BIOTECHNOLOGY

R&D in the pharmaceutical industry

Könczöl Kálmán c. egyetemi docens

Biotech drugs have bee a great success story…

Effective and highly selective

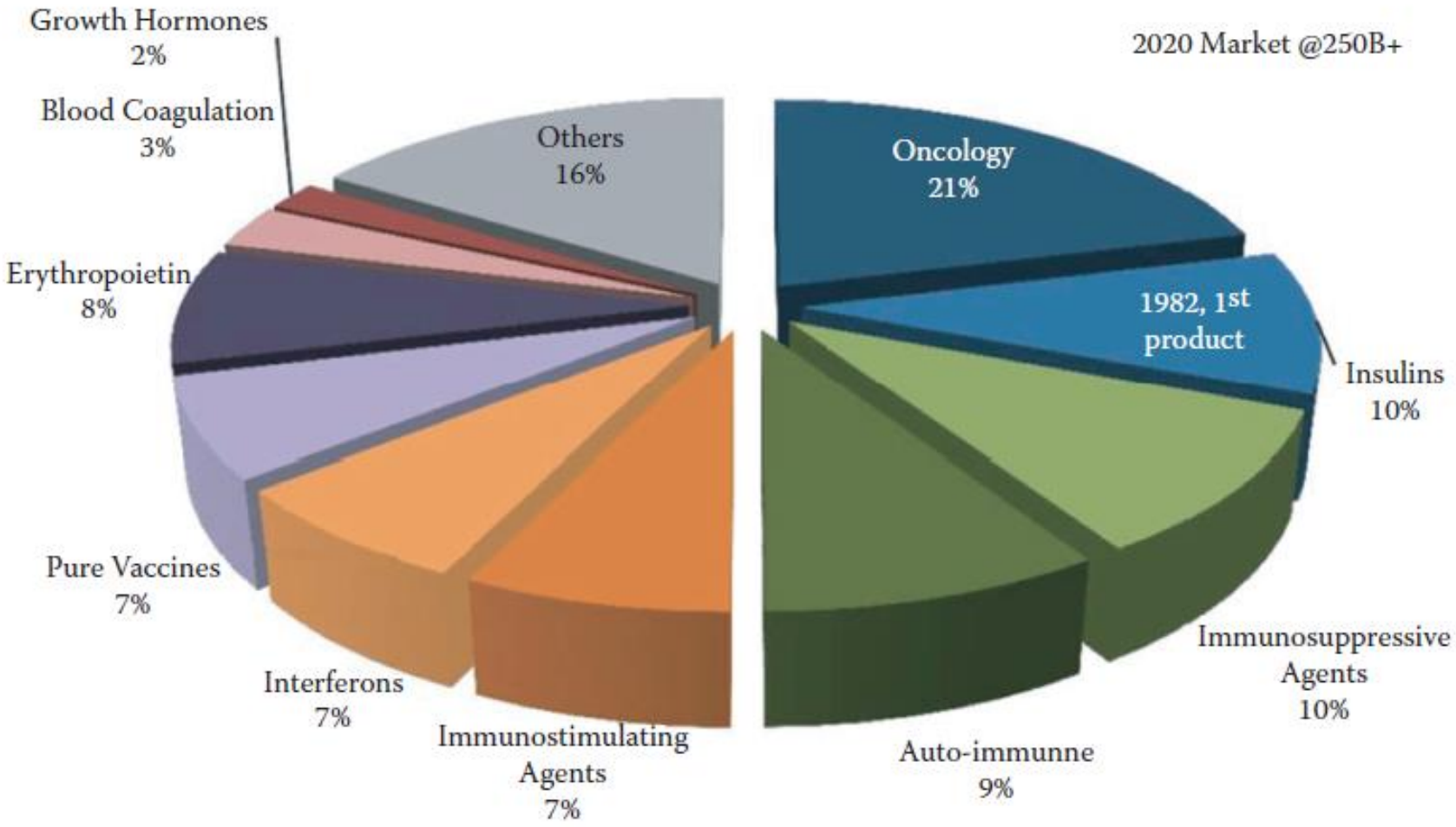
Targeted unmet medical need

- Improving existing therapies: coagulation factors, insulins
- New drugs with new modes of action:
  - oncology,
  - autoimmun diseases,
  - hepatitis,
  - rare diseases

We know how to produce them

➢Success story for patients

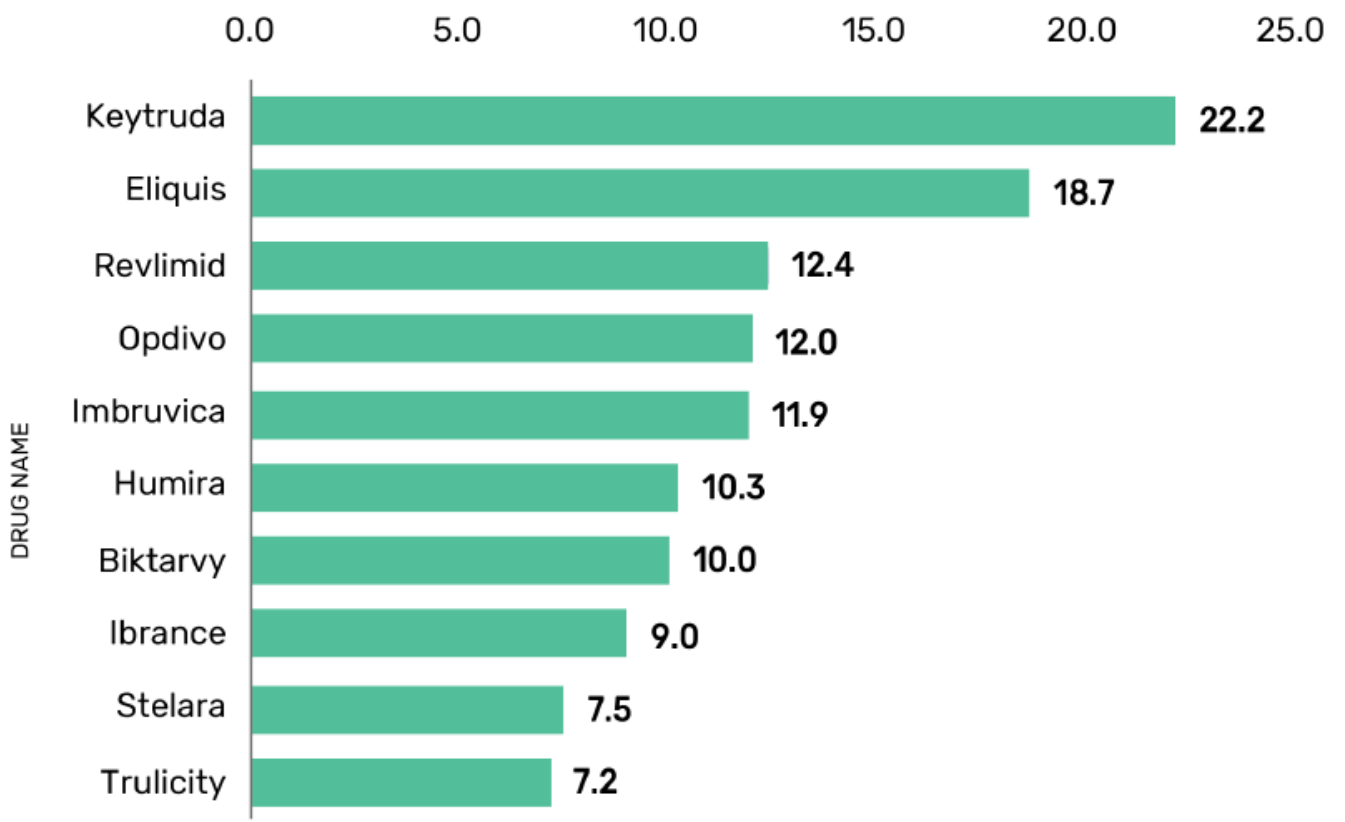
➢Success story for biopharmaceutical companies


2020 Market @250B+
Growth Hormones
2%
Blood Coagulation
3%
Others
16%
Oncology
21%
Erythropoietin
8%
1982, 1st
product
Insulins
10%
Pure Vaccines
7%
Interferons
7%
Immunostimulating
Agents
7%
Immunosuppressive
Agents
10%
Auto-immunne
9%

Top 10 best selling drugs 2018

Rank	Product name	Company	Substance	Sales (billion $)	Patent expiry	
					EUR	USA
1	Humira	Abbvie	adalimumab	19.9	expired	2023
2	Eliquis	BMS/Pfizer	apixaban	9.8	2022	2023
3	Revlimid	Celgene	lenalidomide	9.7	2028	2024
4	Keytruda	Merck (MSD)	pembrolizumab	7.1	2028	2028
5	Enbrel	Amgen	etanercept	7.1	expired	2029
6	Herceptin	Roche	trastuzumab	7.0	expired	2019
7	Avastin	Roche	bevacizumab	6.9	2022	2019
8	Eylea	Regeneron/Bayer	aflibercept	6.7	2022	2020
9	Opdivo	BMS	nivolumab	6.7	2026	2027
10	Xarelto	J&J/Bayer	rivaroxaban	6.5	2024	2024

Forecast of Top 10 best-selling drugs, 2025, Global ($bn)



Source: GlobalData, Pharma Intelligence Center

…too successful?

If the trend continues, healthcare will consume an ever-growing and unsustainable proportion of the developed nations' wealth

Projected healthcare spend

Percent of GDP[1]

OECD countries	2005	2030	2050	2070
US	15.3	24.9	36.7	65.6
Switzerland	11.6	18.8	27.8	49.8
France	11.1	18.0	26.6	47.6
Germany	10.7	17.4	25.6	45.9
Greece	10.1	16.4	24.2	43.3
Canada	9.8	15.9	23.5	42.0
Netherlands	9.2	14.9	22.0	39.5
Denmark	9.1	14.8	21.8	39.0
Italy	8.9	14.5	21.3	38.2
UK	8.3	13.5	19.9	35.6

[1] Linear extrapolation; assumes healthcare continues to grow at +2.0% above GDP

Source: „mHealth: a new vision for healthcare", 2010, McKinsey&Company

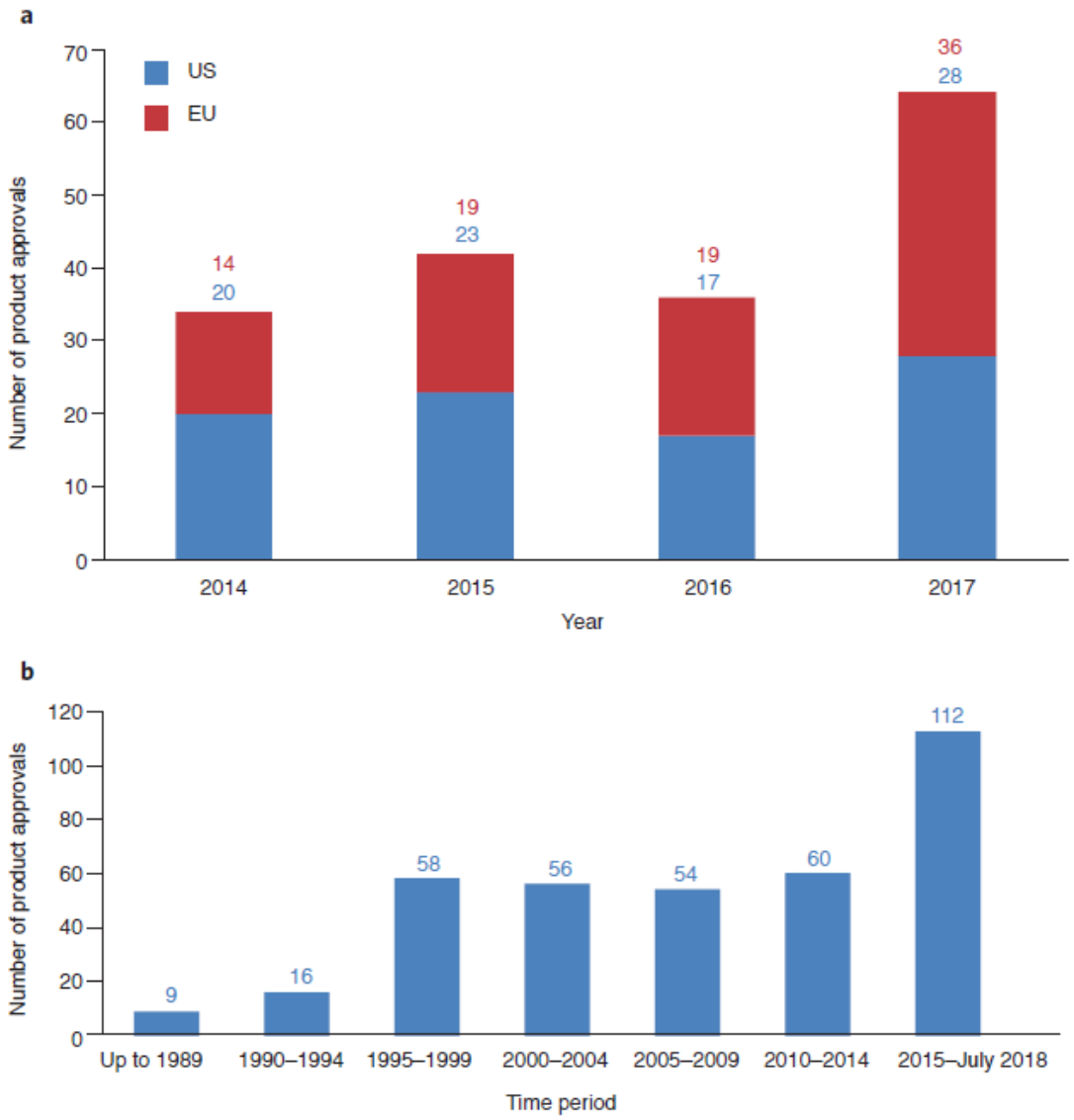


Figure 1 Product approvals profile. (**a**) Annual product approval numbers (by product trade name) by individual region. (**b**) Number of product approvals in one or both regions over the indicated periods.

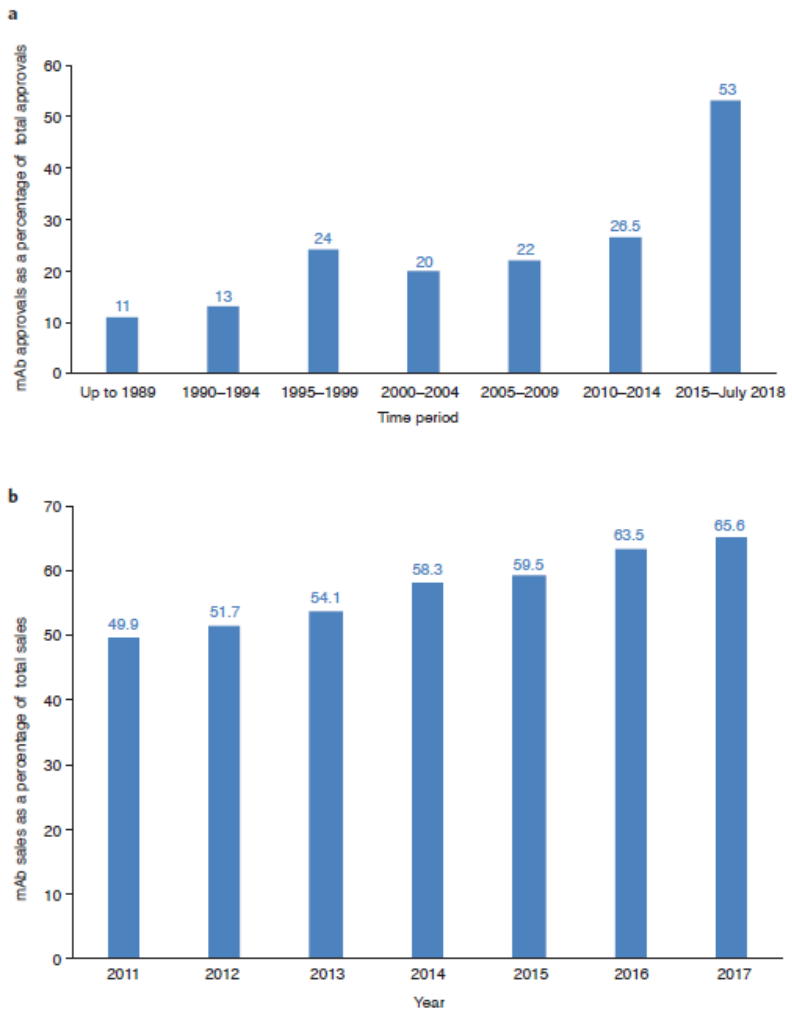


Figure 2 Overview of mAb approvals. (**a**) mAbs approved for the first time in the indicated periods, expressed as a percentage of total biopharmaceuticals approved for the first time in the same time period. (**b**) mAbs global annual sales value expressed as a percentage of total biopharmaceutical global sales for the indicated years. Financial data from La Merie Business Intelligence.

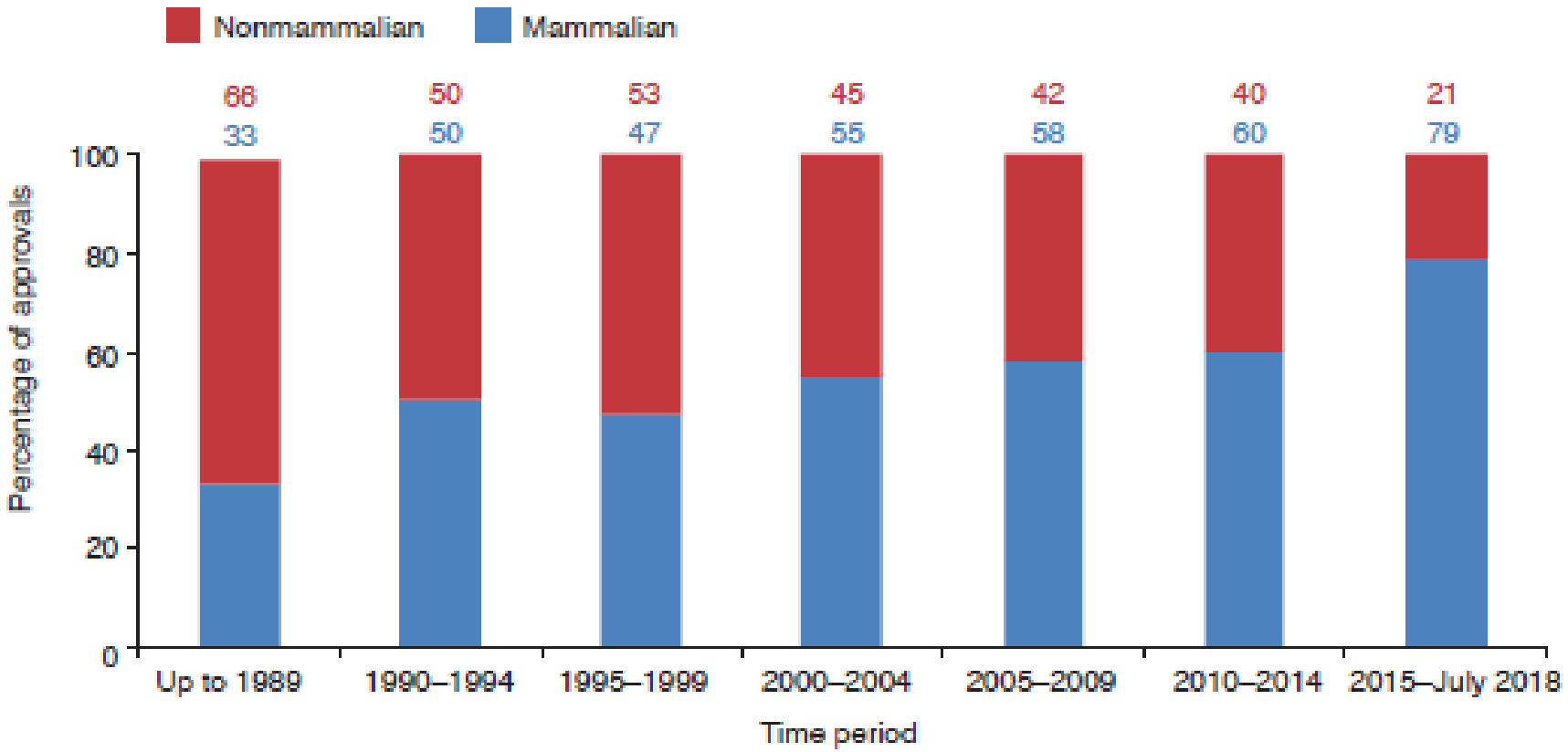


Figure 3 Relative use of mammalian- versus nonmammalian-based production cell lines in the manufacture of biopharmaceuticals approved over the indicated periods. Each dataset is expressed as a percentage of total biopharmaceutical product approvals for the period in question.

Exhibit 3: Biosimilar Savings Potential in the EU5 and U.S., for 8 Key Products in 2015–2020

Source: IMS Health, MIDAS, IMS Health Market Prognosis; IMS Institute for Healthcare Informatics, Dec 2015

EMA (European Medicine Agency)

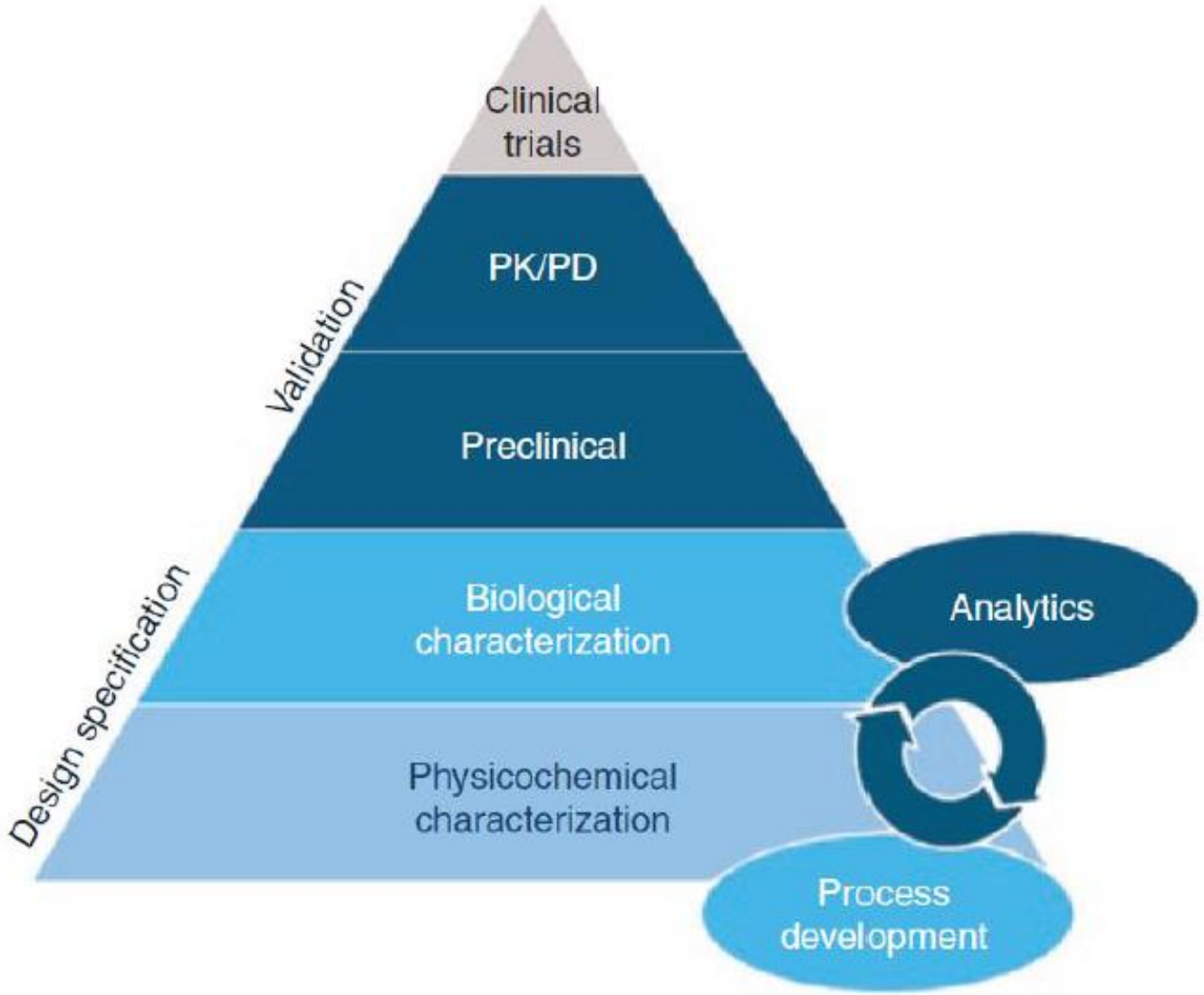
- A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product) in the European Economic Area (EEA).
- Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a con quality characteristics, biological activity, safety and efficacy EMEA/CHMP/BMWP/42832/2005 Rev1

FDA (Food and Drug Administration)

- Biosimilar or biosimilarity means that "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components,"
- There are no clinically meaningful differences between the biological produ safety, purity, and potency of the product potency of the product

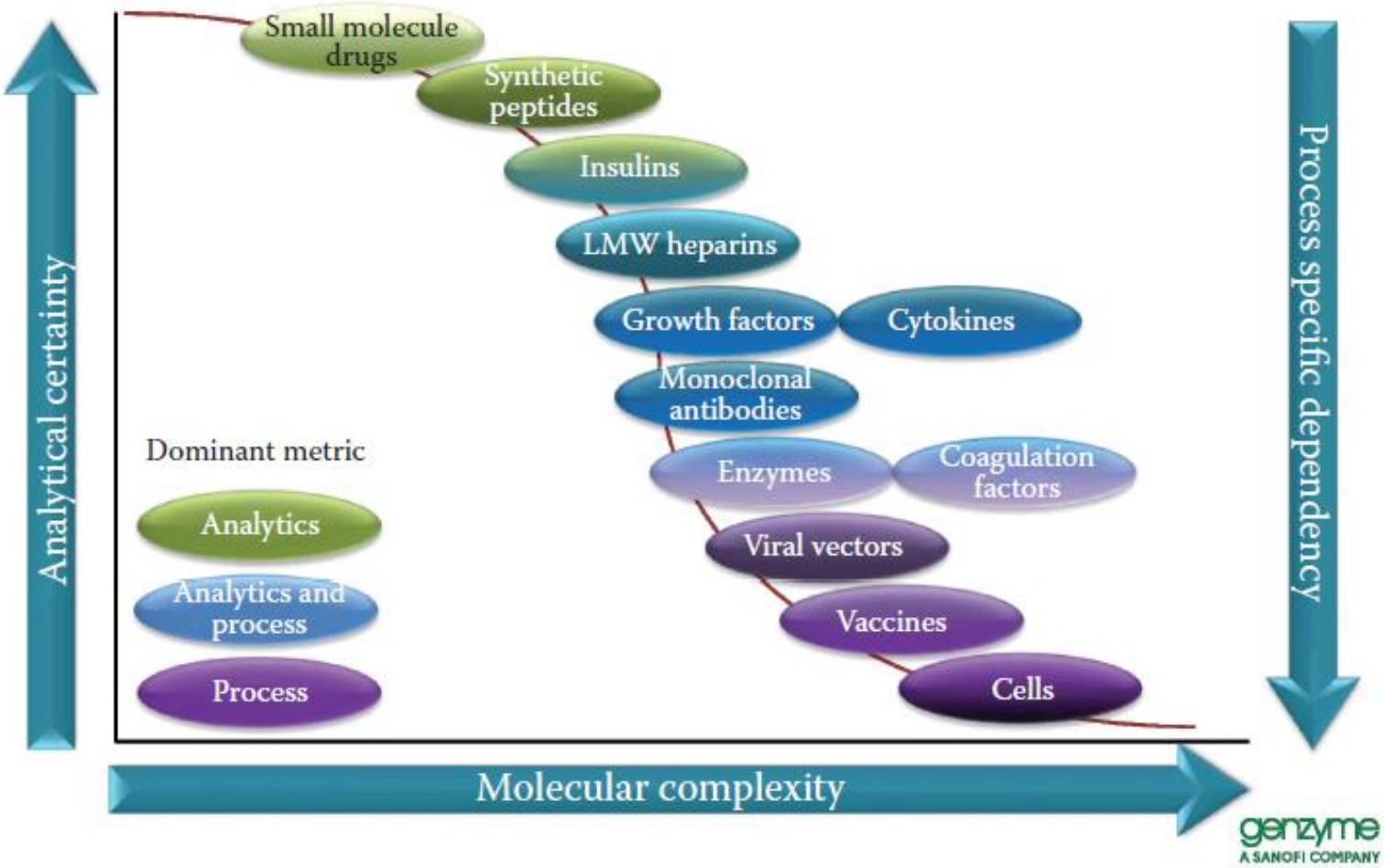
WHO (World Health Organisation)

- A biotherapeutic product which is similar in terms of quality, safety and efficacy to ar erapeutic product. quality, safety and efficacy

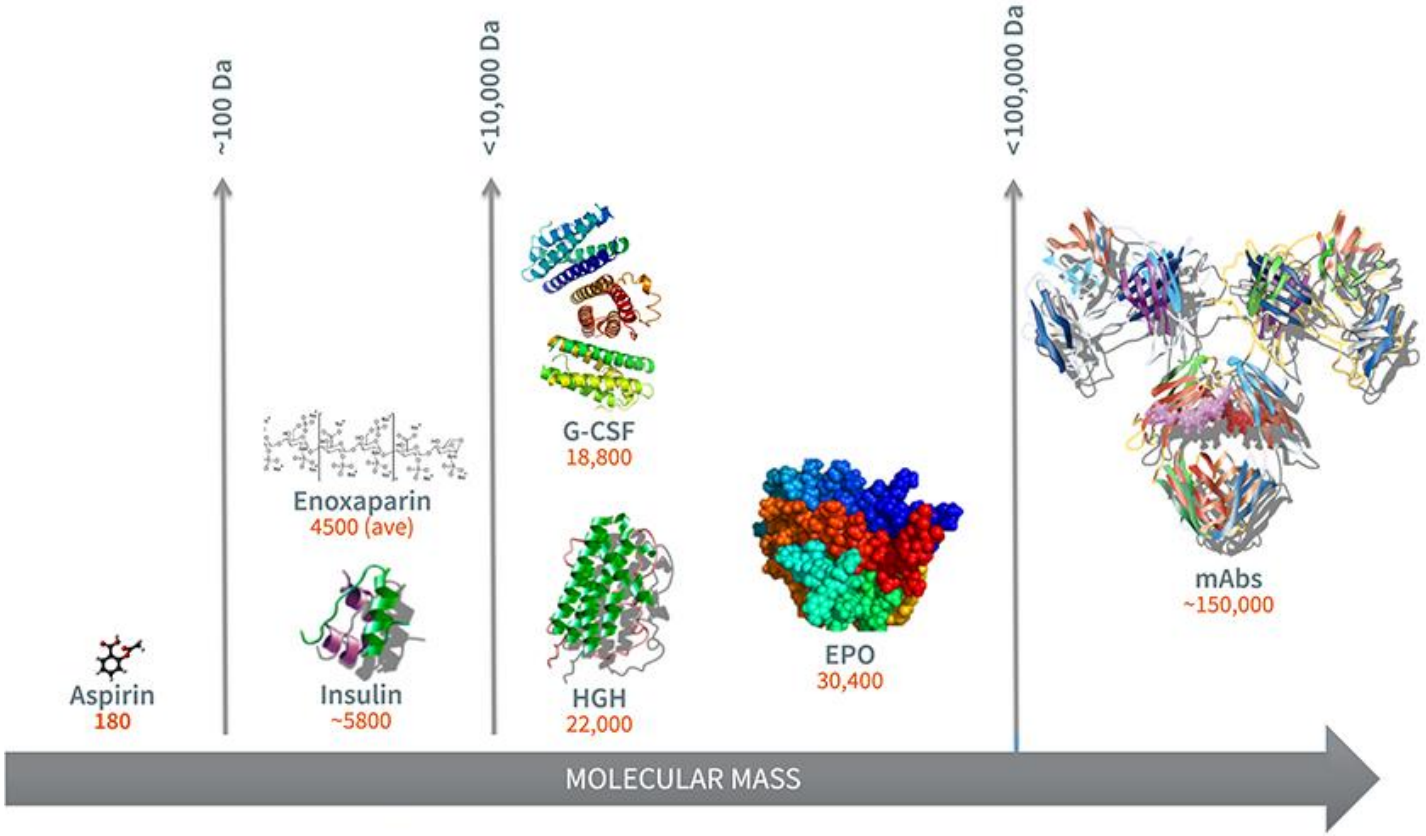


McCamish M and Woollett G. The state of the art in the development of biosimilars. 91(3):405–417)

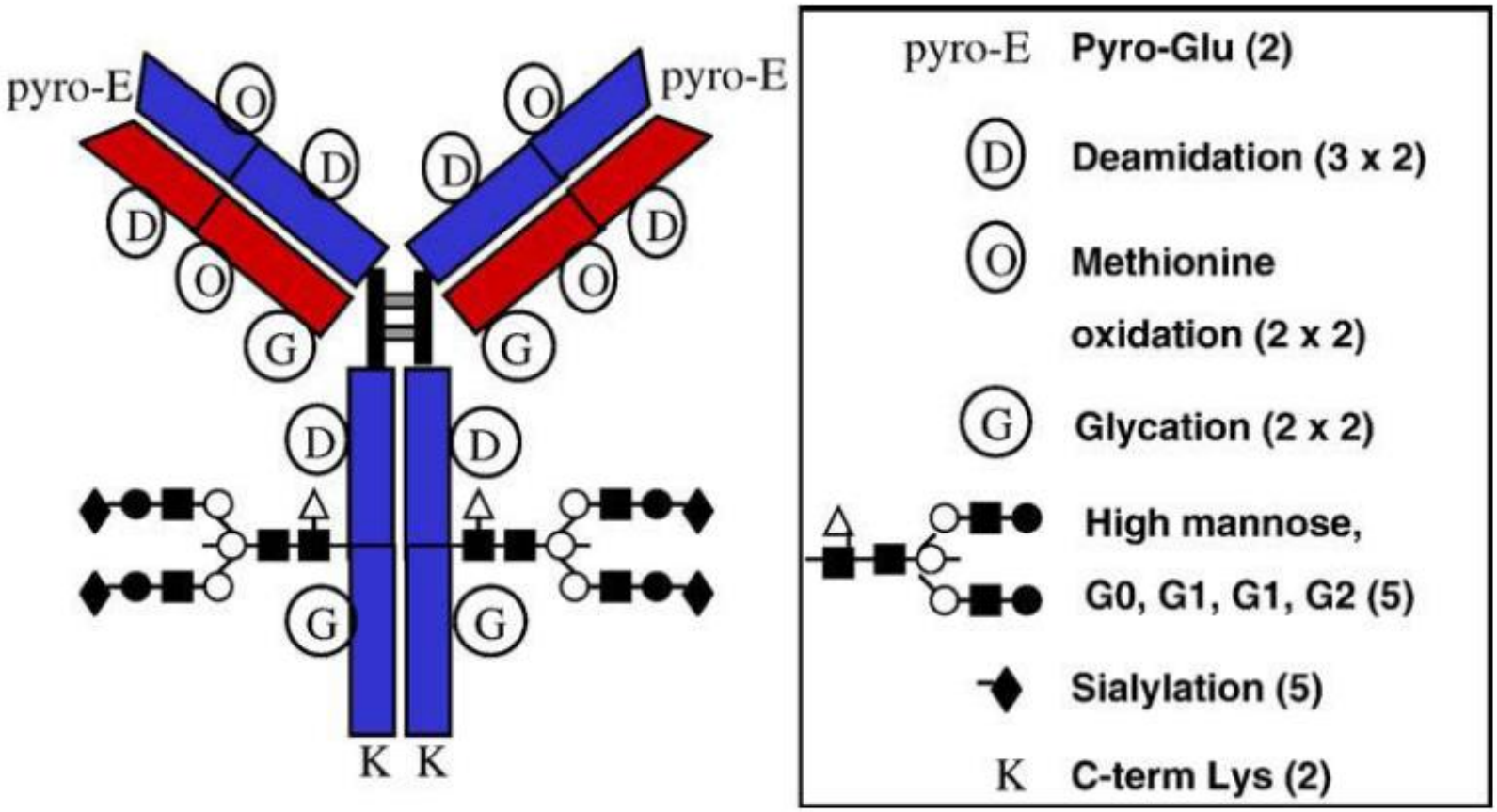
Not all biologics are created equal
Gradations of complexity



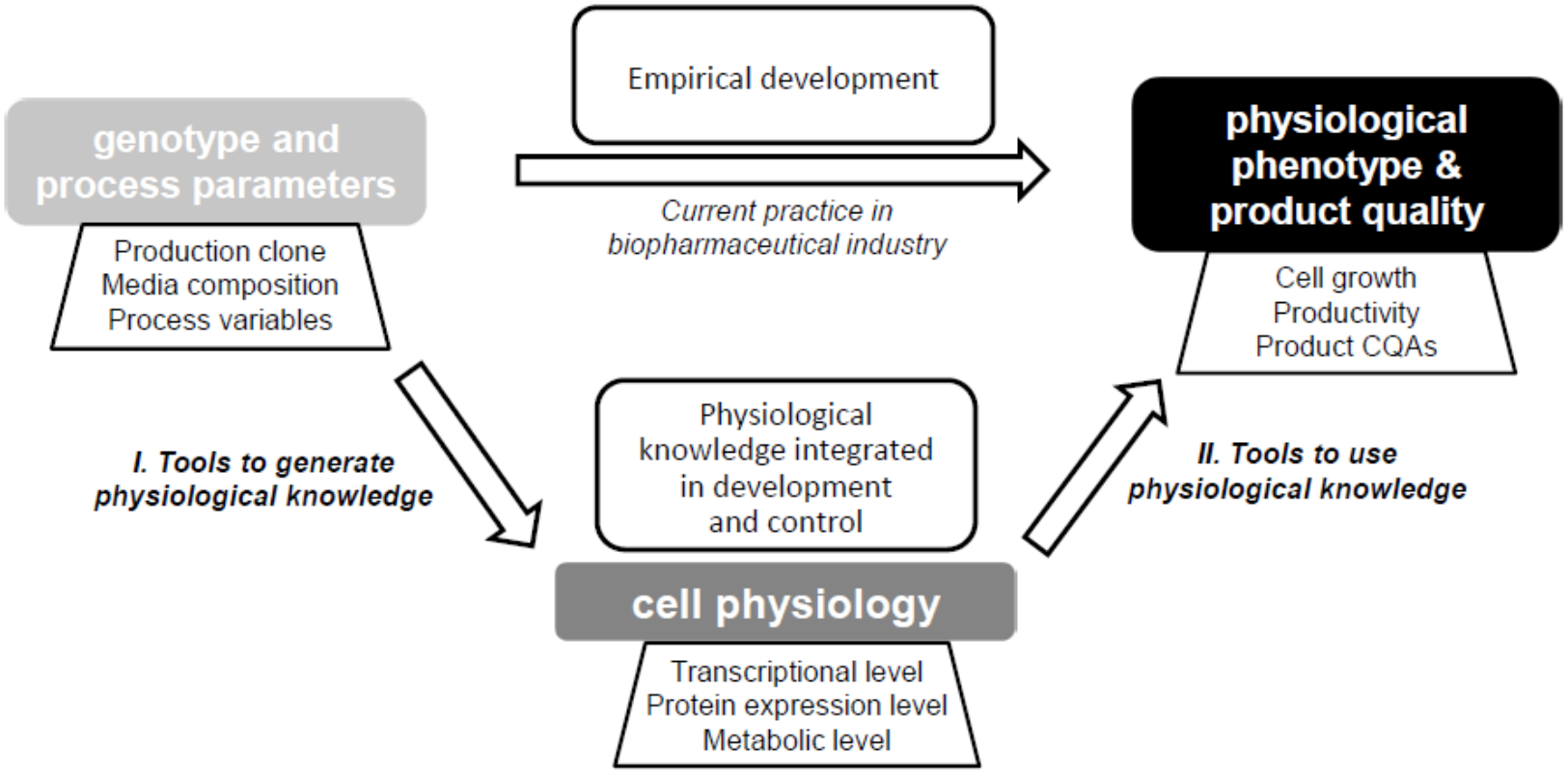
Structural complexity of biopharmaceuticals



Possible structural variants of an IgG1 molecule



Importance of ‚omics' in process development



Zalai et al. (Current Pharmaceutical Biotechnology, 2015, Vol. 16, No. 10)

2002 – FDA initiatives

- Pharmaceutical cGMPs for the 21st Century – A Risk-Based Approach

- Guidance for Industry – Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations

- Guidance for Industry – PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance

<u>2004 – approval of the documents</u>

Widespread acceptance of the initiatives

ASTM Committee E55 on Pharmaceutical Application of PAT

E 2363 - 06a
Standard Terminology Relating to Process Analytical Technology in the Pharmaceutical Industry

E 2474 – 06
Standard Practice for Pharmaceutical Process Design Utilizing Process Analytical Technology

E 2476 – 09
Standard Guide for Risk Assessment and Risk Control as it Impacts the Design, Development and Operation of PAT Processes for Pharmaceutical Manufacture

The overall goal of QbD is to maintain a state of **CONTROL** for biopharmaceutical products and their manufacturing processes over their **LIFE CYCLES** through design, definition, and implementation of proper control strategies.

ICH Guidelies related to Quality by Design

ICH Q8(R2) *Pharmaceutical Development* provides guidelines for drug product development. ICH Q8 defines QbD as "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management" (5). This guideline outlines the principles for potentially achieving increased regulatory flexibility.

ICH Q9 *Quality Risk Management* provides principles and examples of tools for quality risk management that can be applied to all aspects of pharmaceutical quality, including development, manufacturing, distribution, and inspection and submission/review. This document states that risk assessment should be based on sound scientific knowledge and that the level of risk assessment activities should be a function of the level of risk (6, 7).

ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

ICH Guidelies related to Quality by Design

ICH Q10 *Pharmaceutical Quality System* applies to pharmaceutical drug substances and drug products throughout their lifecycles and provides a comprehensive model for pharmaceutical quality based on ISO standards. It is intended to promote innovation and continual improvement in pharmaceutical manufacturing (7). It outlines a pharmaceutical company's responsibilities and ICH expectations (8). This guideline introduces the concept of "phase-appropriate" development.

ICH Q11 *Development and Manufacture of Drug Substances* covers the development and manufacturing process of drug substances (9). It provides an explanation of what should be included in the common technical document submission.

ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Figure 1: The quality by design (QbD) approach aligns with product and process development stages and clinical development phases. QbD provides milestones and assessments to facilitate product development and ensure quality. (BLA = biologics license application)

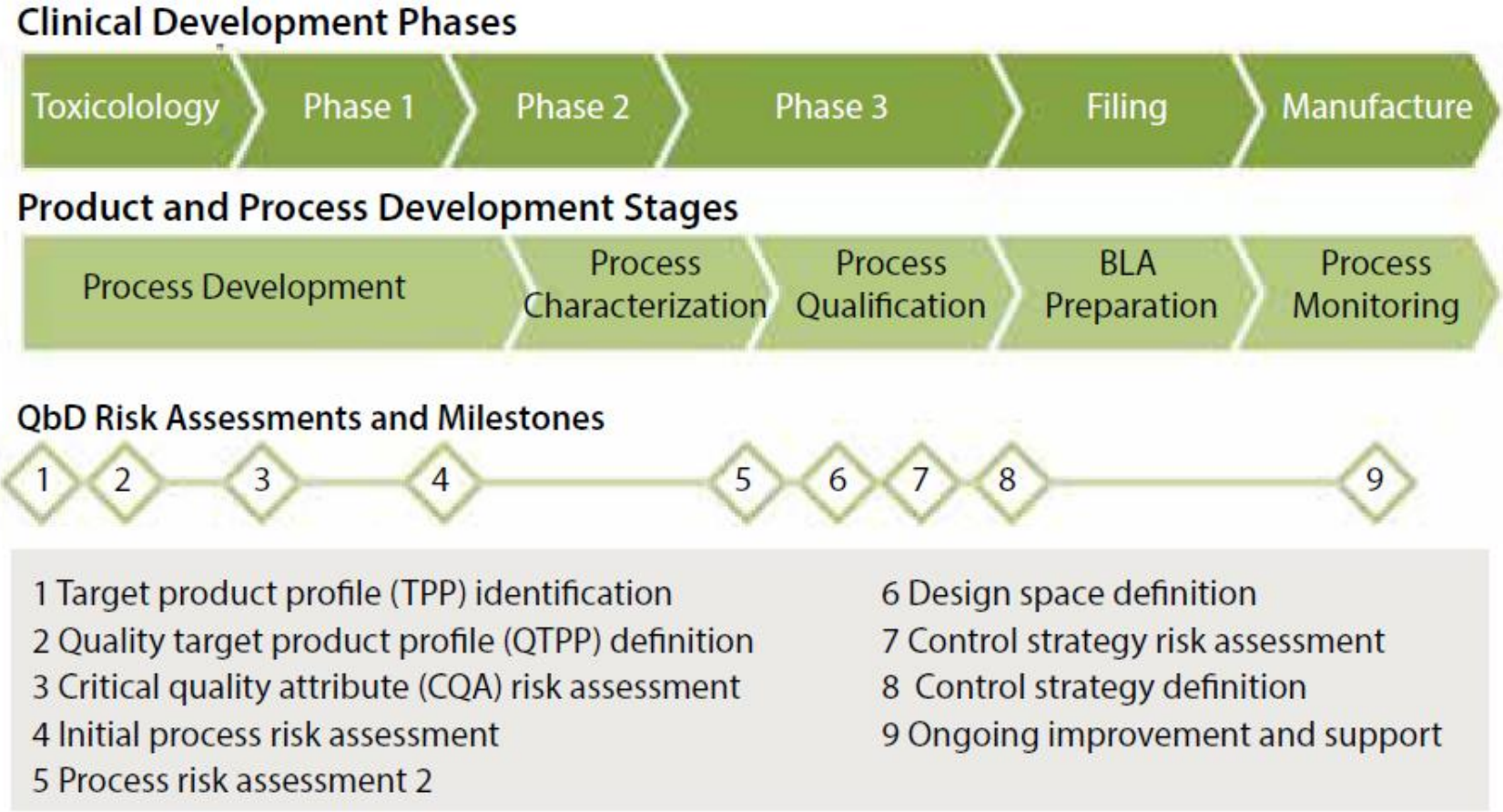


Figure 2: Critical quality attributes (CQAs) are determined by assessing the product quality attributes in a risk assessment. Clinical and nonclinical studies, toxicology studies, and prior knowledge elements are taken into consideration in this process.

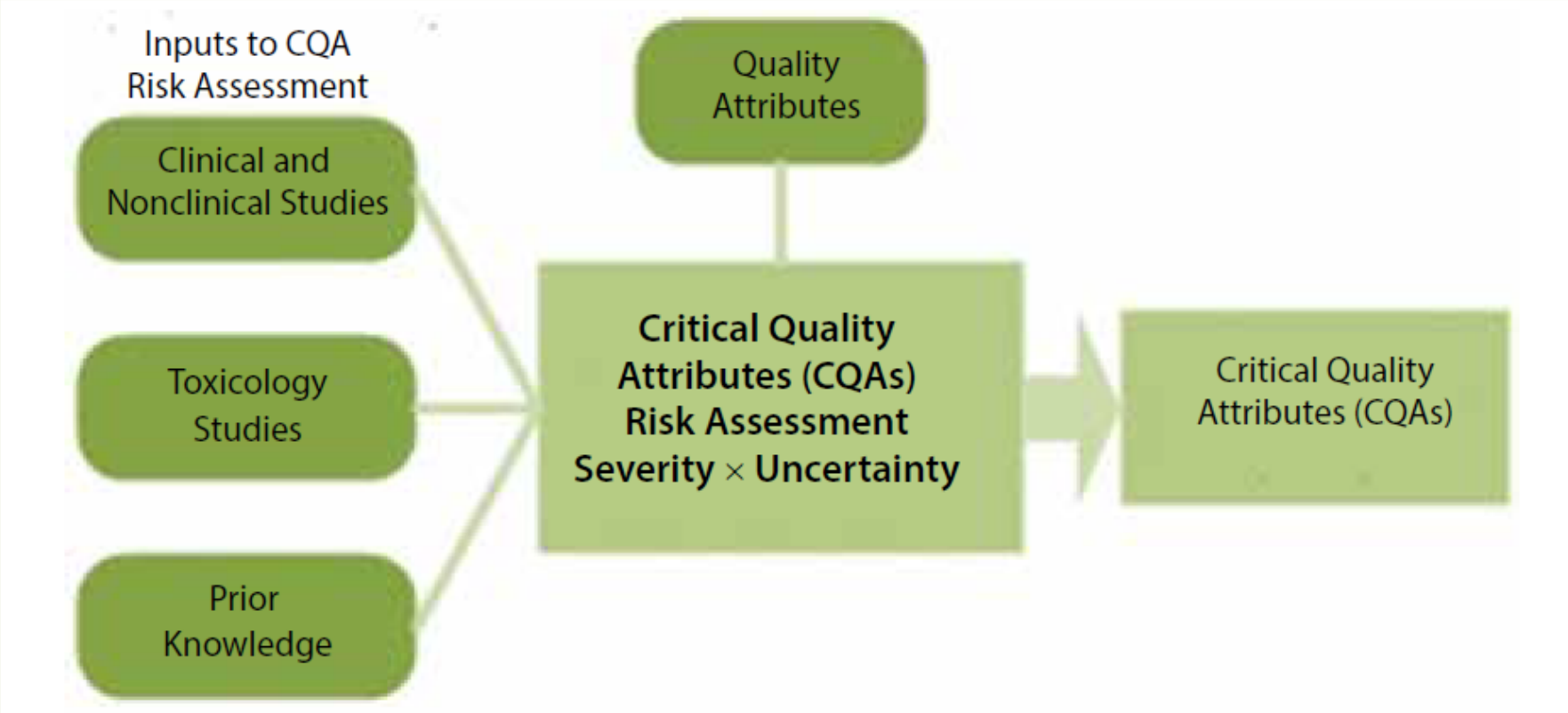


Figure 3: Prior knowledge elements are essential to CQA risk assessment. They are weighted to determine the uncertainty score. A product with no preexisting knowledge would result in the highest uncertainty score whereas a product with existing clinical data would result in a low uncertainty score. (Reprinted with permission from **19**)

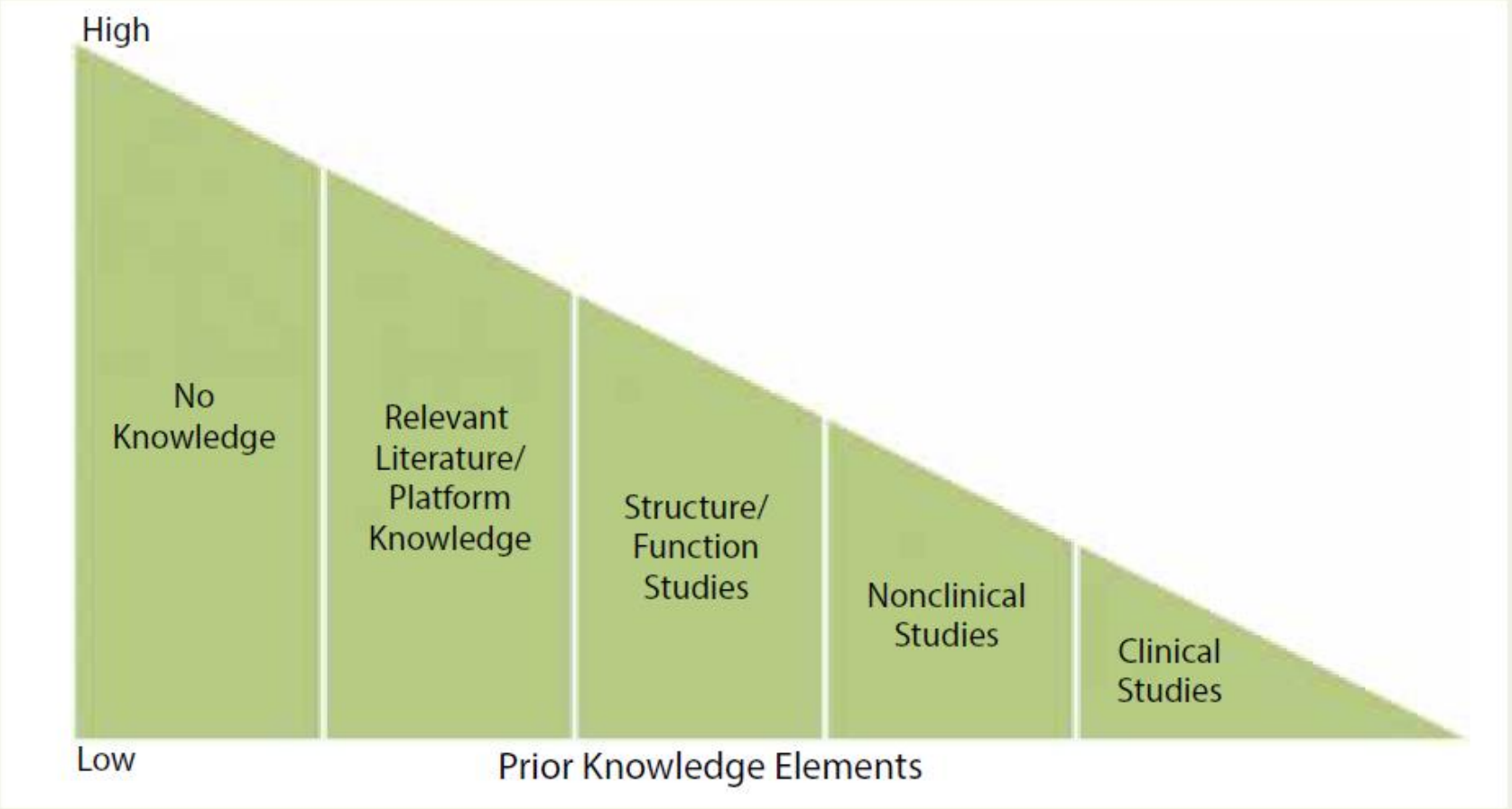


Figure 6: Relationship of process characterization studies to design space; process characterization studies examine the parameters identified as potentially critical by process risk analysis (PRA) to determine the acceptable amount of variability that can be tolerated in a process, which results in the setting of the characterization, acceptable, and operating ranges.

Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory postapproval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval. (5)

Figure 7: Development of a process control strategy

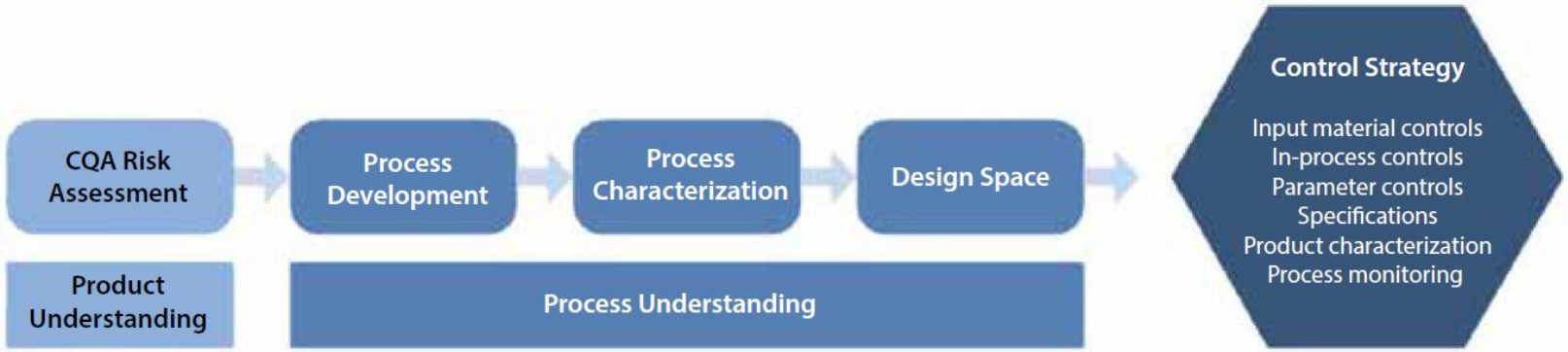


Table 1: Elements of a control strategy

Control Element	Description
Input material control	Control over raw material inputs should be based on the risk their variability poses to a given critical quality attribute (**26**).
Process Control Elements	
In-process controls	In-process controls (IPCs) include controls of facility, equipment, and quality systems ensuring that proper product quality is achieved (**14**). IPCs are inputs to the process that serve as checks to maintain it (**26**).
Process parameter controls	Process parameter controls ensure that CPPs are within limitations established by a design space (**14**).
Performance parameter controls	Performance parameter controls are process outputs that cannot be directly controlled but are indicative of process performance (**26**).
Testing Control Elements	
In-process and release specifications	Specifications and acceptance criteria guarantee that product quality targets are met (**14, 26**).
Product characterization	Product characterization involves testing attributes to monitor a process (**14**).
Process monitoring	Process monitoring consists of testing attributes and parameters used to ensure that CQAs are within a defined design space (**14, 15, 26**).

During commercial manufacturing, process knowledge gained can be used to make **ADJUSTMENTS** to the operating space inside the process design space, which could provide for greater efficiency and reliability.


BIOTECHNOLOGY
THANK YOU FOR YOUR ATTENTION!