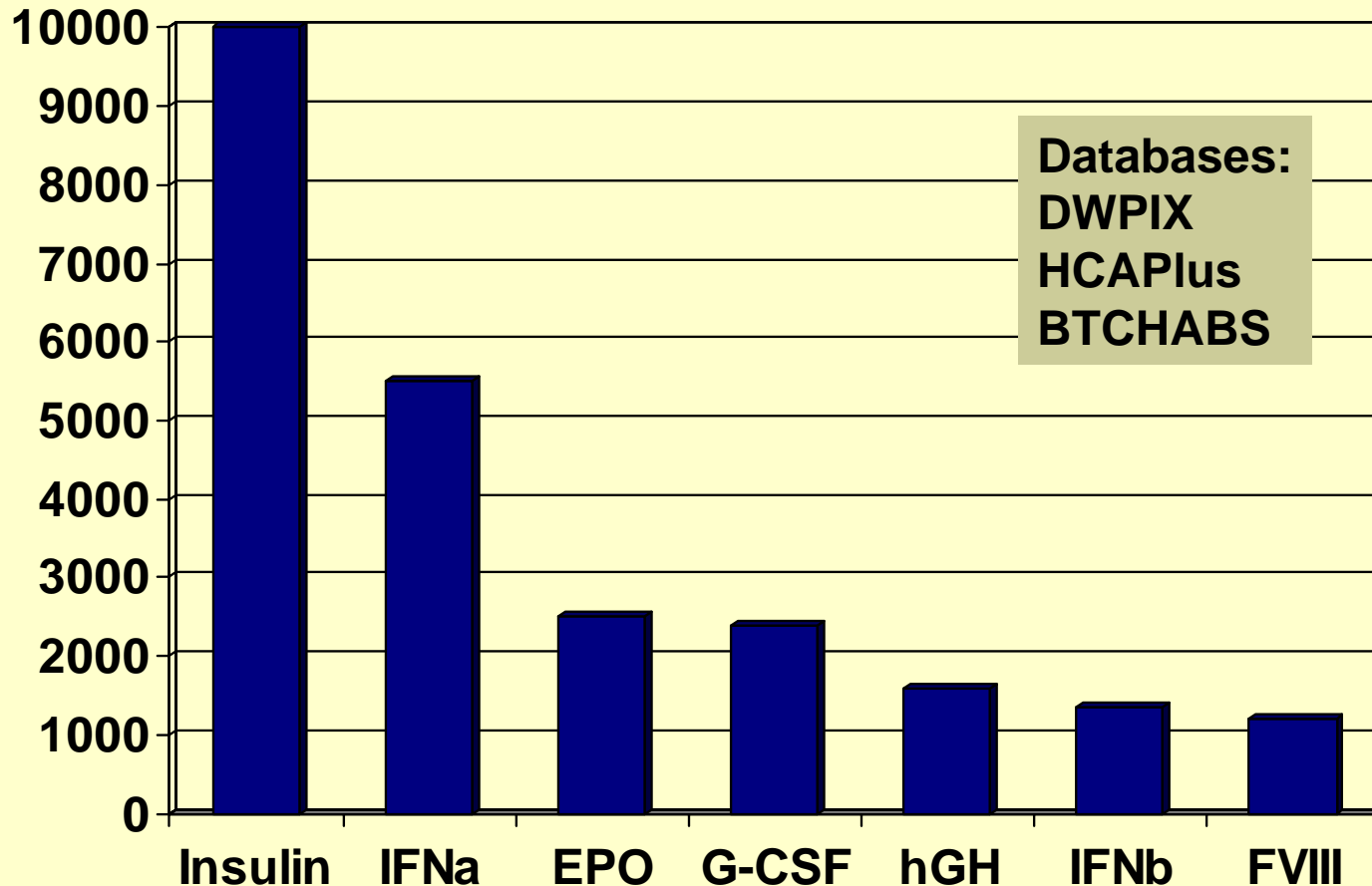
The Bx developers are faced with complicated patent situations:

- The total number of patents for a given target protein is incredibly high
- In many cases the patent claims are difficult to interpret
- The patents are often related to specific methods rather than to the substance. The proteins from natural sources were often state of the art
- No monopolized market or patent exclusivity exists for the first wave proteins. Two or more companies developed similar products in parallel



# Legal Situation (EU) Patent Searches

Number of hits in specific patent searches





# Legal Situation (EU) Biotech Patents

Two categories of patents exist:

## (1) Basic patents

- Define project time lines and market entries for Bx
- Circumvention not possible
- Claims: Substance, DNA-sequence, aa-sequence, recombinant expression,...

## (2) Secondary patents

- Circumvention possible (doctrine of equivalence!)
- Claims: Process, formulation, dosing regime, improved quality, indication,...
- **Secondary patents are a dangerous mine field!**
- **Risk assessment vs. safe harbour strategies**



# Legal Situation (EU)

## Experimental Use Exemption

- Nearly all national patent laws include an "experimental use exemption" or a "research exemption"
- Different scopes of these exemptions exist in different countries (e.g. Germany: Clinical trials decisions)
- Additional rulings for pharmaceuticals ("early working clauses") are widespread (e.g. USA: Hatch-Waxman Act)
- In the best case, the complete development of a generic medicine is allowed (so-called "Roche-Bolar countries" e.g. Canada, Poland, Hungary).
- Until recently, there was no harmonised ruling for generic development within the EU



# Legal Situation (EU)

## EU Roche-Bolar Clause

**Directive 2004/27/EC of March 31, 2004  
amending Directive 2001/83/EC**

Art. 10.5: Conducting the necessary studies and trials with a view to the application of paragraphs 1, 2, 3 and 4\* to a generic medicinal product and the consequential practical requirements **shall not be regarded as contrary to patent rights** or to supplementary protection certificates for those medicinal products.

**\* [§4: Similar biological medicinal products]**

Source: Official Journal of the European Union C297 (9.12.2003)



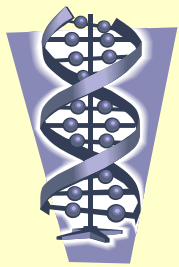
# Legal Situation (EU)

## Roche-Bolar: Summary

- The Eur. Parliament finalised in 2<sup>nd</sup> lecture a compromise for a Roche-Bolar (RB) ruling
- This RB Clause covers biogenerics too
- The revised Pharma Legislation was adopted along with the EU enlargement (May 1<sup>st</sup>, 2004)
- Transportation into National Laws has to be performed within 18 months
- National deviations are possible (innovator lobby)
- Ruling will be effective latest in November, 2005
- This is a milestone for the generic industry

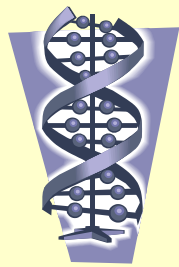
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# First Wave : Overview (Launch < 2010)

- Erythropoietin (EPO)
- Granulocyte-colony stimulating factor (G-CSF)
- Granulocyte/macrophage-colony stimulating factor (GM-CSF)
- Human growth hormone (hGH)
- Insulin
- Hepatitis B virus surface antigen (HBsAg)
- Factor VIII (FVIII)
- Interferon alpha (IFN $\alpha$ )
- Interferon beta (IFN $\beta$ )

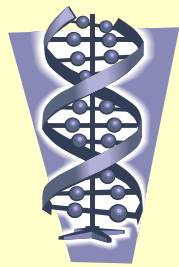


# First Wave : EPO

## Possible Candidates

Two 1<sup>st</sup> generation products launched in the EU:

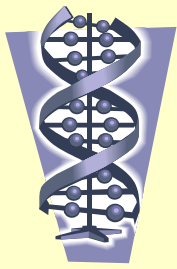
<b>Branded product</b>	<b>Eprex®</b>	<b>NeoRecormon®</b>
<b>Originator</b>	<b>Kirin-Amgen, Johnson&amp;Johnson</b>	<b>Genetics Institute Roche</b>
<b>API (INN)</b>	<b>Epoetin alpha</b>	<b>Epoetin beta</b>
<b>Launch EU</b>	<b>1988</b>	<b>1992</b>
<b>Expression system</b>	<b>Mammalian (CHO)</b>	<b>Mammalian (CHO)</b>
<b>Patent expiry (excl. SPC)</b>	<b>2005</b>	<b>2005</b>
<b>Major indications</b>	<b>Renal anemia CT-induced anemia</b>	<b>Renal anemia CT-induced anemia</b>



# First Wave : G-CSF Possible Candidates

Two 1<sup>st</sup> generation products launched in the EU:

Branded product	<b>Neupogen®</b>	<b>Granocyte®</b>
Originators	Kirin-Amgen (Roche)	Chugai (Aventis)
API (INN)	Filgrastim	Lenograstim
Launch EU	1991	1993
Expression system	Bacterial (E.coli)	Mammalian (CHO)
Patent expiry (excl. SPC)	2006	2006
Major indications	CT-induced neutropenia, BMT	CT-induced neutropenia, BMT

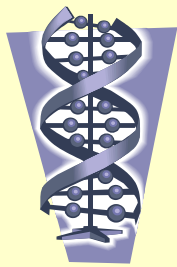


# Second Wave : Overview

## Launch > 2010

- **Mutins (EPO, Insulin)**
- **PEGylation (IFNalpha, G-CSF, EPO)**
- **TNF inhibitors (Enbrel)**
- **New indications (GM-CSF, G-CSF)**
- **"Me too" monoclonal antibodies\***

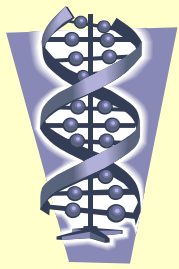
\* Biosimilar approach is not possible



# Second wave: EPO mutein

**One long-acting EPO mutein launched in the EU:**

<b>Branded product</b>	<b>Aranesp®</b>
<b>Originator</b>	<b>Amgen</b>
<b>API (INN)</b>	<b>Darbepoetin alpha</b>
<b>Launch EU</b>	<b>2002</b>
<b>Expression</b>	<b>Mammalian (CHO)</b>
<b>Patent expiry (excl. SPC)</b>	<b>2014</b>
<b>Major indications</b>	<b>Renal anemia CT-induced anemia</b>



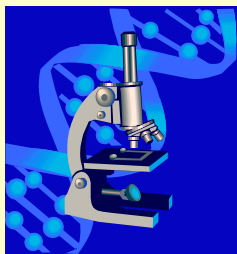
# Second wave: PEGylated G-CSF

**One long-acting PEGylated G-CSF launched in the EU:**

<b>Branded product</b>	<b>Neulasta®</b>
<b>Originator</b>	<b>Amgen</b>
<b>API (INN)</b>	<b>Pegfilgrastim</b>
<b>Launch EU</b>	<b>2002</b>
<b>Expression system</b>	<b>Bacterial (E.coli)</b>
<b>Patent expiry (excl. SPC)</b>	<b>2015</b>
<b>Major indications</b>	<b>CT-induced neutropenia</b>

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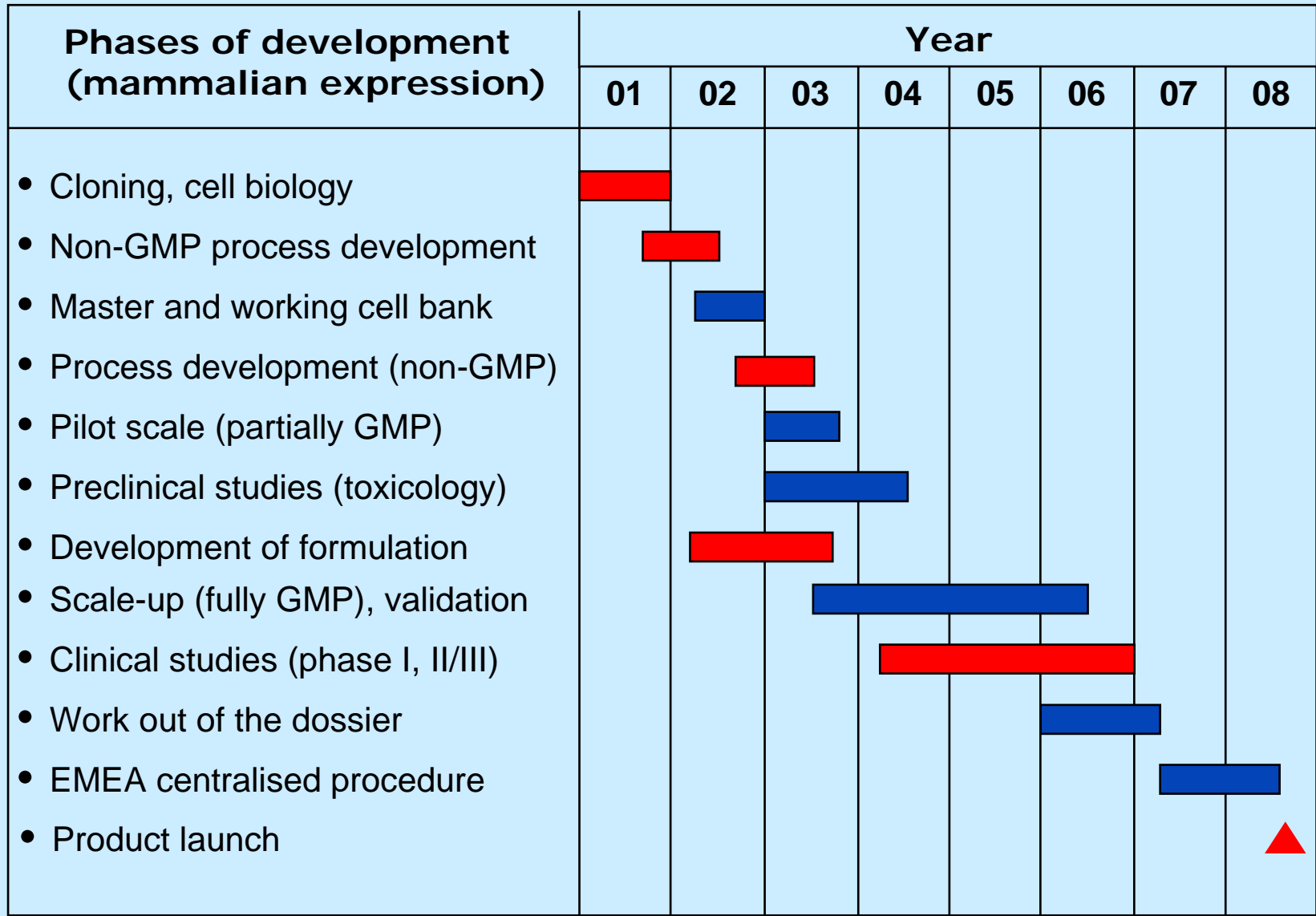


# Practical Aspects Development of Bx

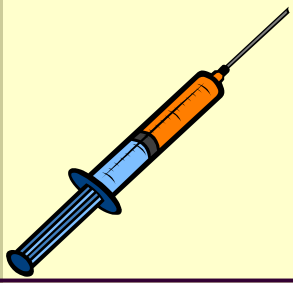
**The projects consist of six blocks:**

- (1) Molecular biology: cloning, expression, cell banks**
- (2) Process development: USP and DSP, scale-ups, GMP, validation**
- (3) Development of analytical methods: GLP, validation, specifications**
- (4) Pharmaceutical development: Formulation, fill & finish, GMP, validation, primary and secondary packaging, stability**
- (5) Preclinical development: PK/PD models, toxicology, immunogenicity**
- (6) Clinical development: Efficacy and safety**

# Development of a Biosimilar Product (Time Schedule)

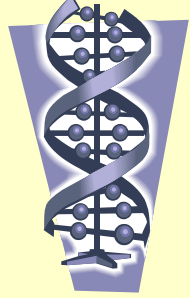


**Strongly influenced by patent department !**



# Practical Aspects Some Key Issues

- **Biosimilar or stand alone approach?**
- **Which reference product?**
- **Toxicology with or without comparator?**
- **Phase I: Bioequivalence yes or no?**
- **Phase III: Equivalence or non-inferiority?**
- **Phase III: Additional placebo arm?**
- ➔ Pre-clinical studies have to fulfill requirements of CHMP and national laws (allowance of clinical trials)
- ➔ Clinical study program has to be in agreement with CHMP Scientific Advice Committee prior to onset
- ➔ Phase III is the most cost-intensive part of the development



# Practical Aspects Summary

- The technical development of a Bx follows the same route as for a new biological
- The requirements are ruled in detail by the ICH and CHMP guidelines
- Advantages for Bx developers are: Monographs (Eur.Ph.), commercial standards, commercial assays, historical data (literature), available reference product, and less risk for failures
- Abbreviations to a certain extent are possible in preclinical and clinical development, e.g. phase II (dose finding) seems not necessary at all
- The design of preclinical and clinical programs has to be discussed with authorities (case by case) in early stages

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# Entrance Barriers and Risks



**Bx**



**Cx**

•Strategy	Not established	Well established
•Approval (EMA)	Case-by-case	Abridged, with reference
•Clinical program	Large, phase I and III	Small, bioequivalence
•Duration of clinical trials	2 - 3 years	< 1 year
•Total development time	7 - 9 years	2 - 5 years
•Total project costs (EUR)	35 – 90 millions	0.5 - 3 millions
•Return of investment	Late, risky	Early, less risks
•Innovation potential	High	Low
•Complexity of projects	Very high	Low
•Patent situation	Difficult, uncertain, risky	Less complex, predictable

# KEY FACTORS FOR SUCCESS IN THE Bx-BUSINESS

## Biogenics

- Integrated project management
- Cross-functional project planning

**Project management**

- Regulatory affairs
- Excellence in development
- Patent expertise
- Practical biotech know how

**Excellence in Biotech**

- Task force patent litigation
- Contract- and deal-making capabilities

**Legal competence**

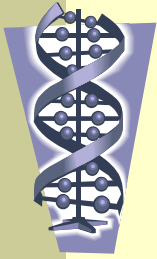
- Co-financing
- Risk-spread
- Global net of experts
- Own patent portfolio

**Alliances and partnering management**

- Strategic portfolio planning
- Licensing
- Global distribution network
- High market penetration

**Marketing & distribution power**

**A successful Bx company will cover all fields by its own**



# Entrance barriers and risks Summary

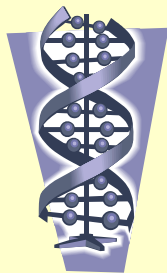
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The major hurdles for generic companies to enter the Bx business are ...

- 1) ...the lack of biotech know how
- 2) ...the significant amount of investment

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# Conclusions

- Bx differ considerably from Cx. With respect to costs and timelines the projects are more close to new developments
- Despite recent up-dates in directives, the regulatory situation is still unpredictable ("case by case")
- The first wave of Bx candidates will include several big blockbuster products
- Within the next few years, numerous of Bx products will apply for market authorisation at the EMEA
- Life-cycle strategies of the originators are obvious and increase the risk for Bx developers
- The competition between originators and generic companies put pressure on both side to innovate. This results in benefits for the patients and the health system