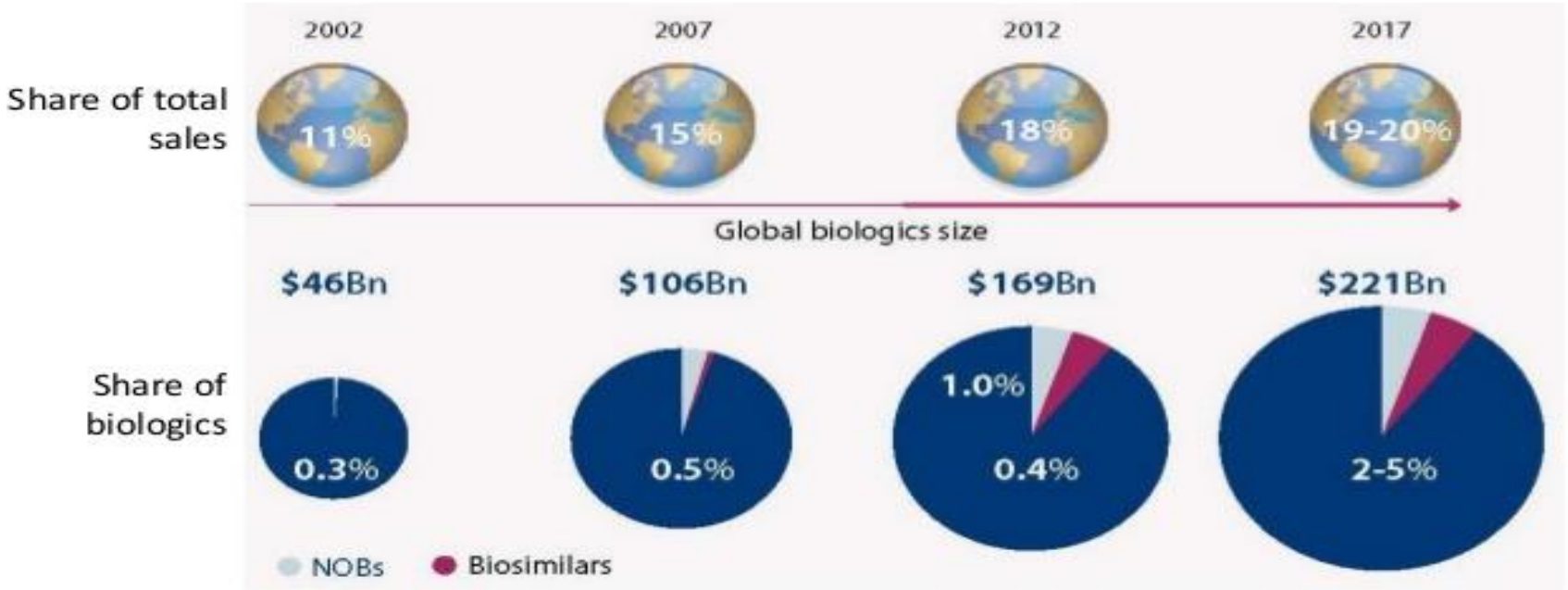
TERROSA - case study

First Biosimilar Approval for Gedeon Richter

dr.Katalin Fogassy

Biosimilars market potential

The world-wide biologics market



Global sales of biologics predicted to grow twice as fast as small molecules. Mark McCamish and Gillian Woollett 2011

IMS Health, Thought Leadership, Sept 2013

Biosimilar Teriparatide: Terrosa

- Teriparatide: biologically active N-terminal 34-amino acid fragment of PTH(1-84)
- Only bone anabolic agent approved – Forsteo/Forteo (Eli Lilly)
  - Treatment of postmenopausal women and men at an increased risk of fracture
  - Treatment of glucocorticoid induced osteoporosis in men and women at an increased risk of fracture

Osteoporosis: the silent epidemic

- Decreased bone mass + microarchitectural deterioration
- → fragile bones → increased risk of fractures

- Statistics:
- 8.9 million fractures/year – 1 in every 3 seconds!
- 1 in 3 women, 1 in 5 men over age 50 will experience osteoporotic fractures
- 2050 - worldwide incidence of hip fracture in men increase by 310% and 240% in women, compared to rates in 1990
- prior fracture → 86% increased risk of any fracture

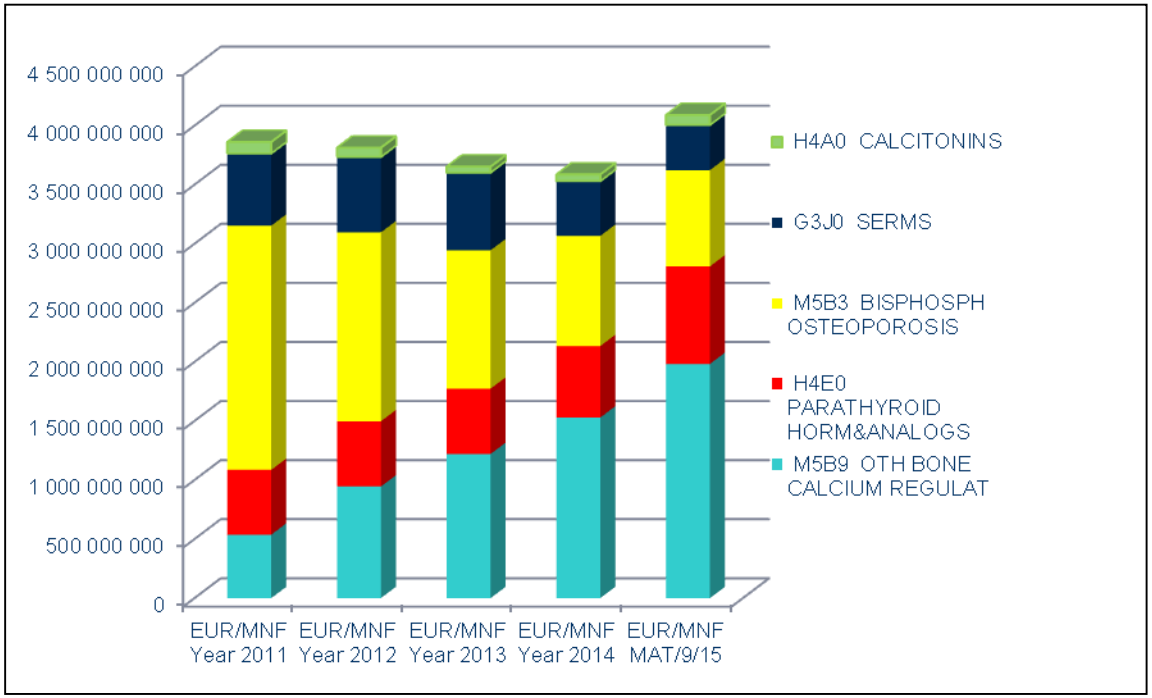
- ≈80% of high risk patients – unidentified, untreated

- 40% of patients take treatment for more than one year

- Osteoporosis treated by rheumatologists and gynaecologists

Osteoporosis market

Product Types
Vitamin D plain
Calcium
Estrogen exluding G3A, G3E and G3F
Estrogen and progestogen
SERM
Calcitonins
Parathyroid hormones
Bisphosphonates osteoporosis
Other bone calcium regulator



EU / US Nos.

- Market access considerations critical for commercial success
- Market access factors vary hugely between different European countries

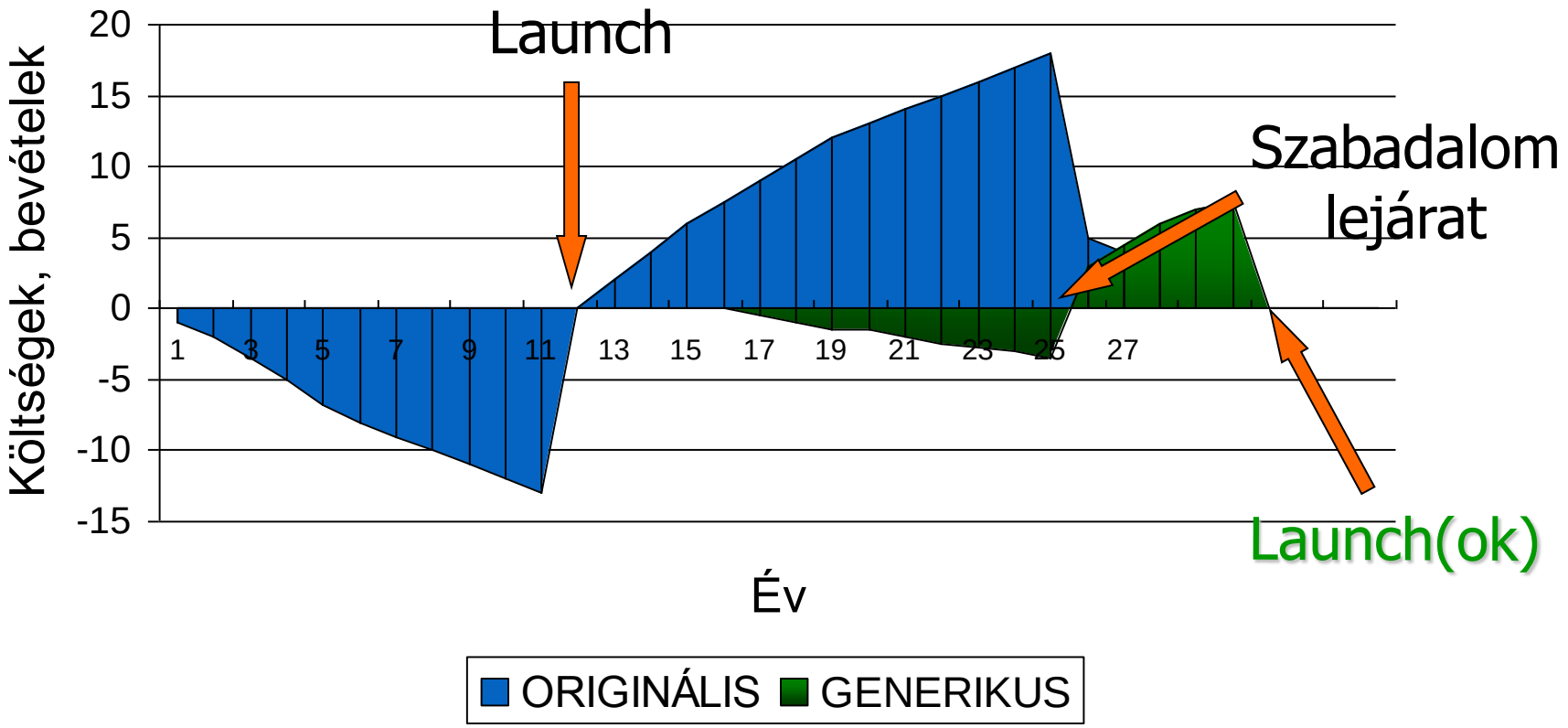
Original vs. generic or biosimilar development

Original R&D: ~15 years, 1000 – 1200 M$

Biosimilar R&D: 7-10 years, 50 – 200 M$

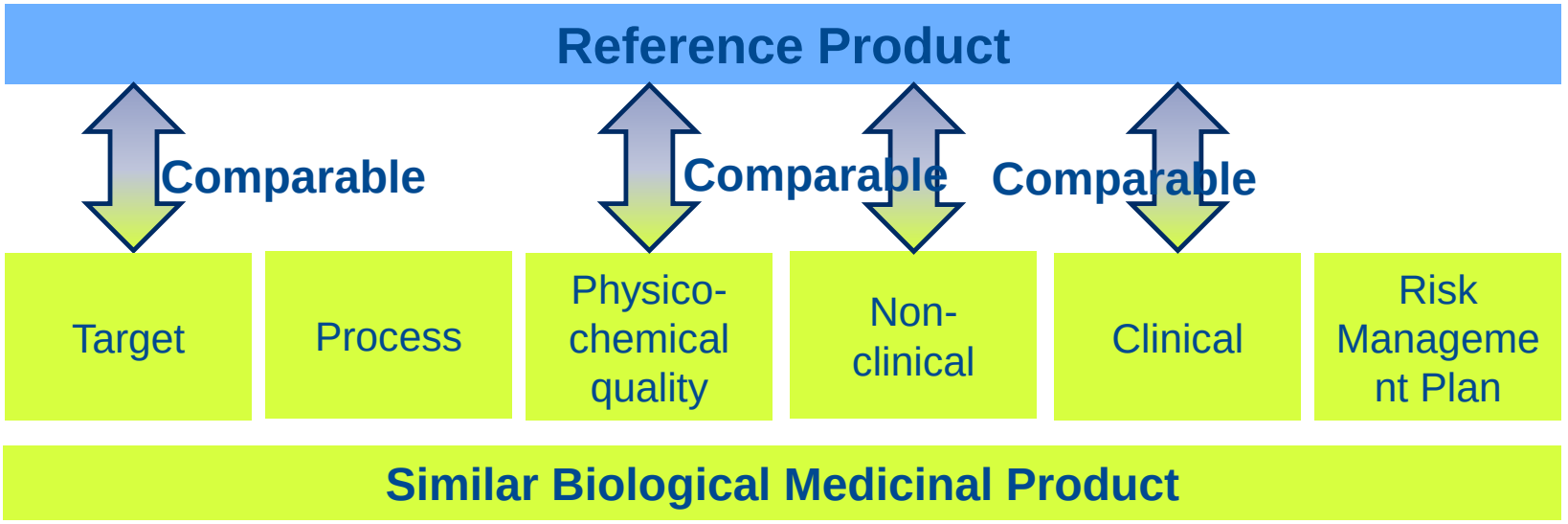
Generic R&D: ~5-7 years, 1-5 M$

Fejlesztési program összeállítása - alapelvek



Development of Biosimilar Medicines – Comparability Exercise

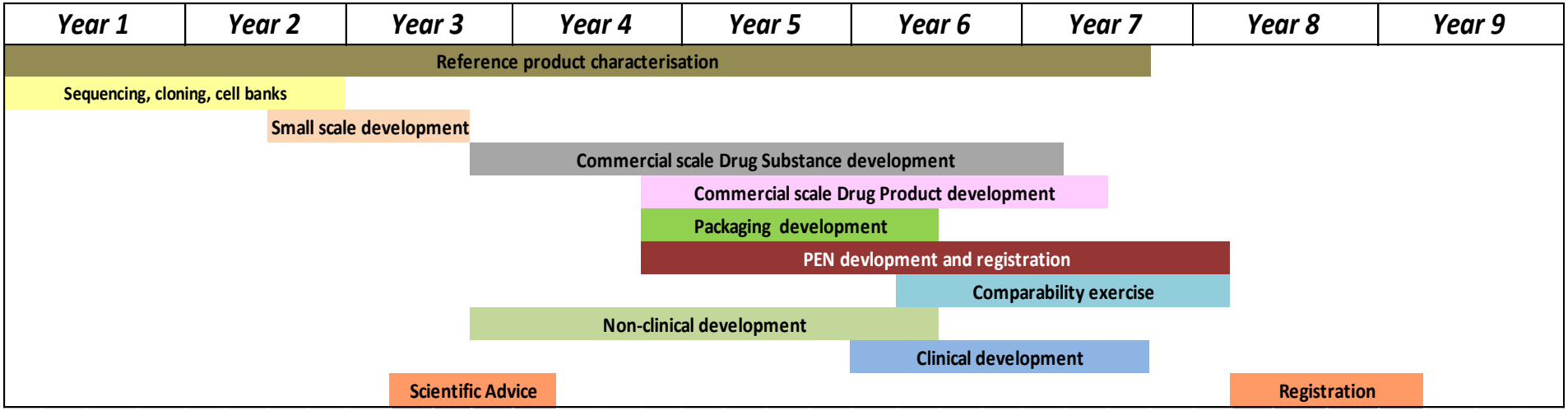
- **Legal basis** in EU -2003/2004, first **biosimilar guidelines**
  - 2005/2006



Complex, tailor made development programme

Terrosa - biosimilar teriparatide

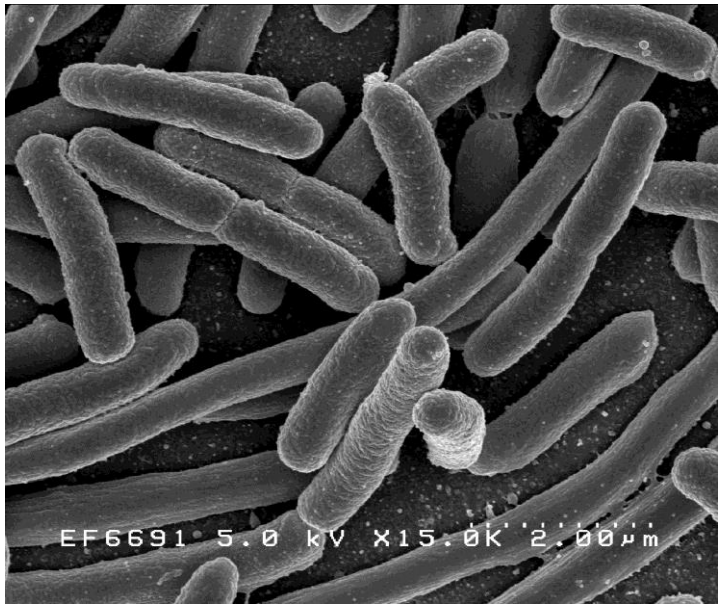
- Demonstration of comparability on quality, non-clinical, clinical levels
- Clinical programme aligned to the extent of quality comparability
- Integration of existing Pen Platform into the development plan



Biosimilar production sites of Gedeon Richter Plc.

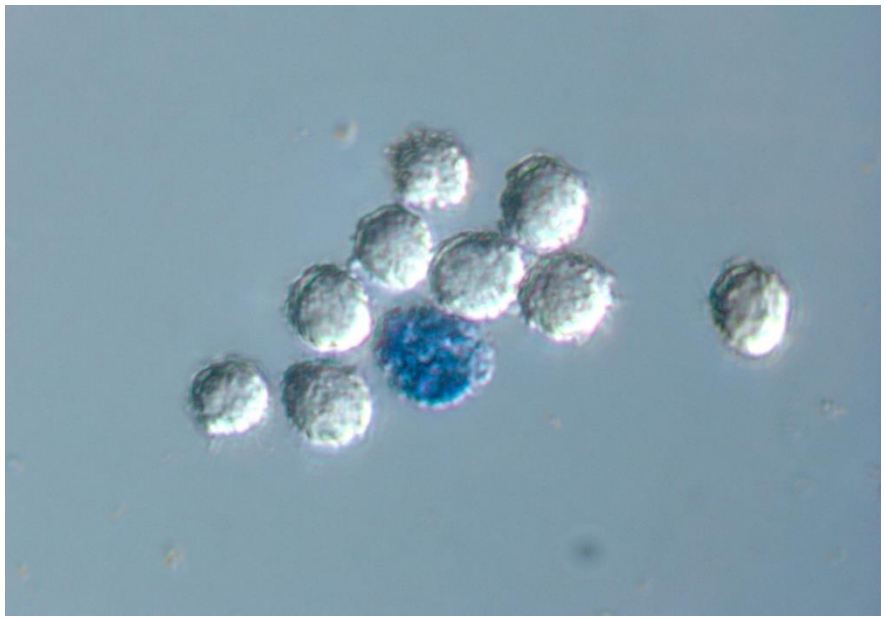
Recombinant expression hosts

E. *coli*



2 µm

CHO



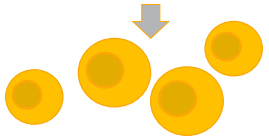
20 µm

Key process technology steps

- Terrosa drug substance is produced in recombinant *E.coli*

Cloning

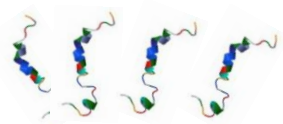
Clone selection



Upstream / Fermentation development

Downstream / Purification development

Drug Substance

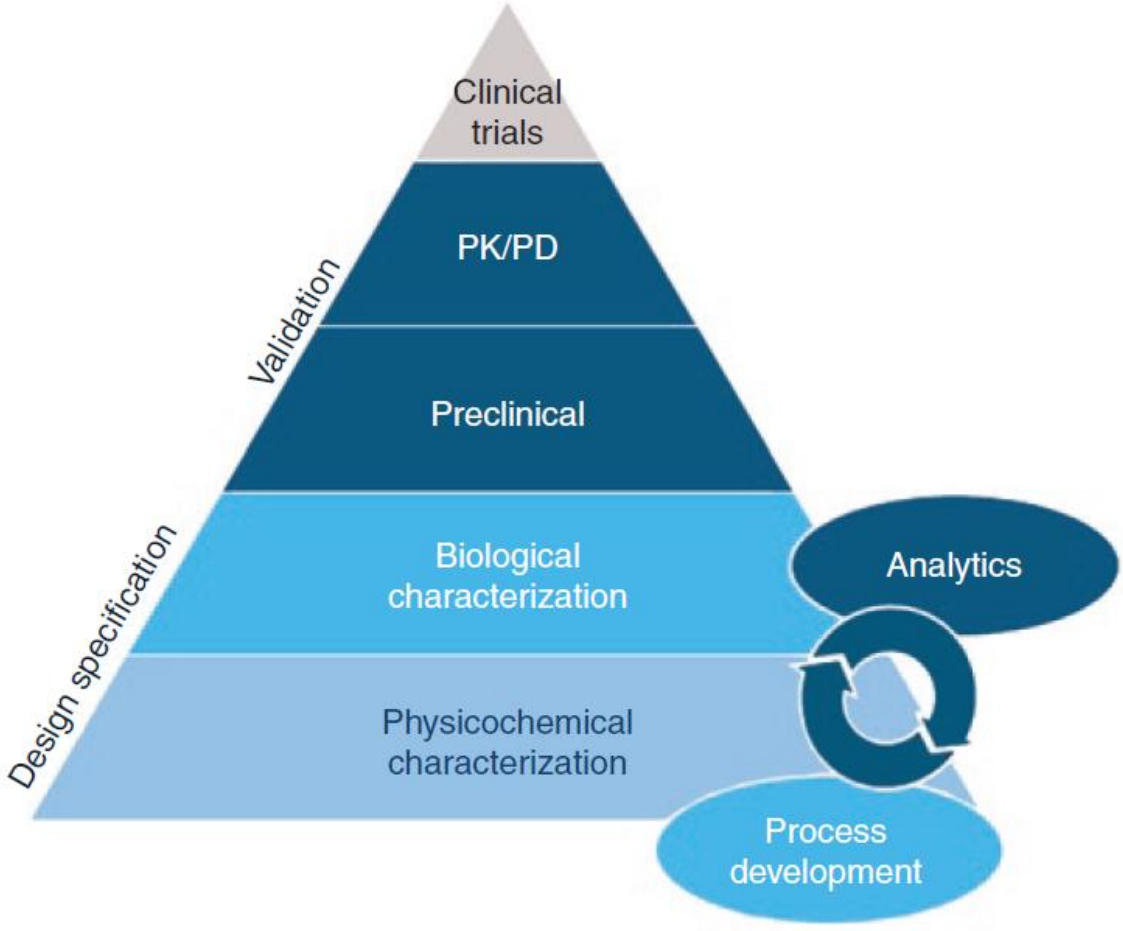


Drug Product

Specifically designed administration device

- Administration device - PEN, customised development to the requirement of the drug
- Specific authorisation procedure – ISO standards, Notified Body approval
- Changing environment - clinical study design

Stepwise approach to development of biosimilars



Scientific Advice procedures - mitigating risk vs. revision of guidelines

Aim of the Biosimilar Clinical Studies: Establishing Clinical Comparability

Comparative PK/PD (i.e. Phase I)
Comparative efficacy/safety/immunogenicity (i.e. Phase III)

Equivalence trials

Clinical studies
single centre or multi-centre
healthy volunteers or patients
n ≈ 100-500
1 to 3-5 years

How much clinical data is necessary?
How much similarity is necessary?
What should be the study population?
What should be the clinical endpoint?
How big safety database is needed?
…

Biosimilars approved in the EEA have equivalent efficacy and safety with the reference product

Clinical Development of Biosimilars

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 December 2014
EMEA/CHMP/BMWP/42832/2005 Rev1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues

Draft agreed by Biosimilar Medicinal Products Working Party (BMWP)	April 2013
Adopted by CHMP for release for consultation	30 May 2013
Start of public consultation	03 June 2013
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This guideline replaces 'Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Non-clinical and clinical issues' (EMEA/CHMP/BMWP/42832/2005).

Keywords	***similar biological medicinal product, recombinant proteins, non-clinical studies, clinical studies, safety, pharmacovigilance, immunogenicity***

- **PRINCIPLES OF CLINICAL DEVELOPMENT**
- Step-wise approach
  - comparative pharmacokinetic (PK) and pharmacodynamic (PD) study
  - comparative efficacy and safety study in one or more indications (extrapolation)
  - sensitive patient population
  - endpoint selection
  - immunogenicity
  - **'specifically tailored' clinical programs**

Revised guideline adopted in July 2015

Tailored Biosimilar Development

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"In specific circumstances, a confirmatory clinical trial may not be necessary. This requires that similar efficacy and safety can clearly be deduced from the similarity of physicochemical characteristics, biological activity/potency, and PK and/or PD profiles of the biosimilar and the reference product."

Guideline on similar biological medicinal products - CHMP/437/04 Rev 1

→PK/PD: in certain cases confirmatory

Weise et al. Biosimilars: Clinicians concerns addressed based on scientific principles

Quality of biosimilars in EU

Biosimilar – why not identical?

Sufficient safety database, including immunogenicity

Efficacy of biosimilars

Extrapolation of indications

Interchangeability/substitution

Sufficient safety database, including immunogenicity

- **General safety experience gained with the reference product applicable to the biosimilar, based on demonstrated close similarity**
- **Demonstration of similar physicochemical characteristics, biologic activity, pharmacokinetics, pharmacodynamics/efficacy and safety data, including immunogenicity, allow reasonable reassurance for comparable safety profile**
- **Immunogenicity testing: same requirements for all biologicals, no specific concern with biosimilars**

Efficacy of biosimilars

- **Biosimilars are as efficacious as their reference products**
- **Equivalence margins for comparative efficacy studies based on statistical and clinical considerations to exclude any clinically relevant difference**
- **Biosimilars are therapeutic alternatives to their reference products using the same posology for the same indications**

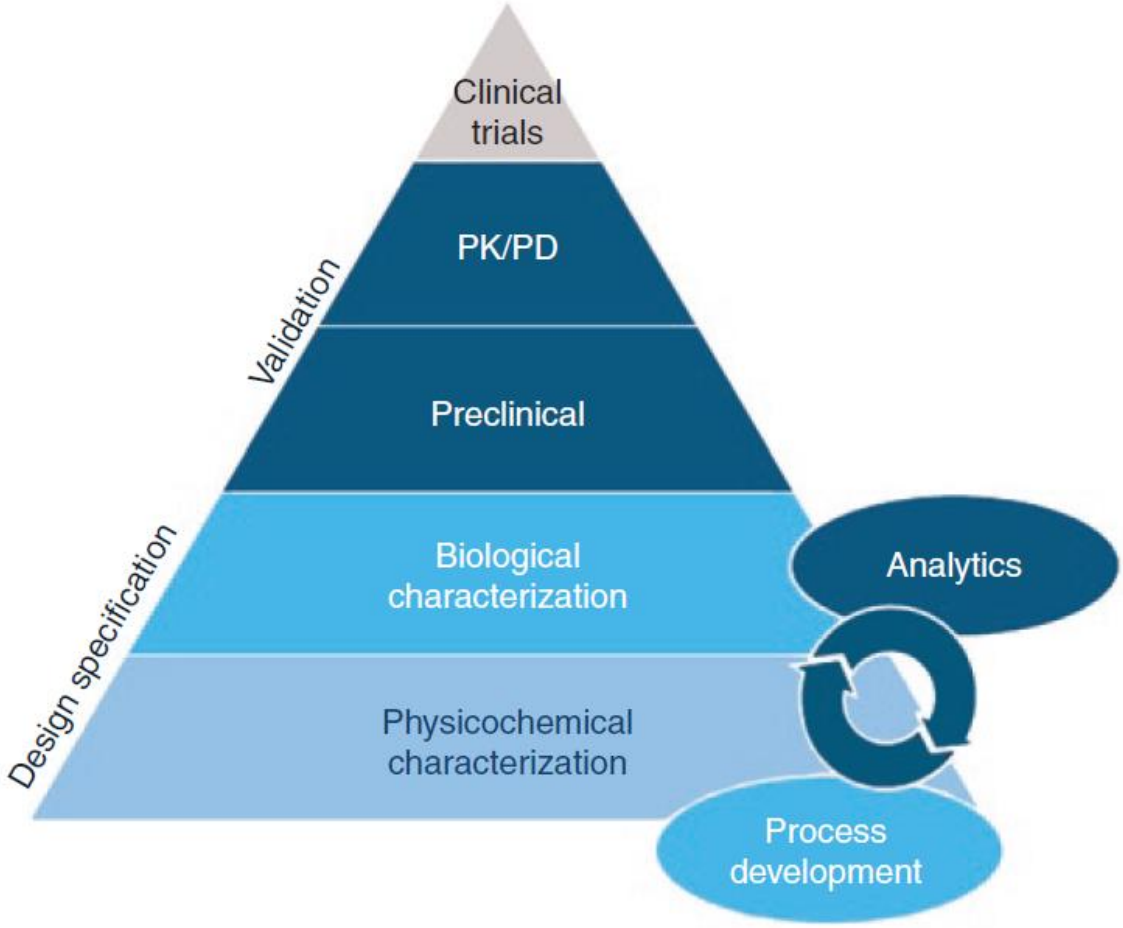
Extrapolation of indications

- **Based on the totality of evidence provided by quality, non-clinical and clinical comparability data**
- **High analytical and functional similarity: If there are no differences relevant to the pharmacology of the molecule, it will behave as the reference product in all patient populations**
- **Extrapolation also applies to pre-and post-change products already on the market**

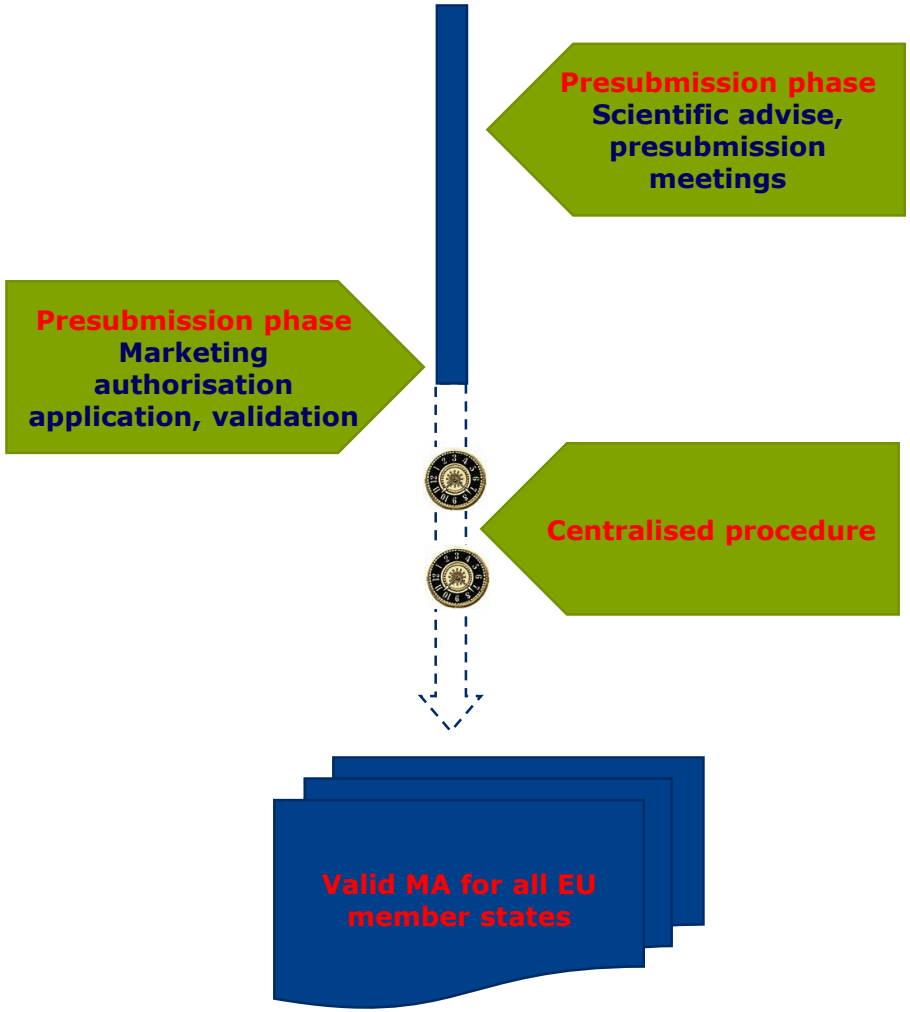
Interchangeability/substitution

- **Biosimilars are therapeutic alternatives to their reference products using the same posology for the same indications**
- **Switching: does not lead to change in clinical management**
- **Traceability: pharmacovigilance legislation in EU**
- **Recent developments, e.g. Norway and Finland**
- **Norwegian switch study (NOR-SWITCH) – initiated in 2014; switch to biosimilar infliximab is almost complete in Norway**
- **Current position of Fimea is that *'biosimilars are interchangeable with their reference products under the supervision of a health care person'***

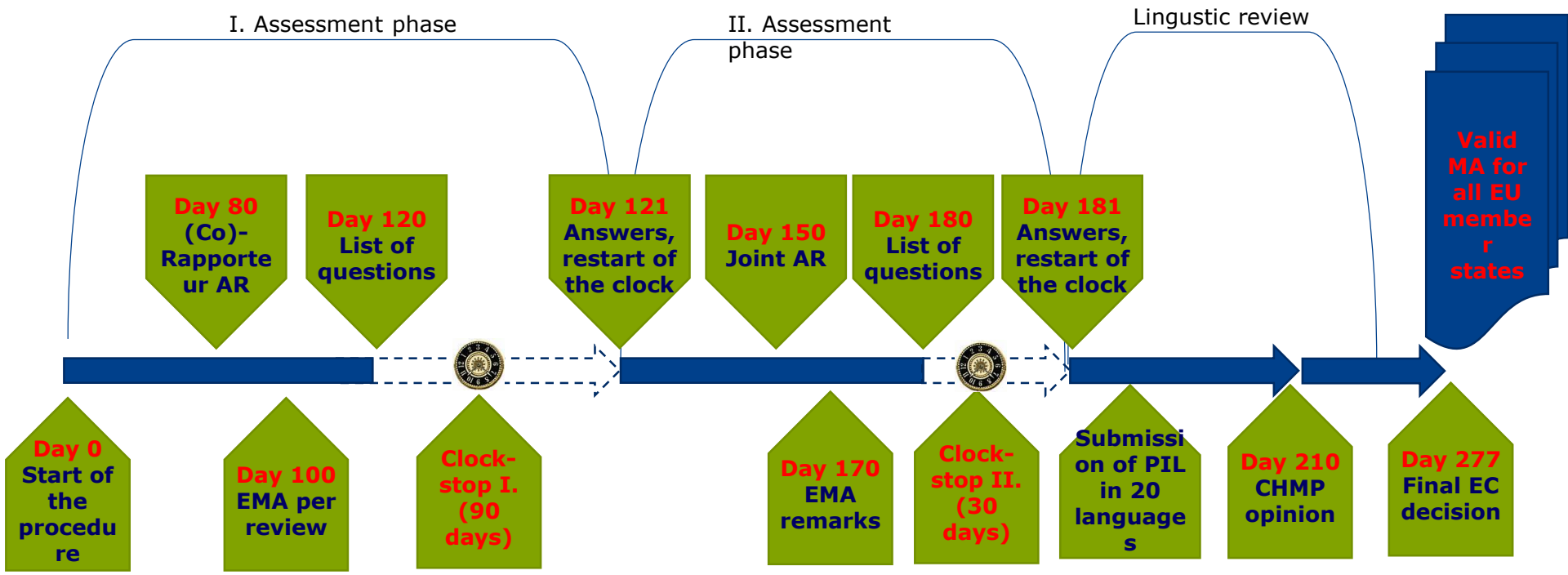
Stepwise approach to development of biosimilars



Terrosa - First experiences with the EMA centralised procedure



EMA centralised procedure – typical timeline

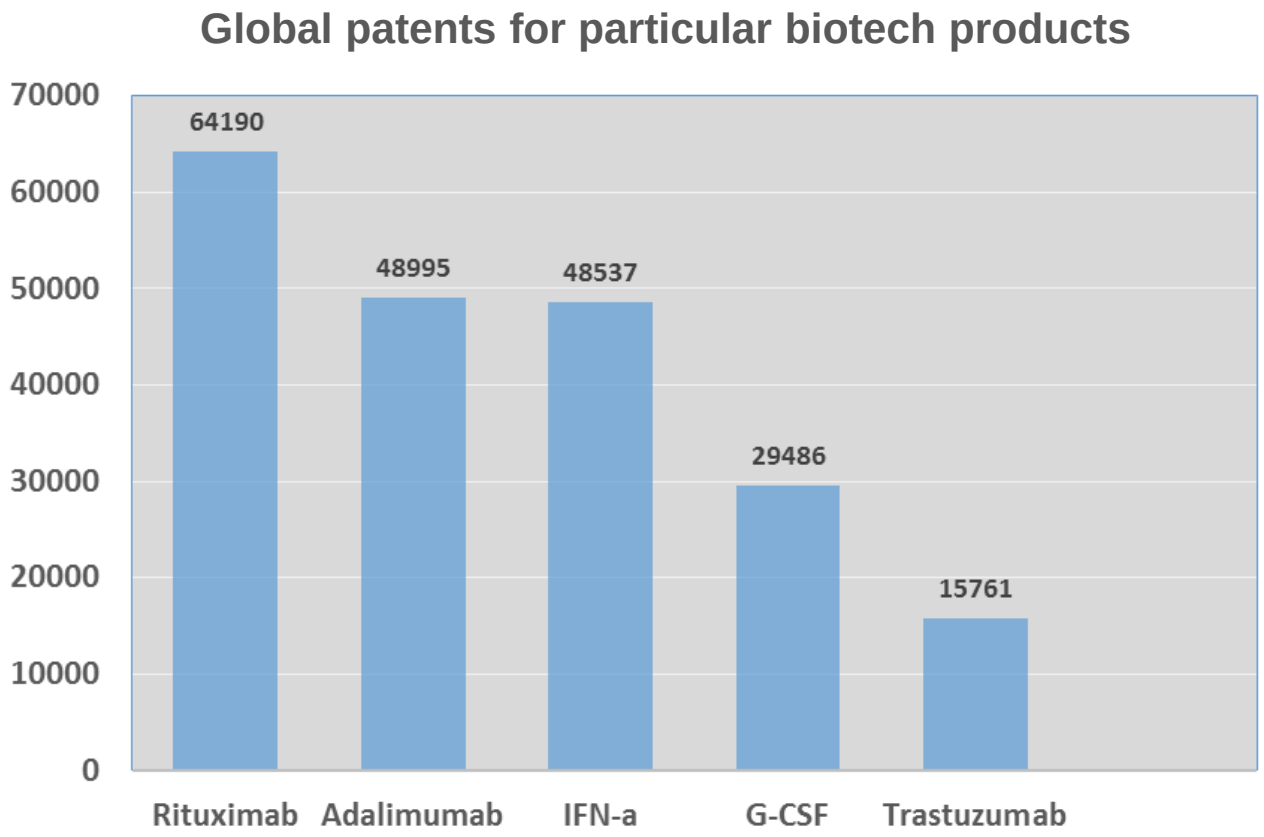


Challenging IP landscape - The patent protection of biotech products is very complex

- Analyses for biotech products are difficult to perform, due to inconsistent nomenclature of the molecules and meaningless titles and abstracts.
- For biotech products not only substance protection has to be considered, but also process patents and in particular “method of use” (indication) patents.
- The amount of process patents for biotech products is high. These patents concern expression technology (cloning), cell culture processes (USP), and purification methods (DSP). Moreover most of the relevant process patents are generic (=not product specific).
- In order to avoid patent infringement of process patents, patent driven technical circumvention strategies have to be established for biosimilar developments .

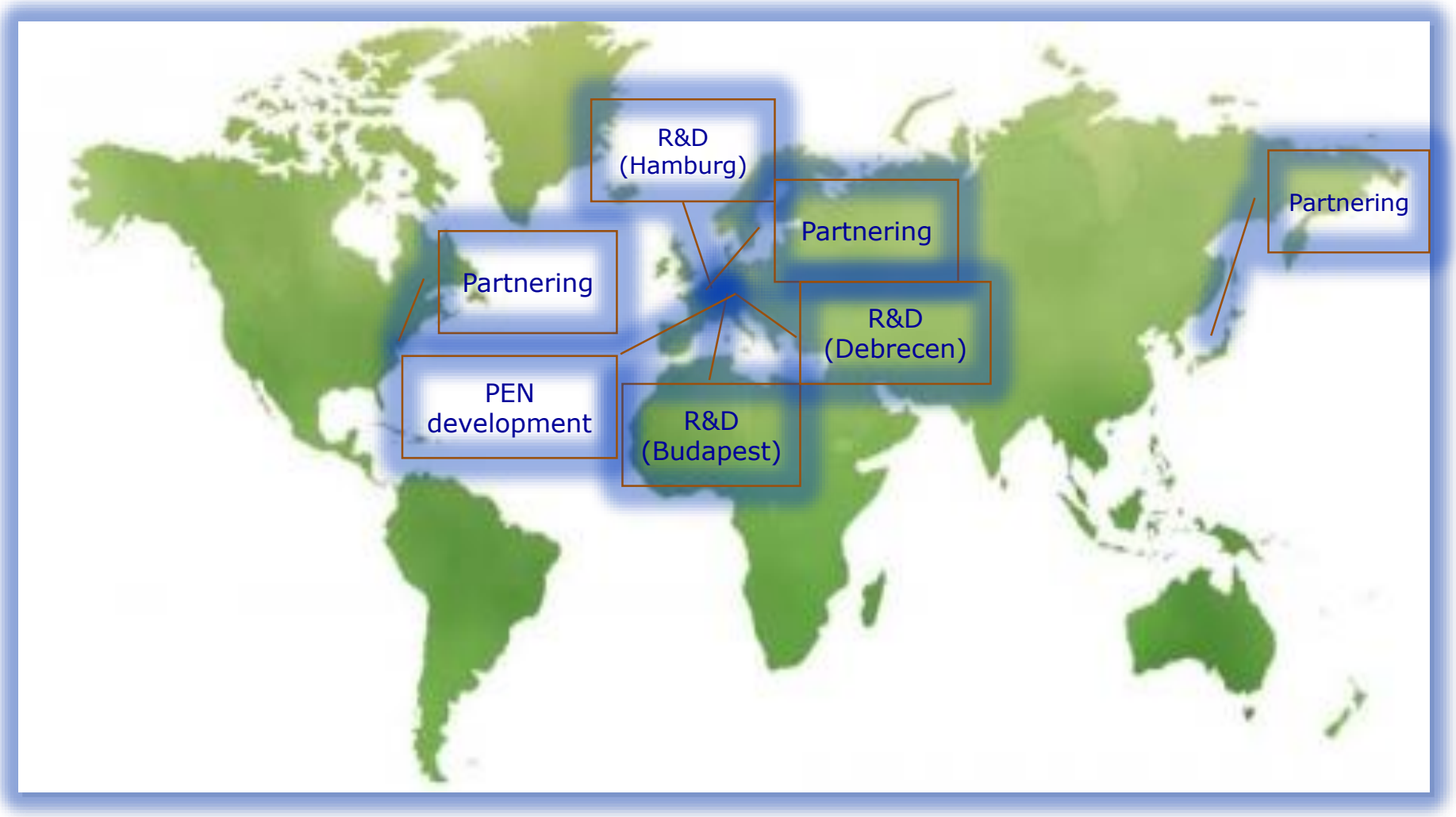
Challenging IP landscape – some numbers

- **The number of patents for biotech target products are very high:**



Source:
Questel (2016)

Challenges of project management




THANK YOU FOR YOUR ATTENTION!