

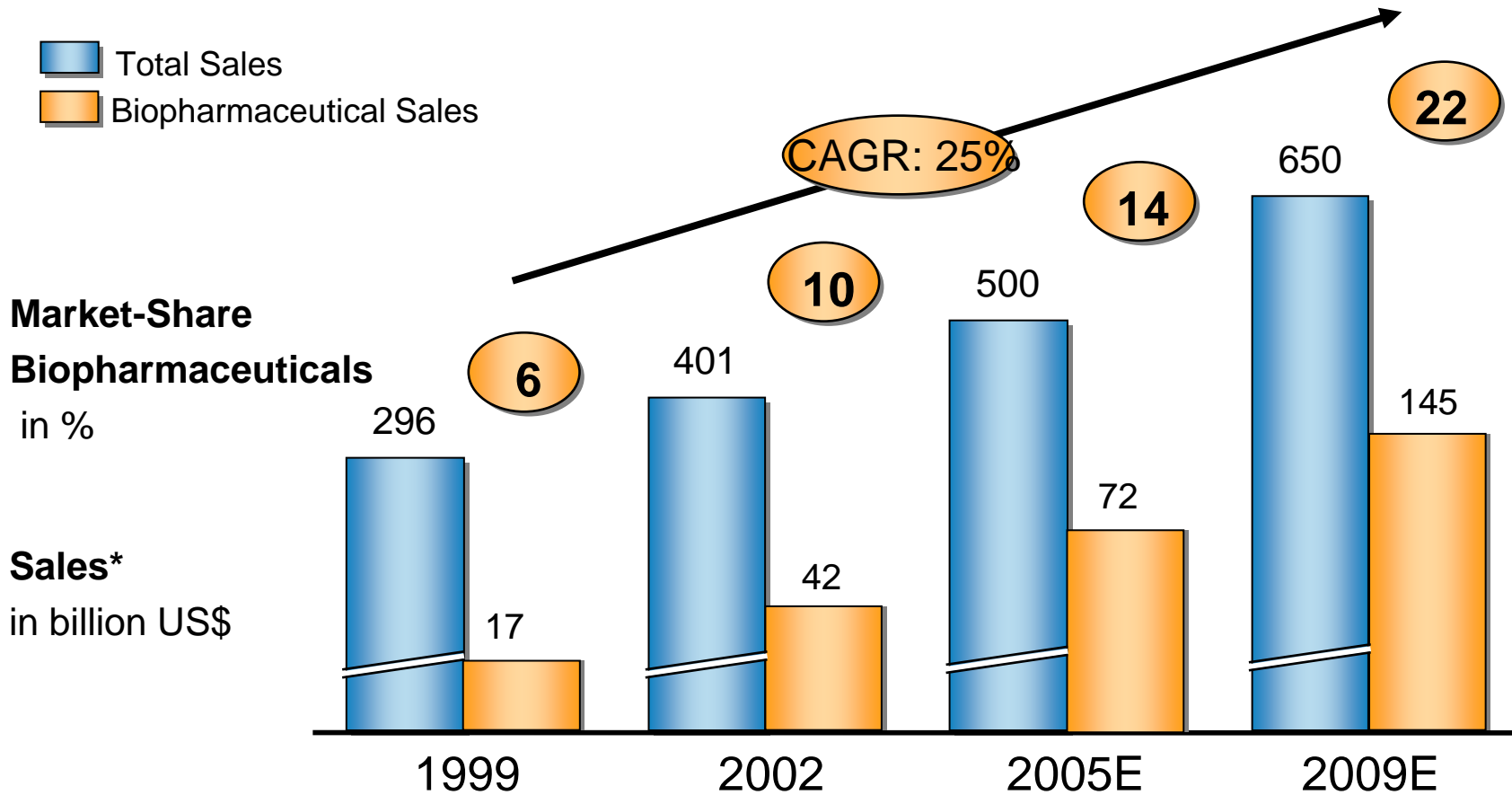
Understanding how BioGeneriX has successfully developed a commercial biogeneric

Biogenerics, 29th – 31st March 2006, Novotel London

Dr. Thomas Brennecke
Head Business Development
BioGeneriX AG

- Identifying strategies necessary for developing biogenerics
- Guidance how to address current barriers
- Learning lessons from BGX

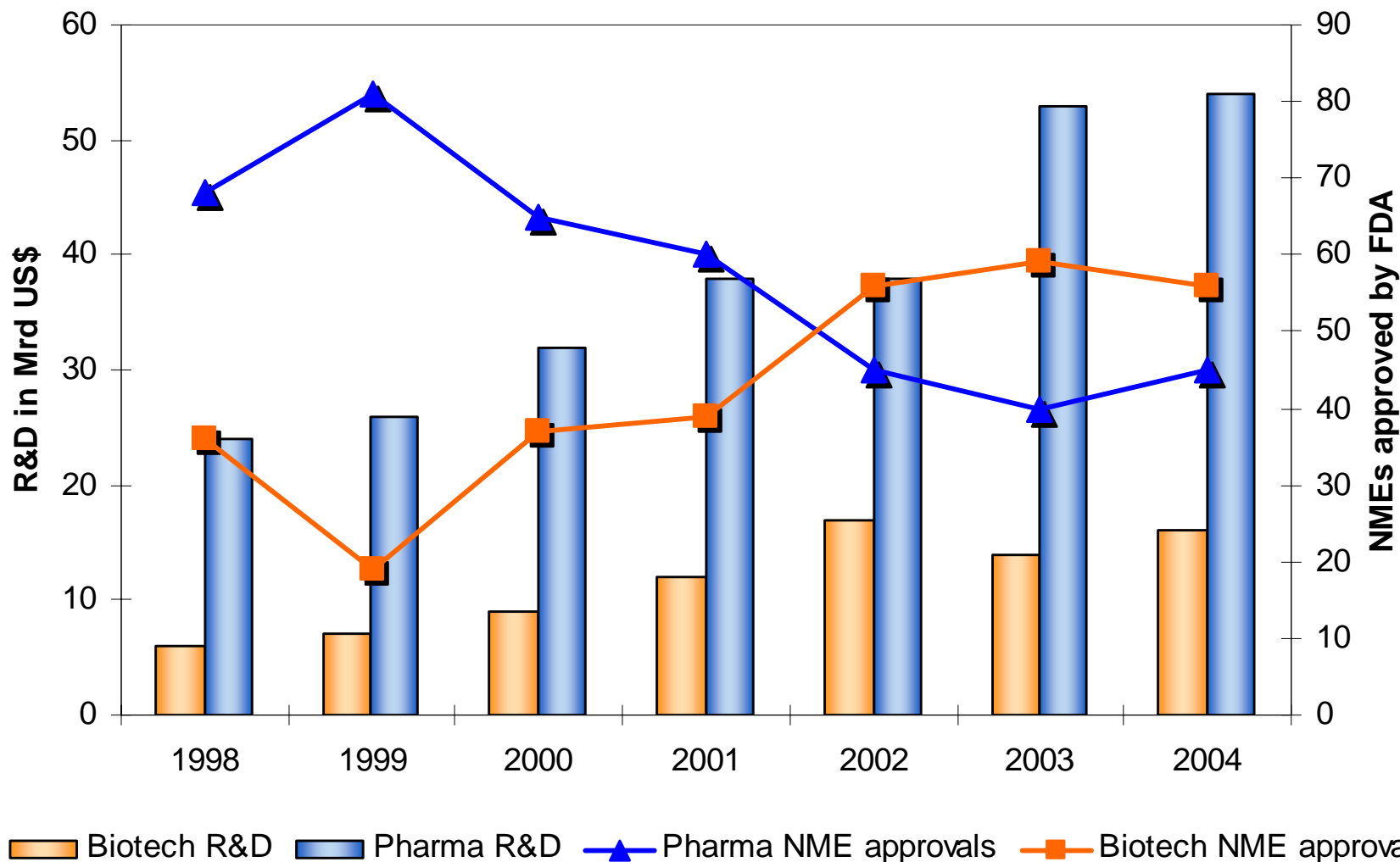
OPPORTUNITY: THE GLOBAL PHARMA MARKET



Biologics are growing at twice the rate of „ Small Molecules“

*Rx
Source: IMS Health, Ernst&Young; BioGeneriX Forecast

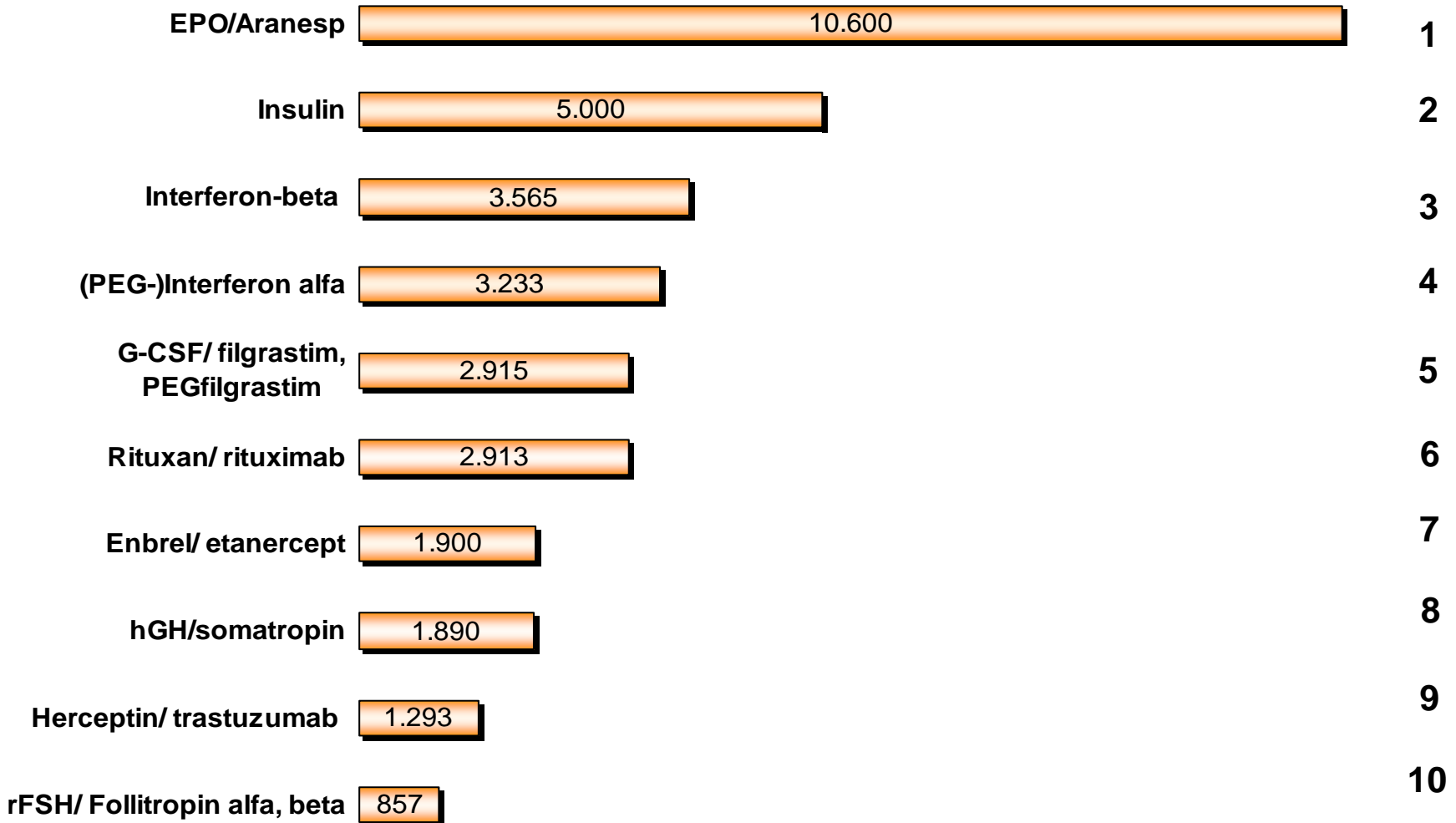
Market Dynamics: The Innovation Gap (US)



Biotech drugs make up more than 50% of new molecular entities

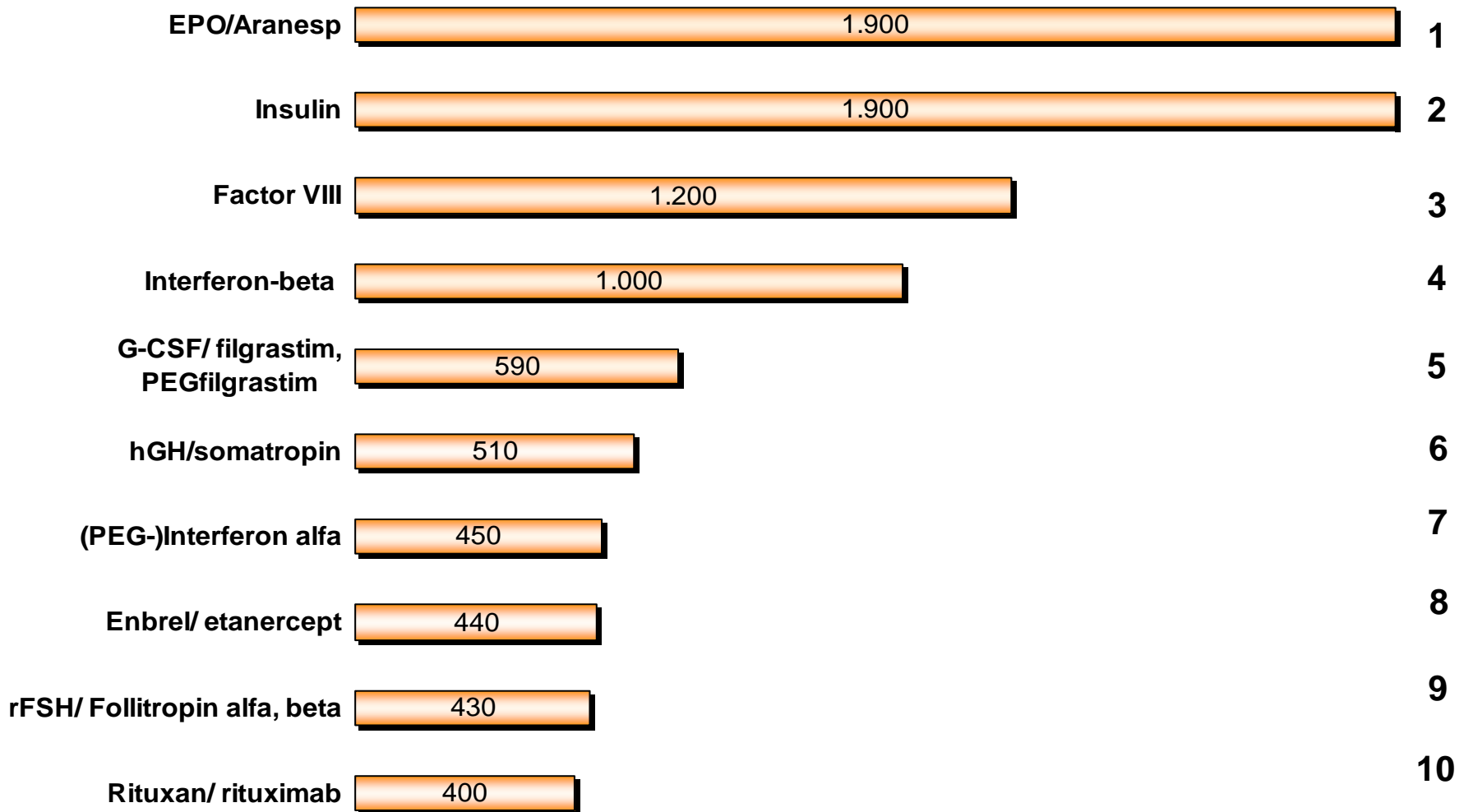
Source: FDA/ Ernst&Young, Global Report 2005

Top 10 Global Biotech-Products 2004 in m\$



Biotech drugs offer a huge market potential, also after patent expiry

Top 10 European Biotech-Products 2004 in m\$

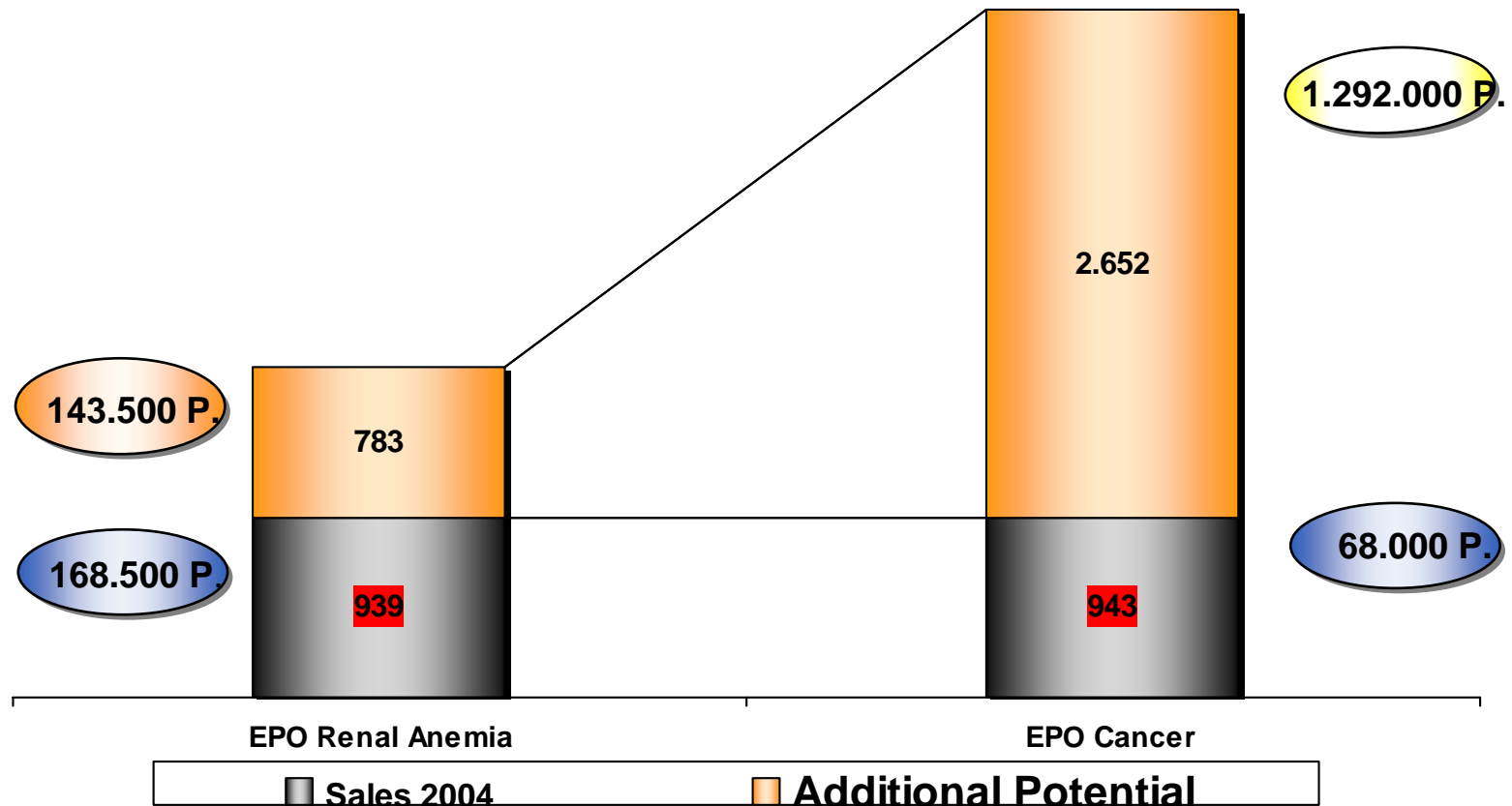


The average sales figure of a top10 Biotech product in Europe is ~ 900 Mio €

Source: IMS Health/ Company Reports/BGX estimates

How to open up the market completely?

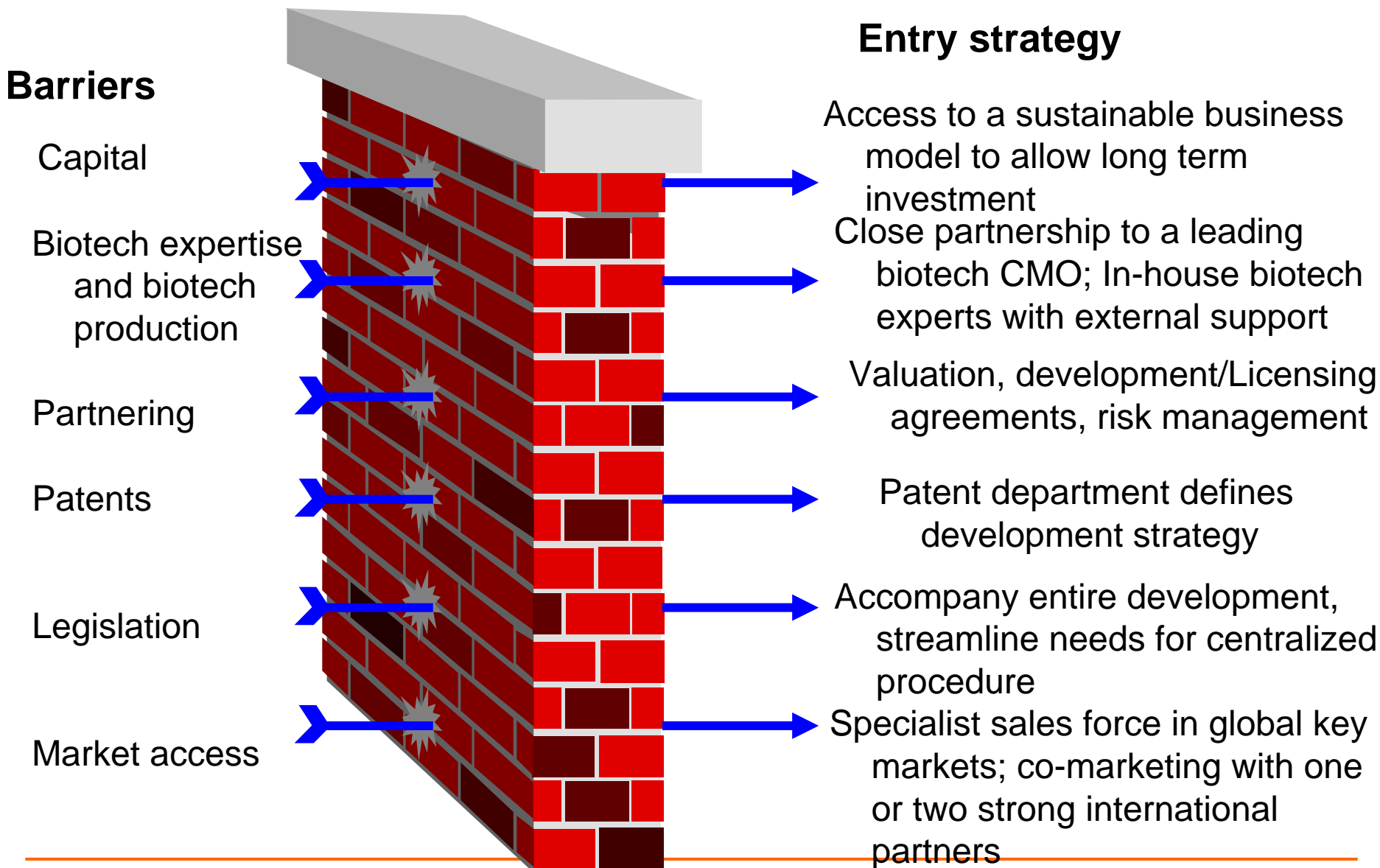
EU - EPO Sales 2004 and additional potential due to Patient Prevalence and Treatment Rate (in Mio €)



Source: IMS/ Patient Population Calculation

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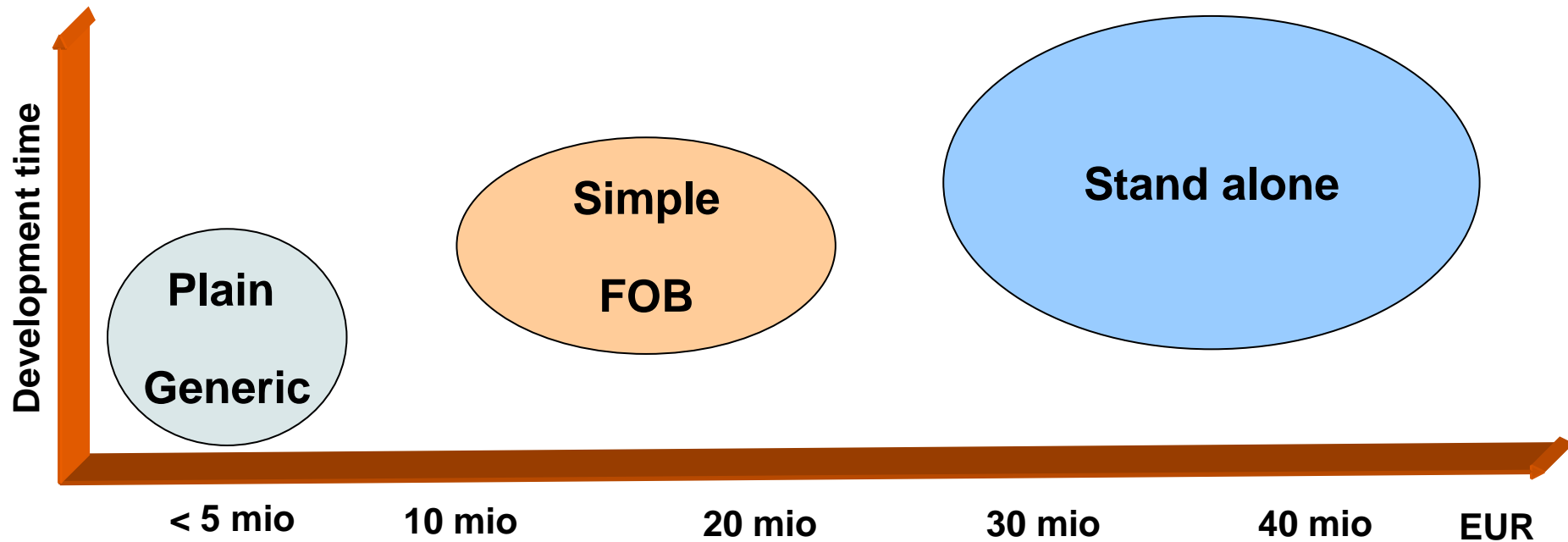
Passing Barriers to Compete in the FoB Market



- 1. Financial strength to back high FoB development costs**
- 2. Regulatory situation**
- 3. Development of scientific Marketing and Sales capabilities**
- 4. Built up in-house Biotechnology know-how**
- 5. Secure adequate Manufacturing capabilities**
- 6. Circumvent existing patent minefields**

Financial strength

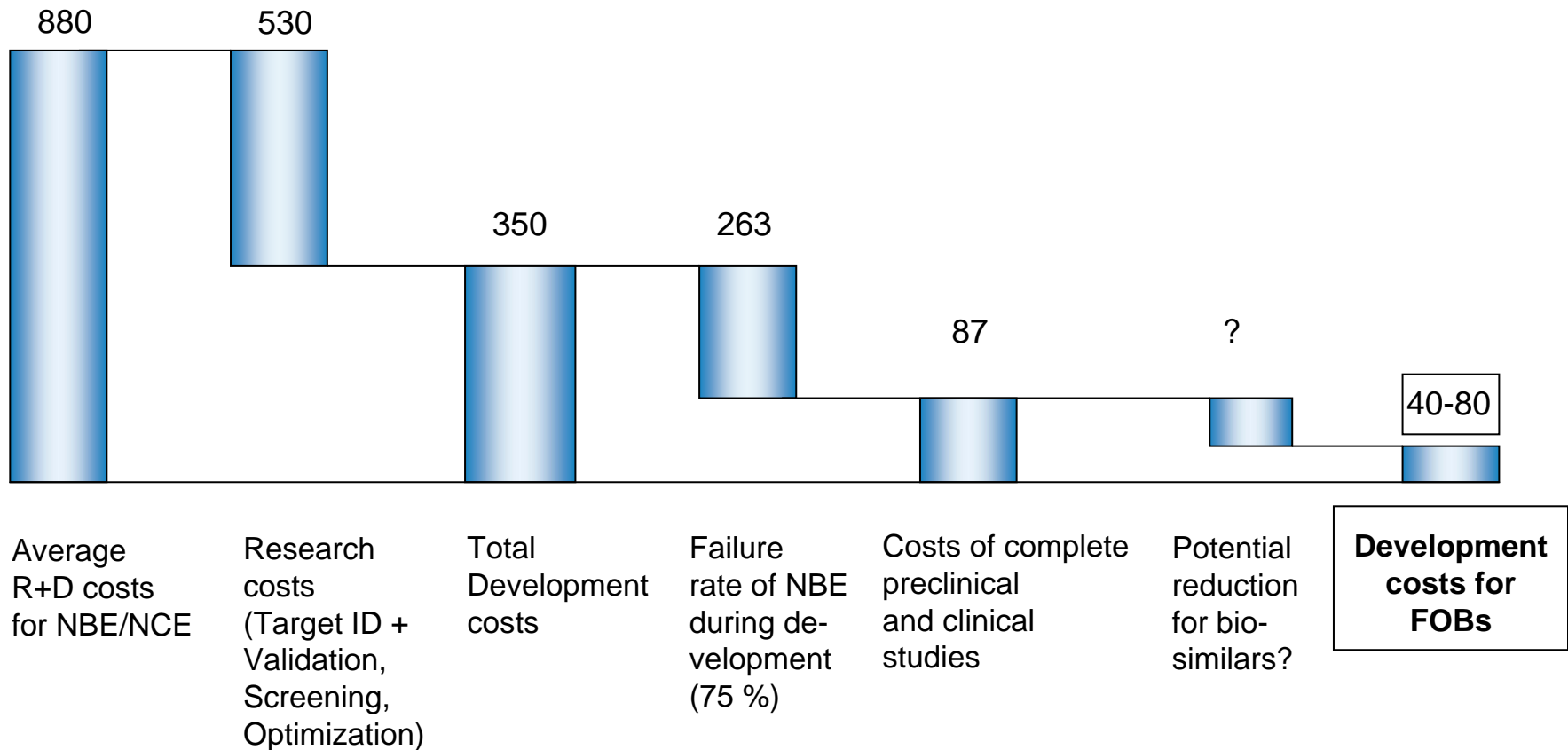
– Viable Development Costs for Generics & FOBs



Development of glycosylated FOBs easily costs > 60 mio EUR per indication

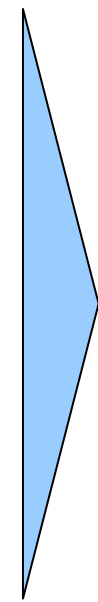
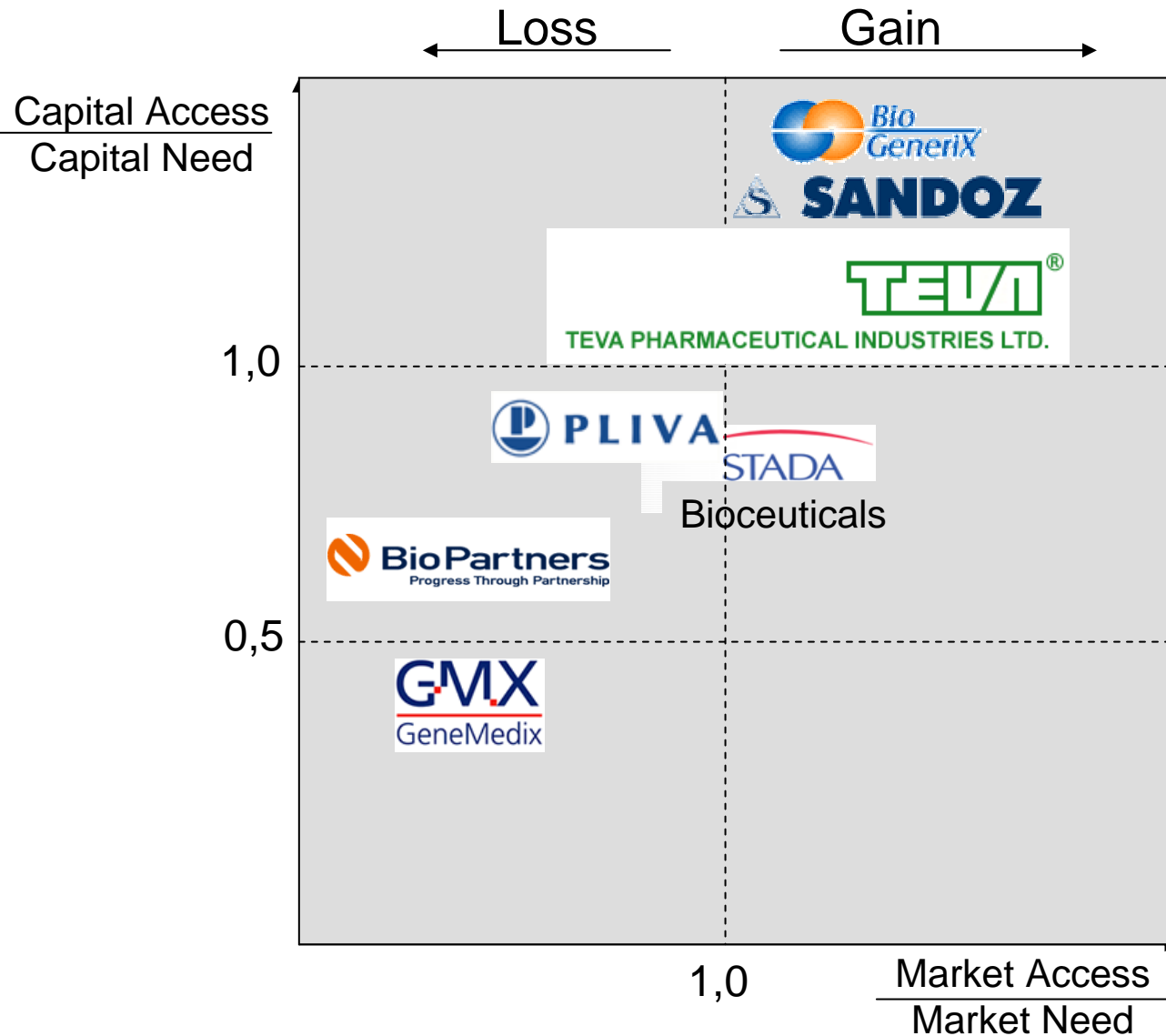
Development Costs

in Mio \$



Due to high development costs, regulatory and GMP-constraints, only few companies will succeed

Competitors in the Field



In Europe, depending on the products, up to four FoB developments will compete on market shares. Rather than „perfect competition“, an **oligopol** with limited price erosion will prevail for some time.

Borderline Scenario for FOBs

■ Critical Market Share (of a 1000 Mio € Market):	3.3%
■ Critical Market Size:	350 Mio €
■ Critical Price Erosion:	80%
■ Latest Launch Date:	2.5 Y after 1st FoB
■ Critical Development costs:	180 Mio €

Under the presented assumptions, the business case is very robust.

- Several **levers** can be used to make it even more valuable:
- Global partnering (to originators)
- Additional patient benefit (multi-dose, pen, sustained release, new combinations, new indications,...)
- Bundling
- Scientific key accounting rather than price-driven generic distribution

To enter the FoB market remains, however, a risky and expensive undertaking

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2. **Regulatory situation**
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- Definition: „**Biogenerics are Copycats of Biopharmaceuticals, i.e. Pharmaceuticals, whose active agents are achieved by biotechnological Methods using recombinant Cell Cultures.**“

- Approval process distinguishes FoBs from generics:
Centralized procedure mandatory, two basic legal bases
 1. **Biosimilar approach:** comparative toxicology; bioequivalence studies, one limited pivotal, comparative efficacy study (caveat: statistical power and assay sensitivity)

 2. **Stand-alone approach:** non-clinical part without comparator, phase I/II/III, against comparator (no reference citation)

CHMP released „final“ regulatory guidelines for

1. Insulin
2. G-CSF
3. hGH
4. Epoetin,

will come into effect on June, 1st 2006

Despite this guidelines no guarantee for a „golden“ development plan

- Therefore:
 - early Scientific Advise from EMEA is highly recommended
 - in the next 3-4 years flexibility on scientific / clinical arguments at CHMP might be possible – and case by case decisions likely

(Nearly) Successful FoB application

CHMP gave positive opinion on two human growth hormone products:

- 1. Omnitrope (Sandoz)
- 2. Valtropin (Biopartners)

BUT

- hgH is a „simple“ product to approve, compared to a product like glycosilated Epoetin



Situation remains thrilling!

Which development route will succeed ?



?



TEVA PHARMACEUTICAL INDUSTRIES LTD.

- Most companies will follow the biosimilar approach but.....

1. Financial strength to back high FoB development costs
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6. Circumvent existing patent minefields

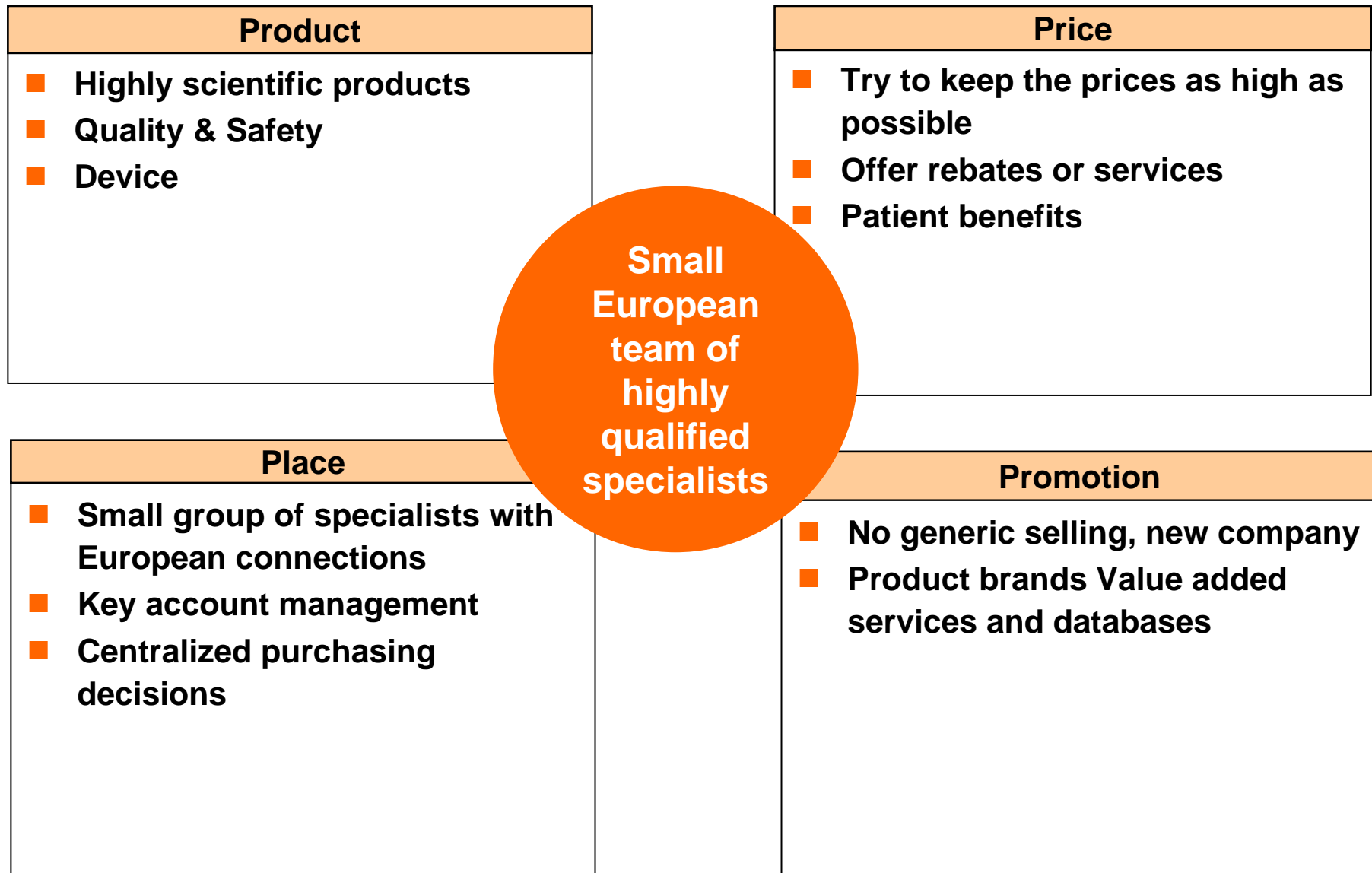
- Most biotech products are sold in restricted markets by scientifically trained key accounters
- Highly competitive direct marketing
- Limited number, well informed patients



Usual generic sales organization will not do the job,
need for a specialized unit/company



High costs for set-up and operations (25% of net sales; or bottom-up)



1. Financial strength to back high FoB development costs
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4. **Built up in-house Biotechnology know-how**
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There are severe barriers for a generic approach or a pure comparability exercise:

- FOBs will be produced with (new) specific methods and processes
- FOBs possess modified formulations (patent reasons)
- FOB developers have neither access on data of the originator's processes nor on material from intermediate steps

- From the first Steps until Launch it could take approx. 6-9 Years



The development timelines are similar to NBE development, only the risk of failure is smaller

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

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

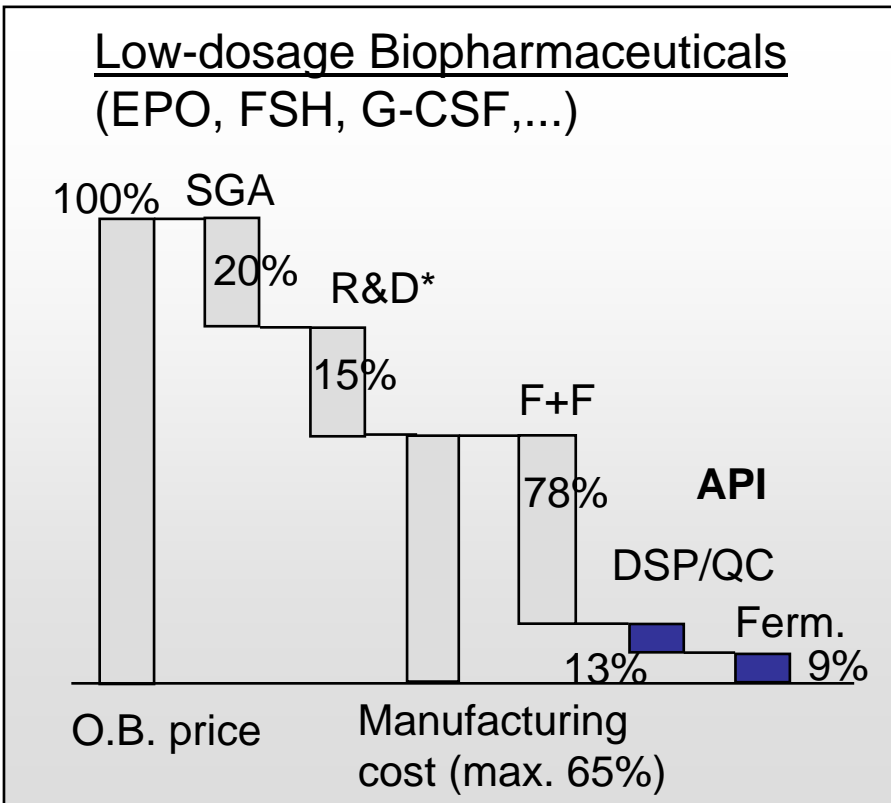
These three parts build an inseparable package for approval!

- Change of the process or transfer to another production site requires comparability exercise and a revised approval (variation).**
- This strongly influences the development strategy of FOBs**

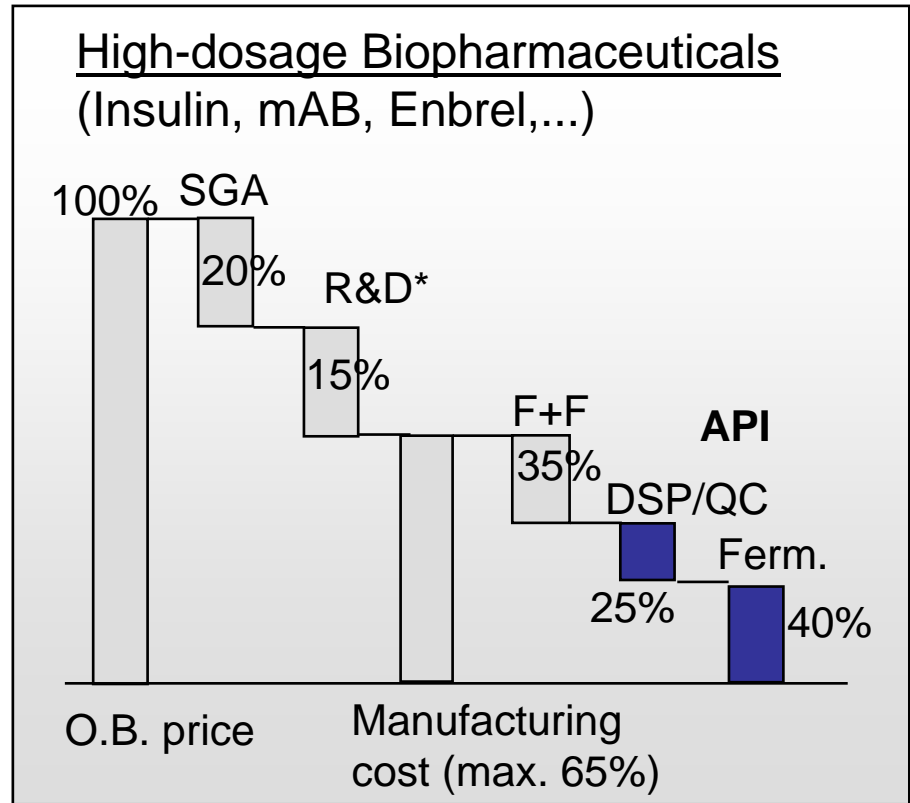
Production capabilities for Biologics:

- Limited capacities of qualified biotech facilities, available in a few countries (strong competition between FOB companies)
- Switch to another production site requires additional comparability studies. Transfer is time-consuming, expensive and risky
- Legal situation is more uncertain for FOBs
- No established strategy

Cost of Manufacturing: CoGS



API manufacturing represents max. **14%** of the total costs



API manufacturing represents max. **42%** of the total costs

Manufacturing becomes a key business driver only in high-volume, mature markets (e.g.commodity goods, or bio-generics?)

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The innovator companies have several possibilities to protect their IP from generic competition:

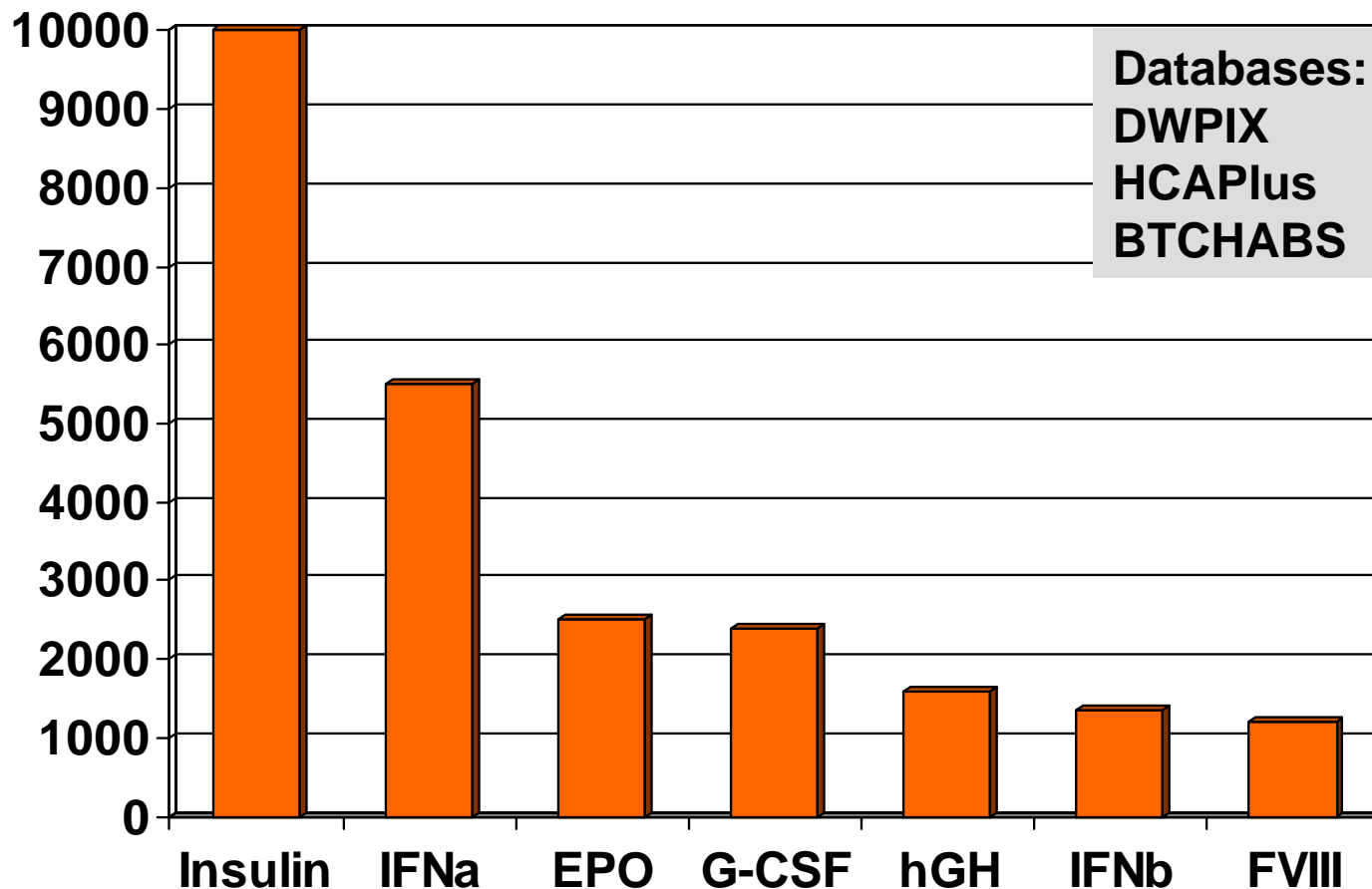
- (1) Patents
- (2) Supplementary Protection Certificates
- (3) Data exclusivity (not relevant for FOBs)
- (4) Orphan Drug Status

These legal instruments maintain a reasonable period of market exclusivity for the originator.

FOB developers are faced with complex patent situations:

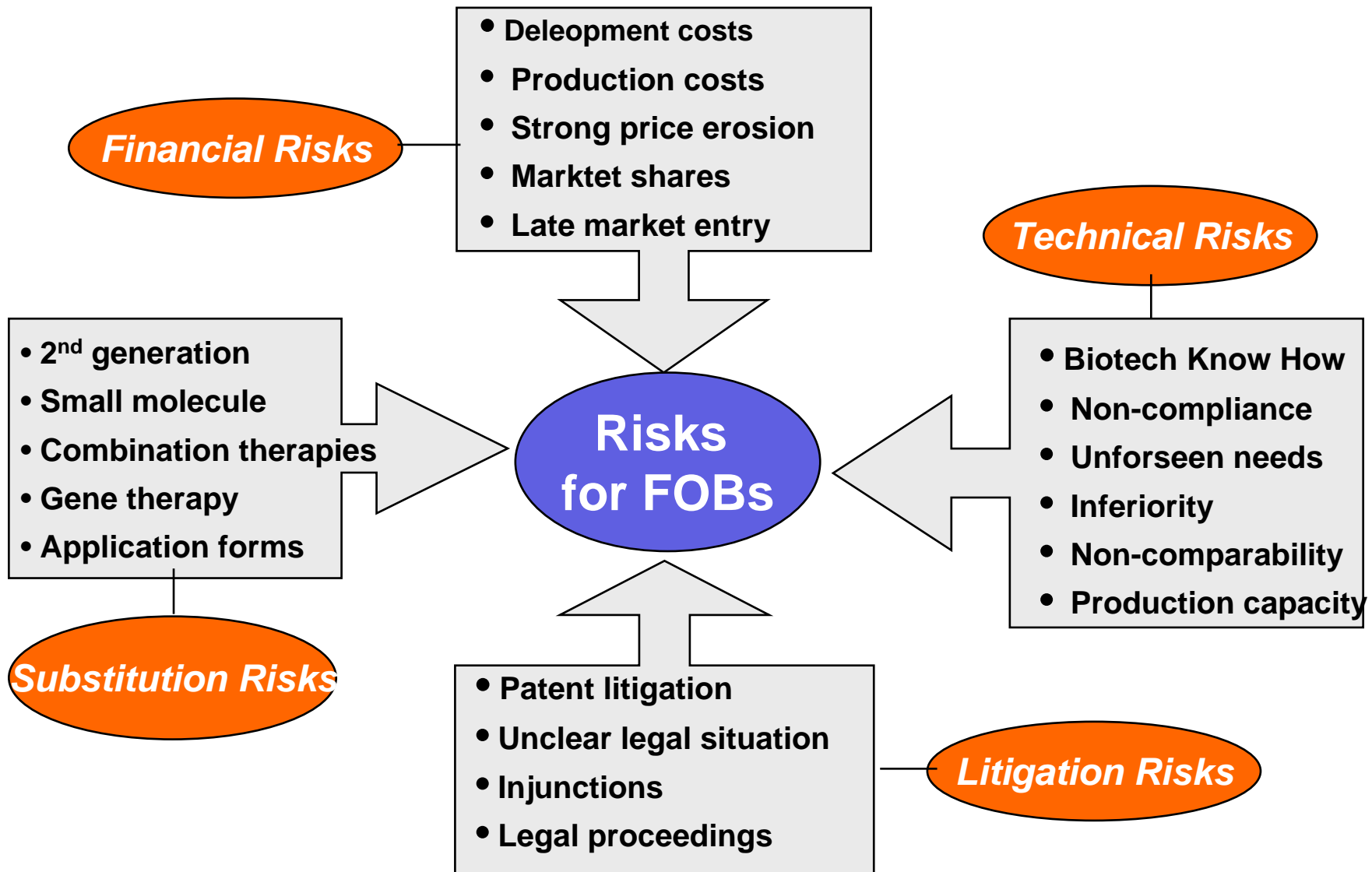
- Total number of patents for a given target protein is extremely high
- Patent claims bear an inherent threat of interpretation
- Patents on biologics are related to specific methods rather than to the substance

Number of hits in specific patent searches



- Initial screening for patent applications
- Identification of relevant patents
- Analysis of patent families
- Examination of the legal status
- Risk assessments
- Examination of SPCs
- Evaluation of expiries (country by country)

**This requires excellence in biotechnology along with experience
in databases and patent law**



Best Owner Biosimilar Products

Owner	Patent Know-how	Biotech	Partnering	Capital	Legislation	Market access
Pharma	3/4	3/4	100%	1/2	3/4	100%
Biotech	1/4	1/2	1/4	1/2	1/4	1/4
Generics (EMEA/FDA)	100%	0%	1/4	100%	1/2	1/2
Generics (others)	3/4	0%	1/2	1/4	0%	0%
Specialist bio-generic company	1/4	1/4	3/4	1/4	1/4	0%
Biotech-manufacturer	1/4	100%	3/4	1/2	1/2	0%

- Big Pharma would be able, but is not willing to enter
- All others need to complement gaps through partnering
- Capital and market access are/will be strongest selectors

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

- 1. lack of biotech & regulatory know how**
- 2. significant amount of investment**

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- The bio-generic industry saw a peak in numbers of companies, but is now starting to sort out
- Successful FoB companies have as a minimum a profound expertise in **biotechnology, the financial strength, patent knowledge** and access to pharmaceutical marketing including a trusted brand and product portfolio
- Cost leadership might become an issue, depending on the price erosion witnessed (number of competitors)
- Originators in Europe defend their markets by building up regulatory hurdles, marketing tools and switches to second generation products
- Generic industry is likely to reduce investments due to margin pressure in their main business