CMC Regulatory Compliance Strategy For Biopharmaceuticals

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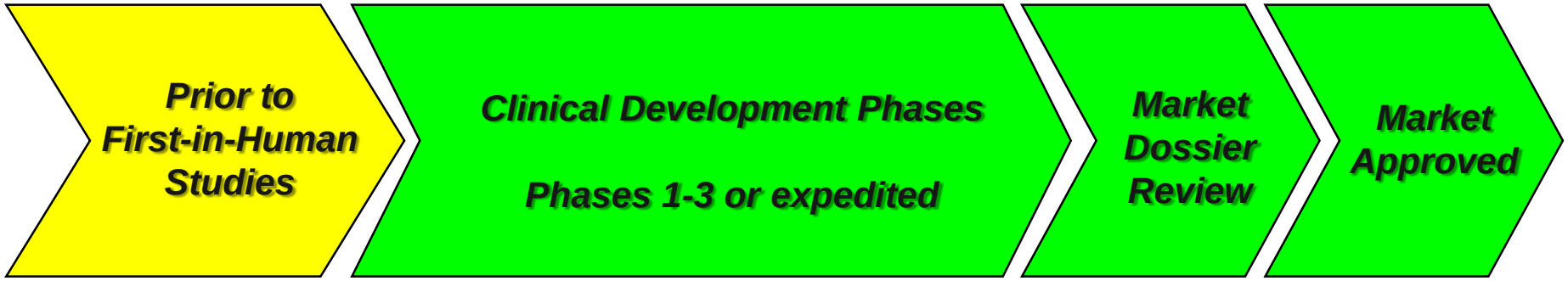
CMC Regulatory Compliance Strategy For Biopharmaceuticals

Course Goal

To help you, the attendee, develop a cost effective, risk-managed, CMC regulatory compliant strategy across the lifecycle of the diverse biopharmaceutical manufacturing processes and products



CMC Regulatory Compliance Strategy For Biopharmaceuticals

Course Outline

1. CMC Regulatory Challenges for Biologics Are Different
2. How to Develop an Effective Corporate Risk-Managed CMC Regulatory Compliance Strategy For Biopharmaceuticals
3. Applying a CMC Risk-Managed Control Strategy Throughout the Entire Biopharmaceutical Manufacturing Process
4. Major Challenge of Demonstrating Biopharmaceutical Product Comparability After Manufacturing Process Changes

Who is John Geigert, Ph.D., RAC?

"If you are humble, nothing will touch you, neither praise nor disgrace, because you know what you are"
Mother Teresa, Missionaries of Charity in Calcutta India, 1910-1997

- ***25 years corporate leadership in Chemistry, Manufacturing & Control (CMC) strategies, resulting in successful FDA and EMA market approval for six biopharmaceuticals***
- ***10 years as Vice President Quality & Compliance; CMC Expert (Immunex Corporation, IDEC Pharmaceuticals)***
- ***Chair, PDA's Biopharmaceutical Advisory Board***
- ***15 years as a CMC regulatory consultant to the biopharmaceutical industry, covering monoclonal antibodies, biosimilars, and gene therapy***

Who are you?

- ***My name is …. And I work at …. And I do the following ….***
- ***My experience with CMC regulatory compliance is ….***
- ***I have a burning CMC question which is ….***

Disclaimer

A number of biopharmaceutical companies will be mentioned in this course

There is no intent to criticize any specific company!
But thank you, for messing up so we can learn what not to do!

Plenty of information is included in my presentation

But, there is no inclusion of proprietary information!
Public references are provided in the notes!

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housekeeping

CMC Regulatory Compliance Strategy For Biopharmaceuticals

Course Outline

1. CMC Regulatory Challenges For Biologics are Different

- ✓ *Painting the terminology landscape used in our industry*
- ✓ *Biopharmaceuticals are not chemical drugs; regulatory compliance consequences of the CMC differences*
- ✓ *Biopharmaceutical medicines today can be non-living (protein-based) or living (virus-/cell-based)*

Biologic/Biological: Consensus Definition

(EMA, FDA, HC, WHO)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Definition of biological medicinal product

According to Part I of Annex I of Directive 2001/83/EC, it is a product that contains a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing together with the production process and its control.

3 components

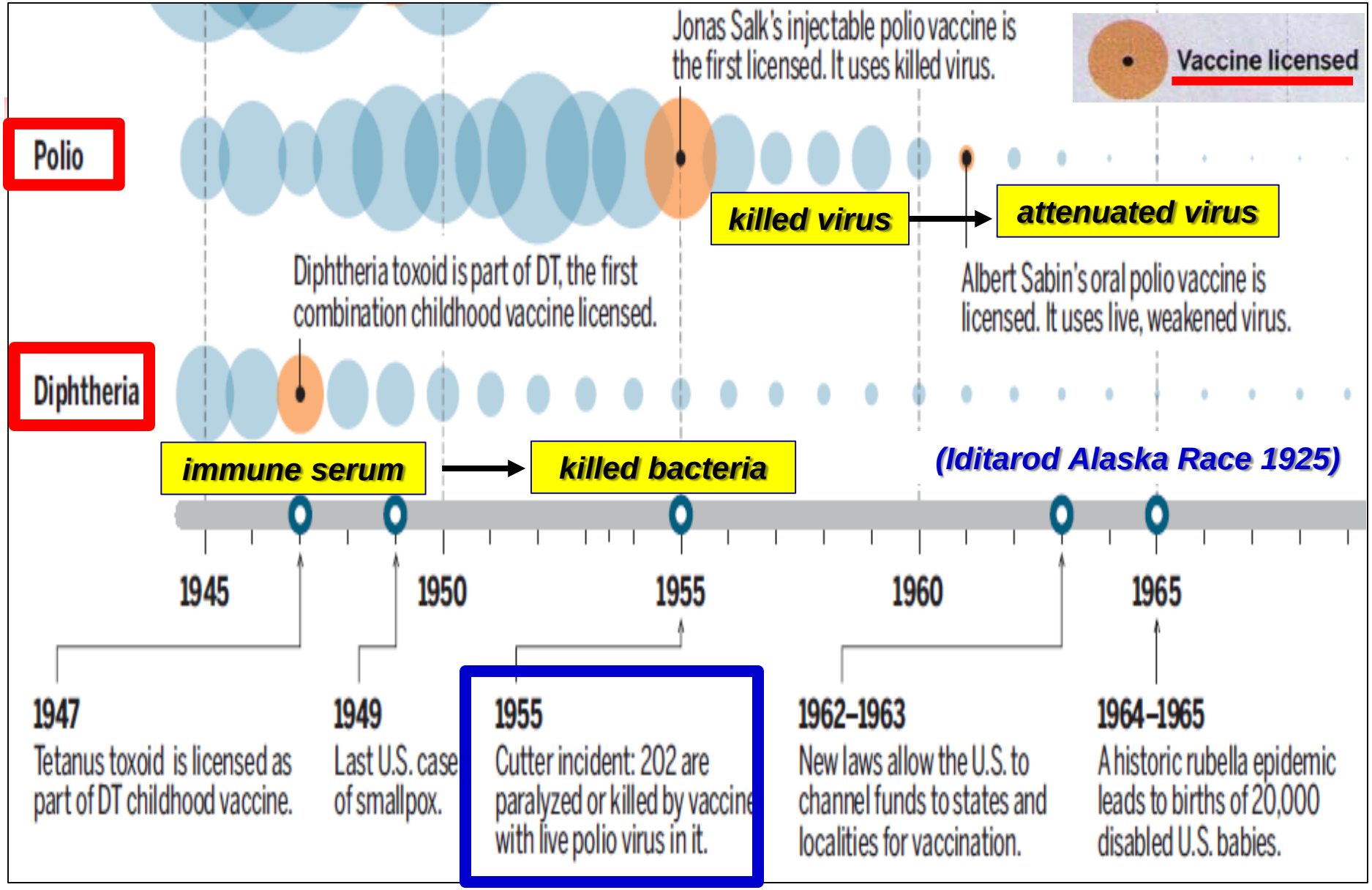
1) Derived from a living system
2) Challenging manufacturing process
3) Complex molecule

Biologics before Genetic Engineering

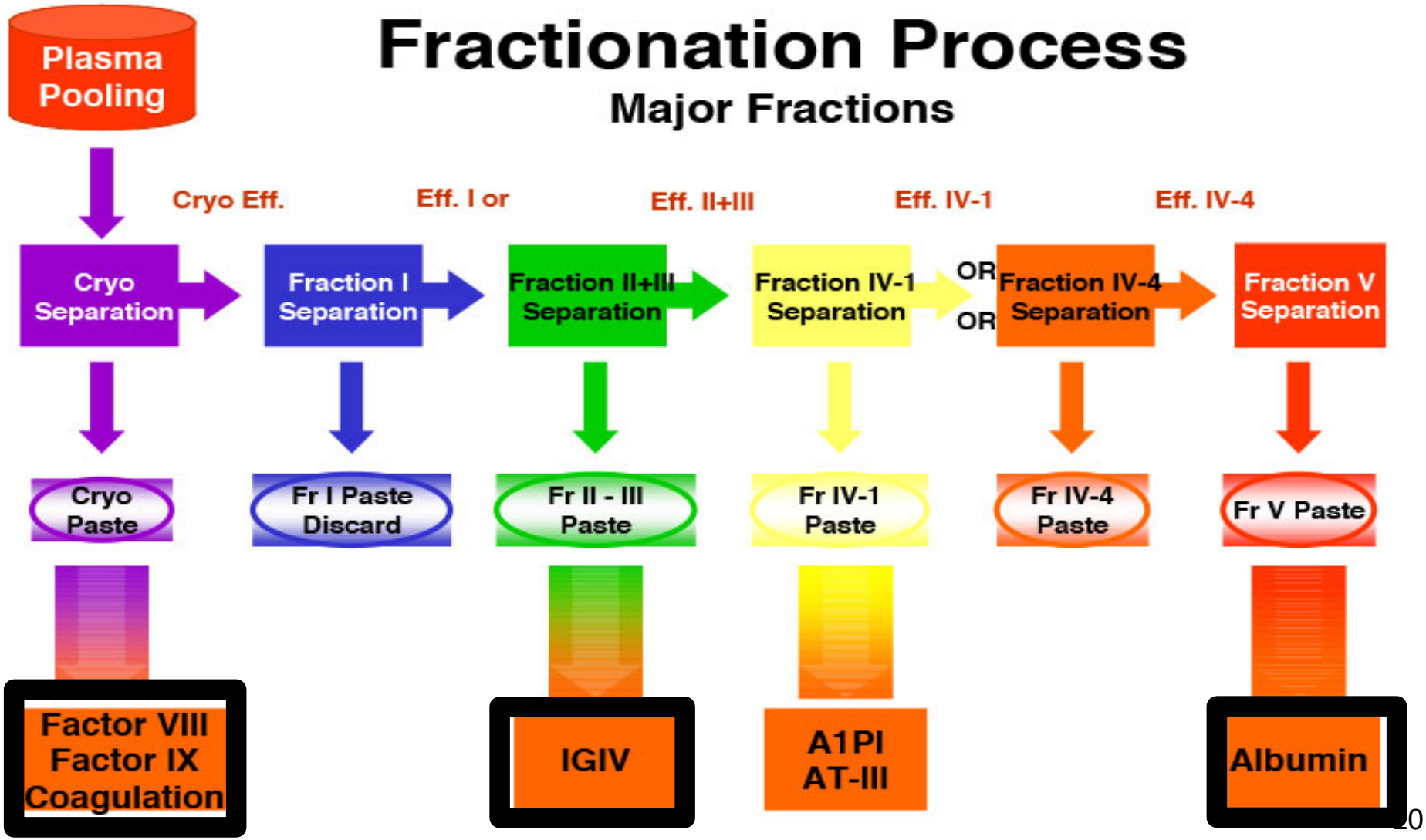
- ***Vaccines***
- ***Plasma-derived proteins***
- ***Protein Hormones***

Vaccines since 1940's

SCIENCE
28 APRIL 2017 • VOL 356 ISSUE 6336



Plasma-derived proteins extracted from human blood since 1940's



Extraction of porcine insulin from pig pancreases since 1930's

2 tons to make 8 oz of insulin

Eli Lilly porcine insulin final product

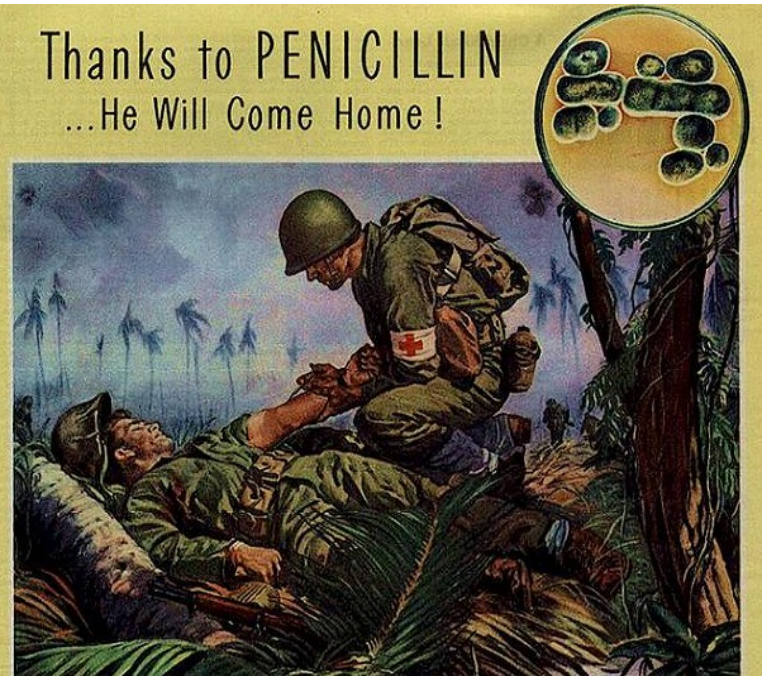
Caution: *just because a product is produced by a living organism does not make it a biologic!*

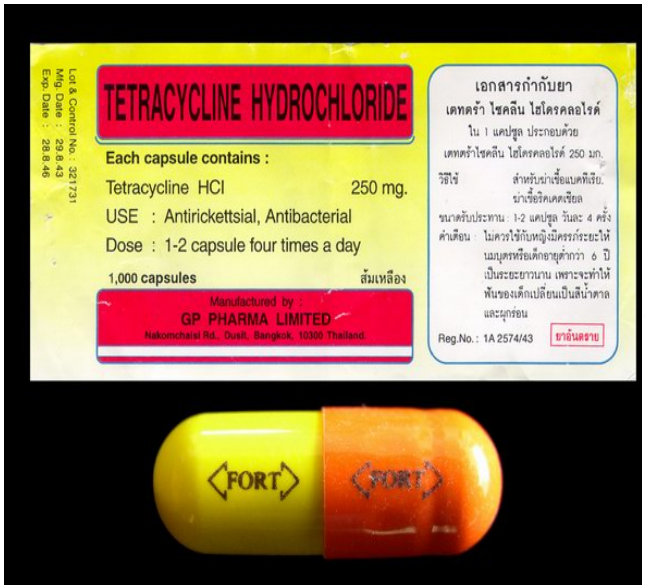
(also needs the other two components – challenge of the manufacturing process and product complexity!)

***Chemicals* also derived from a living source!**

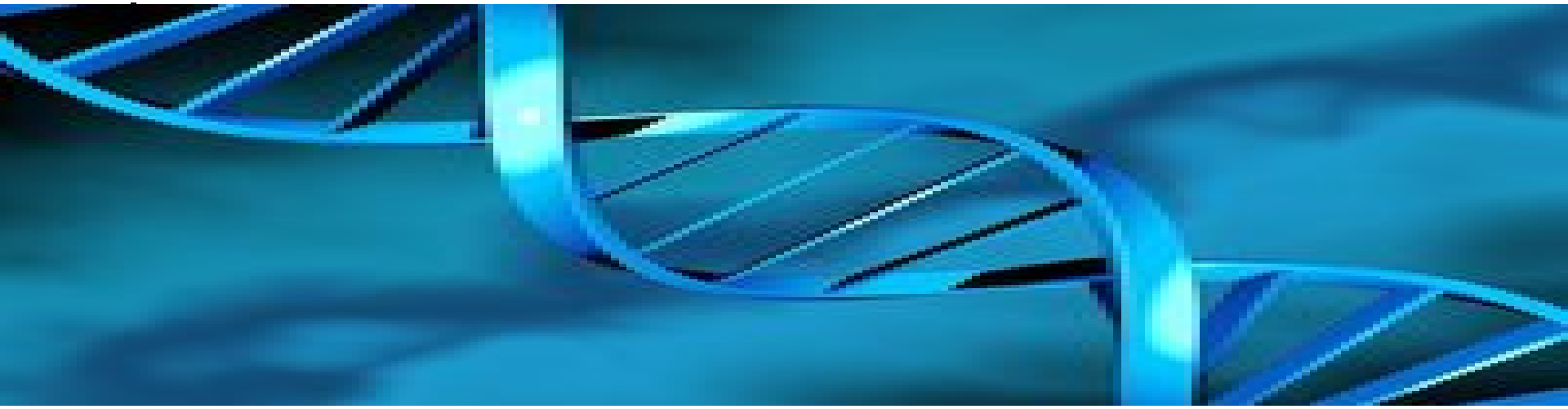
Antibiotics from living microorganism fermentations

(penicillin, cephalosporin, tetracycline, gentamicin)





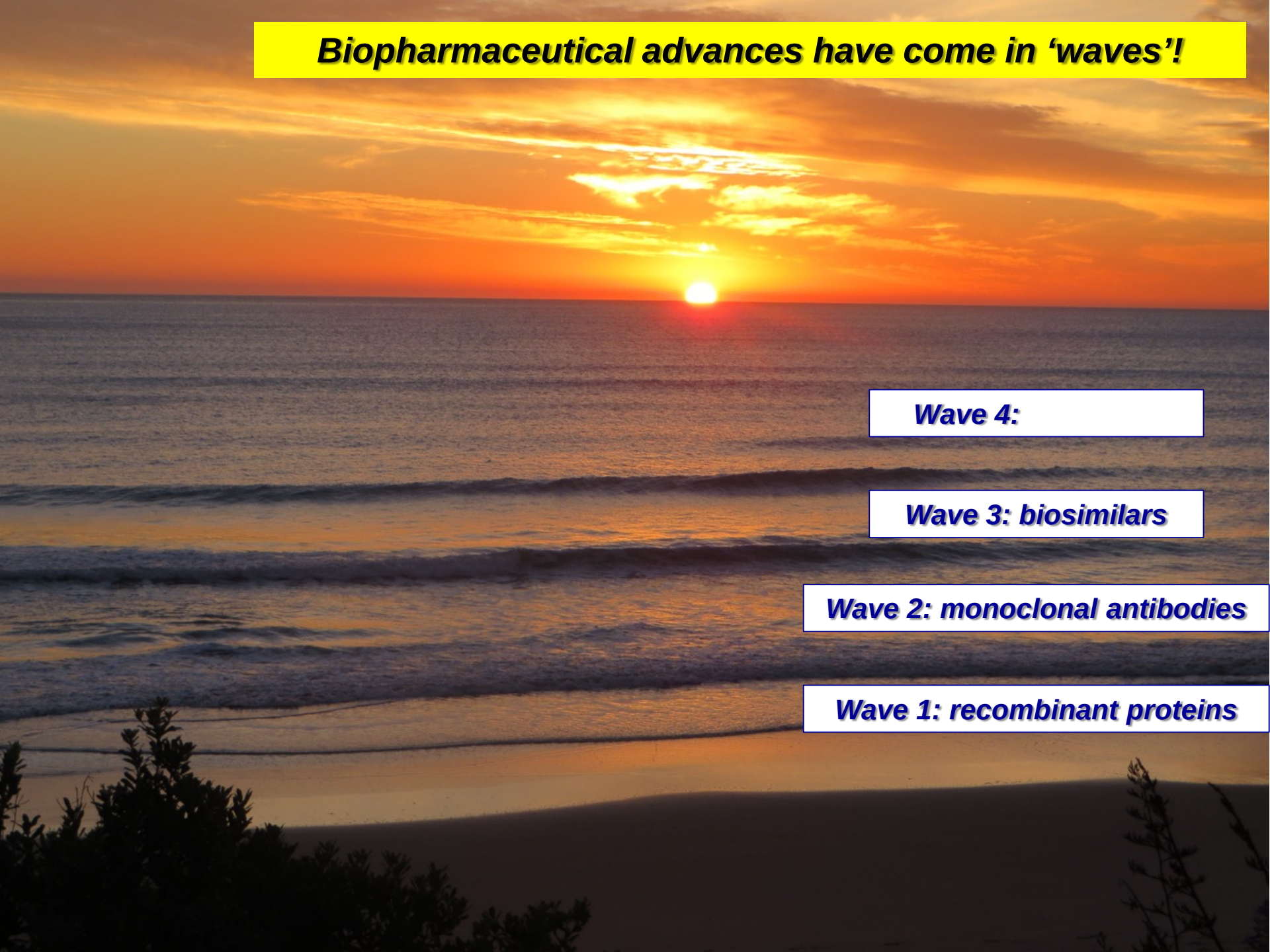
Biologics



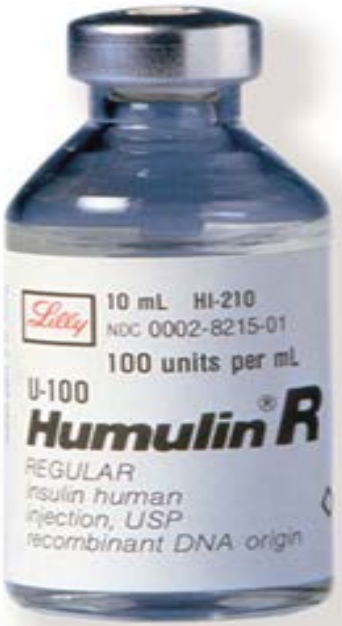
Biopharmaceuticals after Genetic Engineering

3 components

- Derived from a genetically engineered living system
- Challenging manufacturing process
- Must be a complex molecule


Biopharmaceutical advances have come in ‘waves’!
Wave 4:
Wave 3: biosimilars
Wave 2: monoclonal antibodies
Wave 1: recombinant proteins

WAVE 1:
Recombinant proteins



1982 1st recombinant protein

- ***Today, over 100 recombinant proteins on market***
- ***Enbrel (recombinant etanercept fusion protein)***
  – 3rd best selling drug in the world (2017)

www.nature.com/nrd 232 | APRIL 2018 | VOLUME 17

WAVE 2:

Monoclonal antibodies (recombinant clonal immunoglobulins)

1986 1st monoclonal antibody

- Murine → chimeric (part murine/part human → humanized
- Today, over 80 monoclonal antibodies on market
- Humira (adalimumab) – 1st best selling drug in the world (2017, >$16 billion)

www.nature.com/nrd
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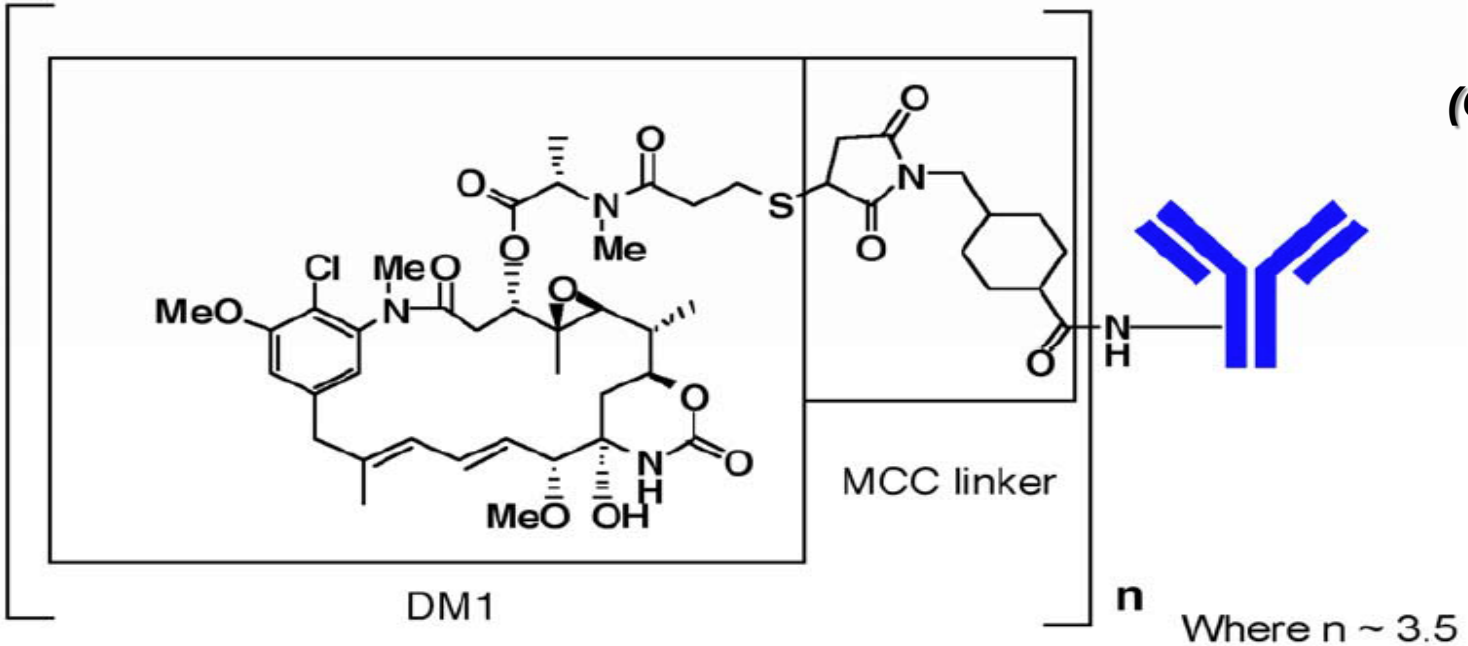
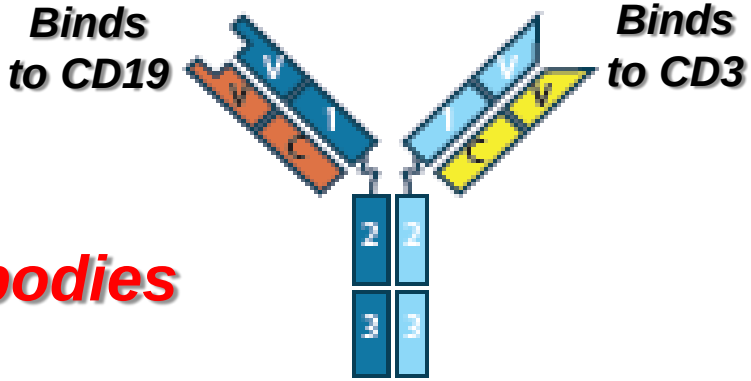
Antibody Drug Conjugates (ADCs)



Kadcyla (Genentech)

Note: The bracketed structure is DM1 plus MCC which represents the emtansine component. The n is, on average, 3.5 DM1 molecules per trastuzumab (Mab) molecule.

Bispecific Antibodies



Blincyto (Amgen)

***Caution*: 'Biopharmaceutical' term misused today!**

Most likely your company has the word "biopharmaceutical" on its website!

***current definition*: 'bio-health medicine'**

The term 'biopharmaceutical' has been applied to many chemically-synthesized drug products: antisense DNA, interference RNA, Hepatitis C medicines and HIV antivirals

Regulatory Authorities do not use the term 'biopharmaceutical'

- ***Biotech drug product***
- ***Biotechnology-derived drug***
- ***rDNA drug product***
- ***Recombinant DNA-derived drug***
- ***Biotherapeutic protein***

Not to be confused with 'biopharmaceutics'
(the study of drug properties related to patient administration)

WAVE 3:
Biosimilars

Innovator biopharmaceuticals that are off-patent; having no marketing exclusivity

'highly similar' to innovator's biopharmaceutical

Biosimilars to
<u>Recombinant Proteins</u>

Erythropoietin (EPO)
Follicle Stimulating Hormone (FSH)*
Parathyroid Hormone (PTH)*
G-Colony Stimulating Factor (G-CSF)
Human Insulin (HI)*
Human Growth Hormone (HGH)*
TNF-α/Fc Fusion Protein (Enbrel)
Pegylated-G-CSF

Biosimilars to
<u>Monoclonal Antibodies</u>

Infliximab (Remicade)
Adalimumab (Humira)
Rituximab (Rituxin/MabThera)
Trastuzumab (Herceptin)
Bevacizumab (Avastin)

Due to limited scientific understanding, biosimilars are currently limited to recombinant proteins and MAbs

**** Follow-on proteins in USA***

The biopharmaceutical industry 'may' experience a 4rd wave of advance in the near future

Gene therapy products that produce durable effects may be part of the larger class of regenerative medicine products. And the pace of progress in gene therapy has been somewhat breathtaking… Just this year we saw the first three approvals of gene therapies: two cell-based gene therapies for blood cancers, and a directly administered gene therapy to address a form of hereditary retinal dystrophy. The promise is very much becoming a reality. These recent product approvals represent just the tip of the iceberg. FDA has more than 500 active investigational new drug applications involving gene therapy products. We've received more than one hundred such applications last year alone.

FDA – Speeches by FDA Officials: Remarks by Commissioner Gottlieb to the Alliance for Regenerative Medicine's Annual Board Meeting (May 22, 2018)

WAVE 4:
Living virus and cell biologics

US Food and Drug Administration (FDA)

Cellular and Gene Therapy Products (CGTPs)

- Gene Therapy
- Cellular Therapy
- Tissue-Product

(RMATs)

European Medicines Agency (EMA)

Advanced Therapy Medicinal Products (ATMPs)

- Gene Therapy
- Somatic Cell Therapy
- Tissue Engineered

Oncolytic Virus: genetically engineered virus that infects target tumor cells

Gene Therapy: rather than inject proteins into humans, inject the genes that can produce the protein in a human – either directly or ex vivo

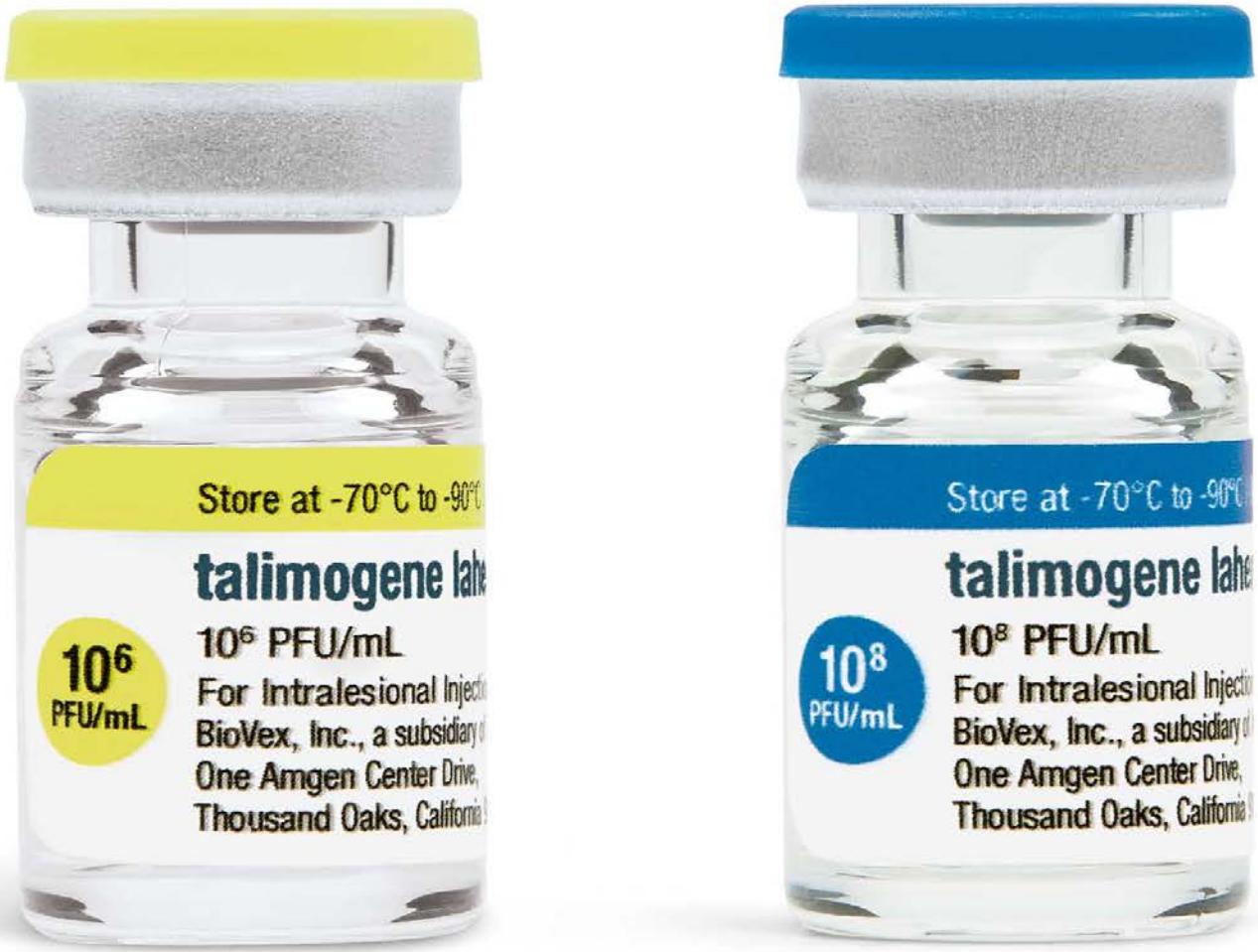
Cellular Therapy: manipulating ex vivo cells to enhance a medical effect

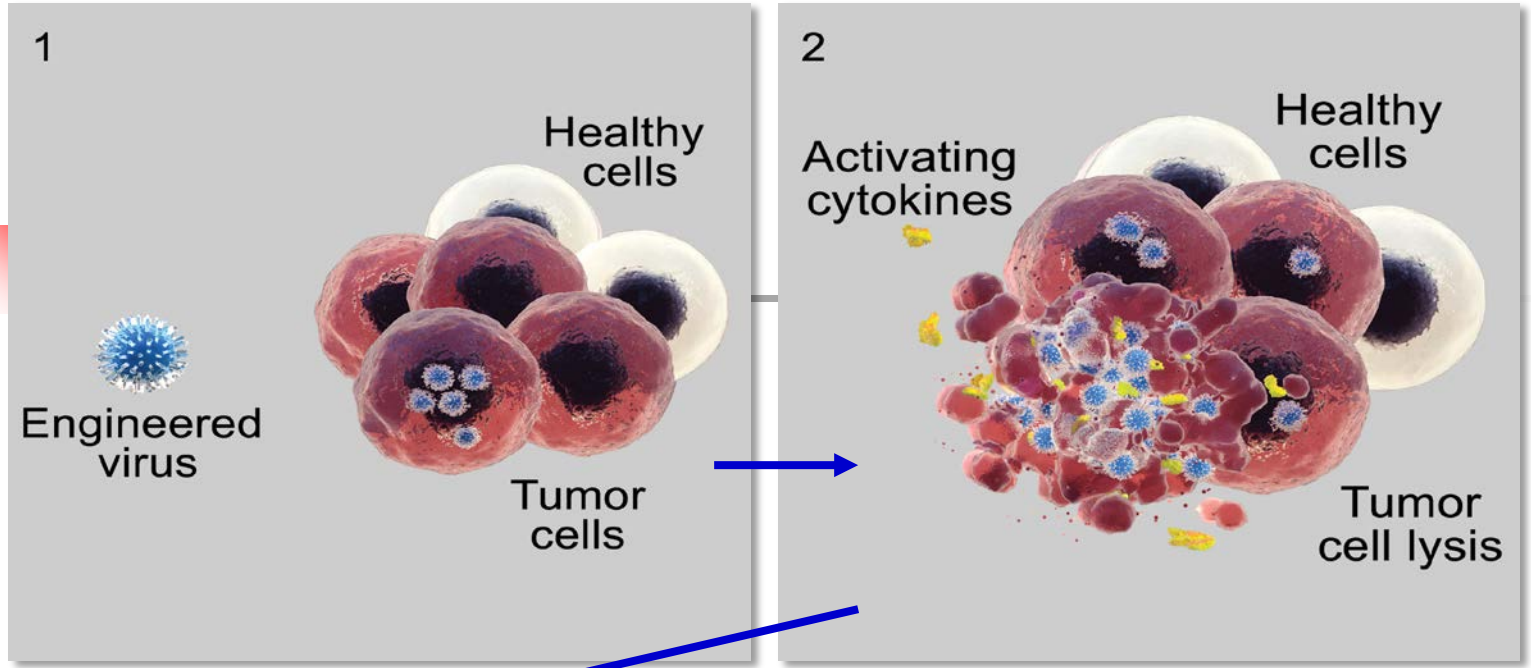
Oncolytic virus – in vivo

Amgen IMLYGIC

genetically engineered HSV virus (GM-CSF gene)

to treat melanoma FDA/EMA approved 2015





Local effect

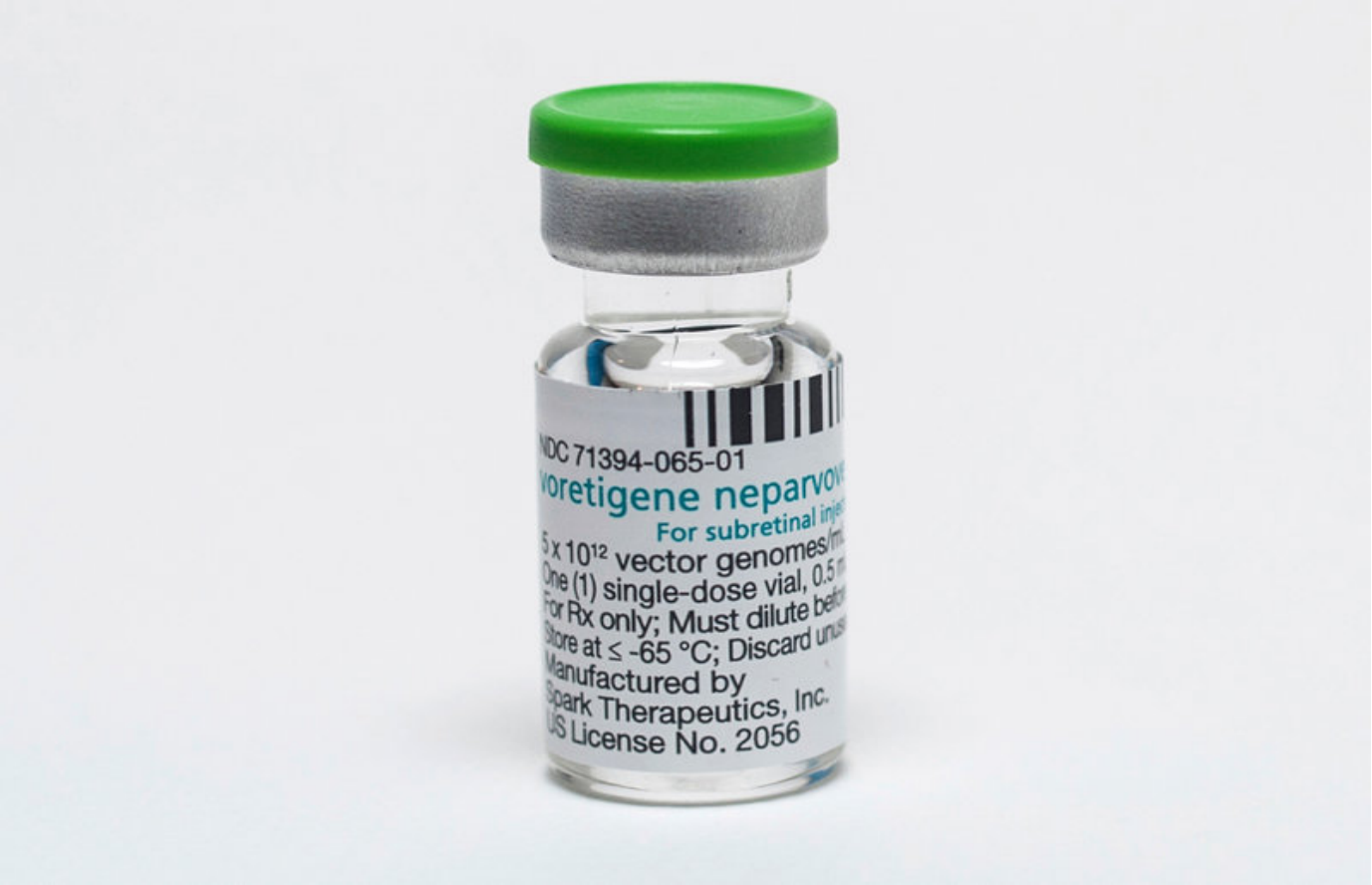
Systemic effect

Gene therapy – in vivo

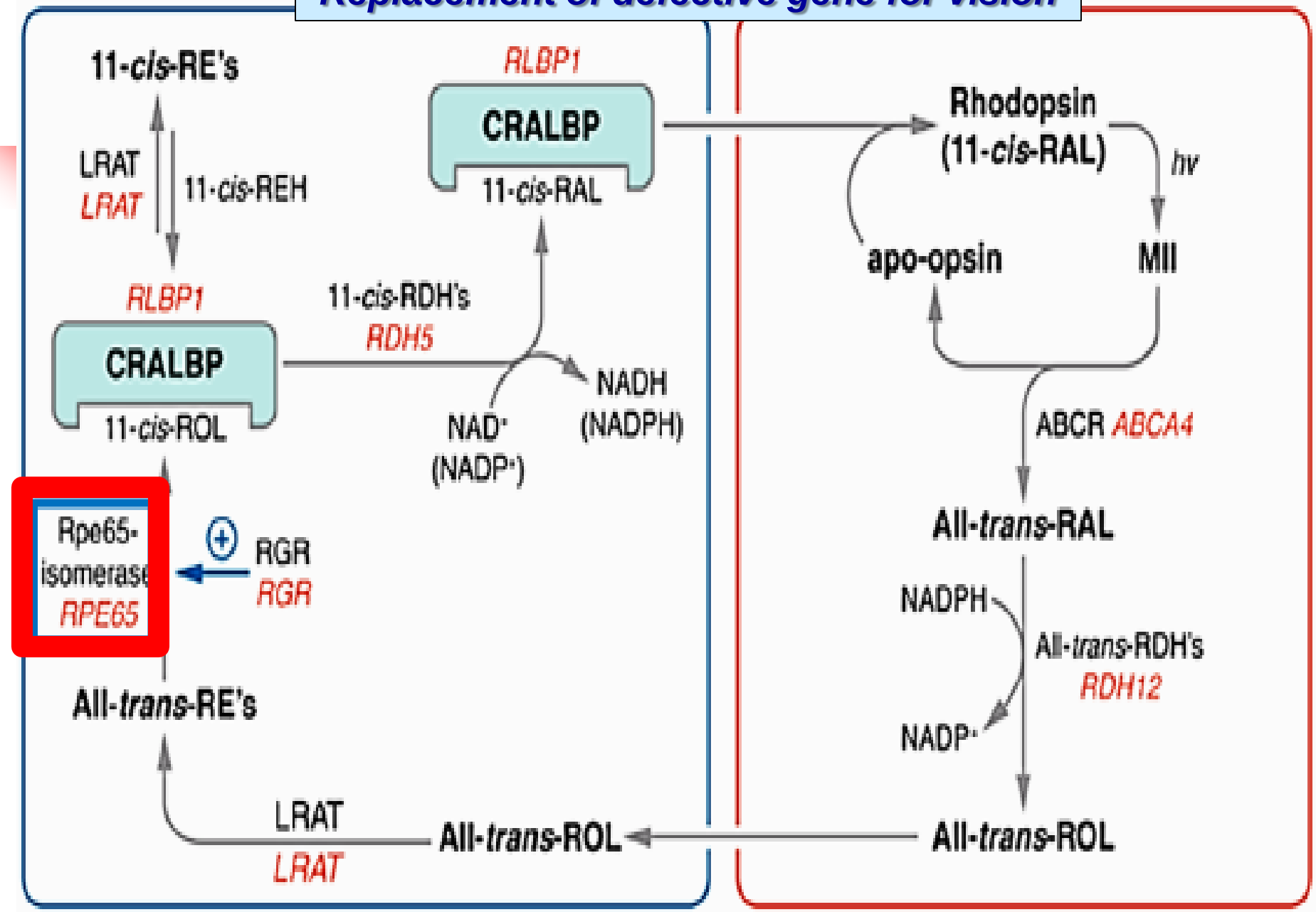
Spark Therapeutics LUXTERNA

adeno-associated virus vector

for the treatment of biallelic RPE65 retinal dystrophy FDA approved 2017



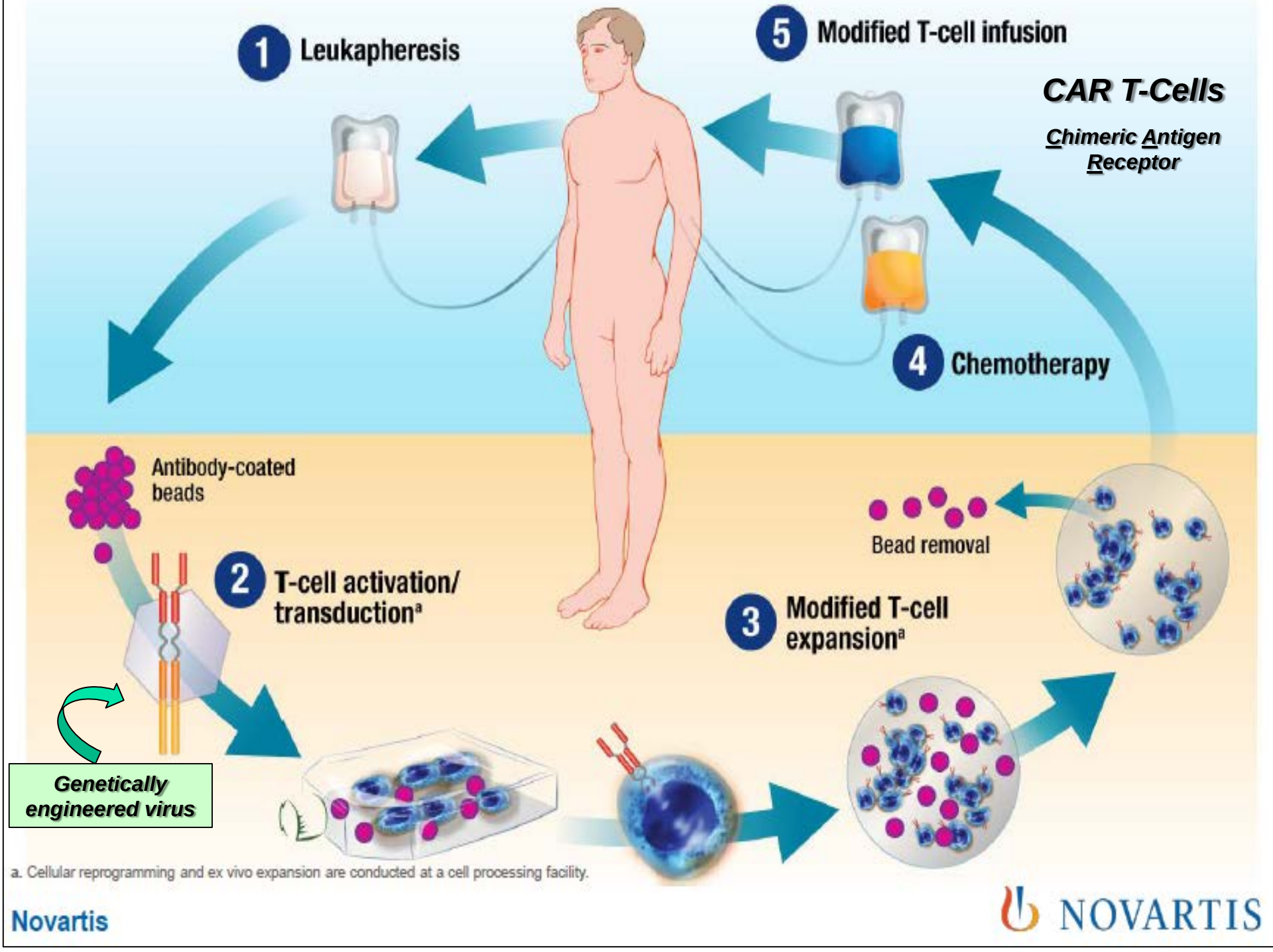
Replacement of defective gene for vision



Gene therapy – ex vivo

Novartis KYMRIAH

CD19-directed genetically modified autologous T cell immunotherapy to treat acute lymphoblastic leukemia (ALL) FDA approved 2017


1 Leukapheresis
5 Modified T-cell infusion
CAR T-Cells
Chimeric Antigen Receptor
4 Chemotherapy
Antibody-coated beads
2 T-cell activation/ transduction[a]
Bead removal
3 Modified T-cell expansion[a]
Genetically engineered virus
a. Cellular reprogramming and ex vivo expansion are conducted at a cell processing facility.
Novartis
NOVARTIS

Pharmaceutical

Chemical Drug

- Chemical Synthesis
- Natural Sourced

Generics

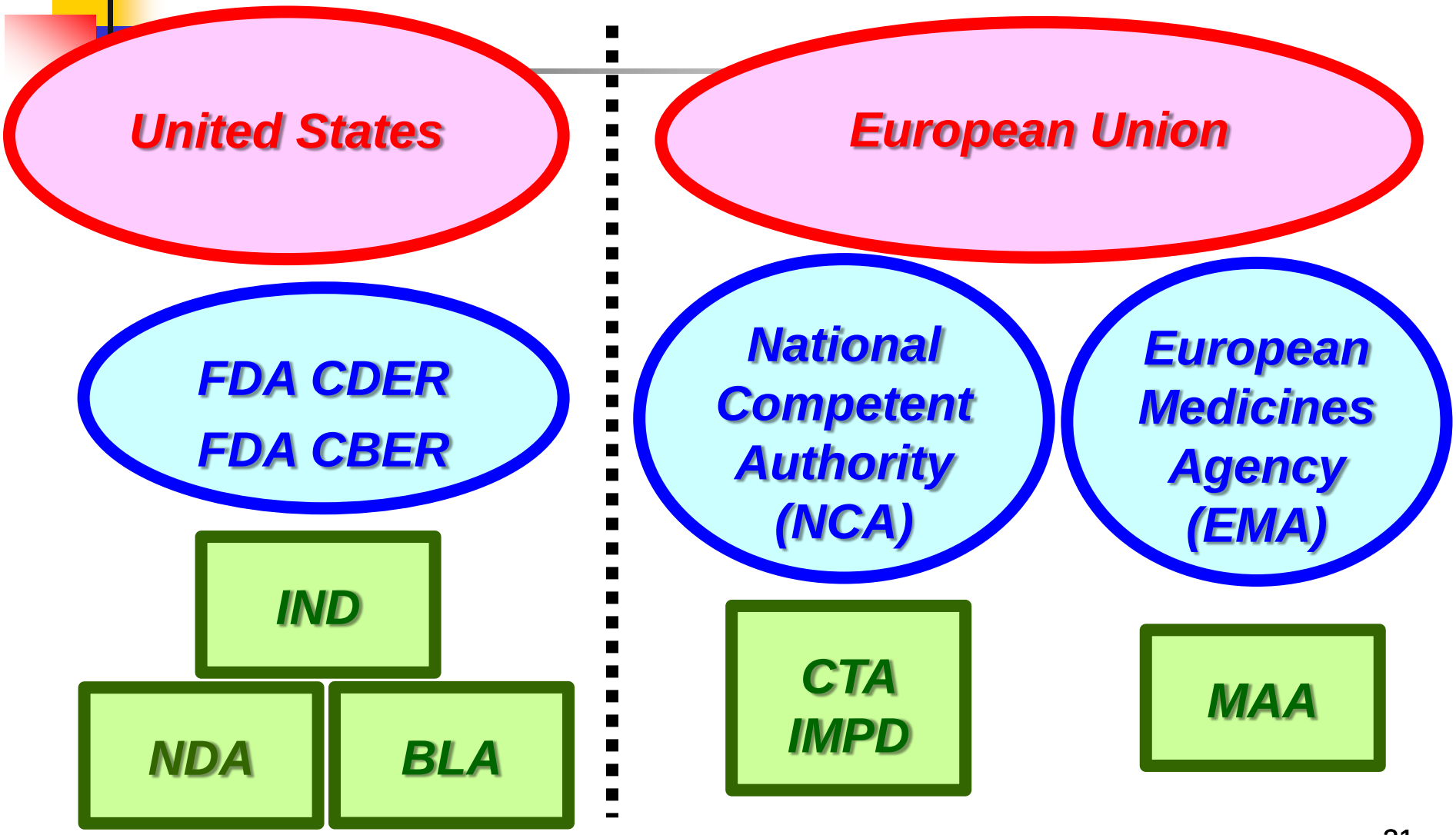
Biologic/ Biological

- **Natural Sourced**
  - Plasma-Derived Proteins
  - Human Cell Medicines
  - Vaccines
- **Biopharmaceutical**
  - Recombinant Proteins
  - Monoclonal Antibodies
  - Genetically Engineered Viruses and Cells

Biosimilars

CMC Regulatory Compliance Terminology

Regulatory Authority Landscape



United States Pharmaceutical Laws

U.S. Congress passes a law (USC)

↓

Executive Branch (FDA) interprets the intent of the law

↓

FDA proposes regulations to enforce the law;
publishes their intent in the Federal Register (FR)

↓

FDA publishes final regulation in
the Code of Federal Regulations (CFR)

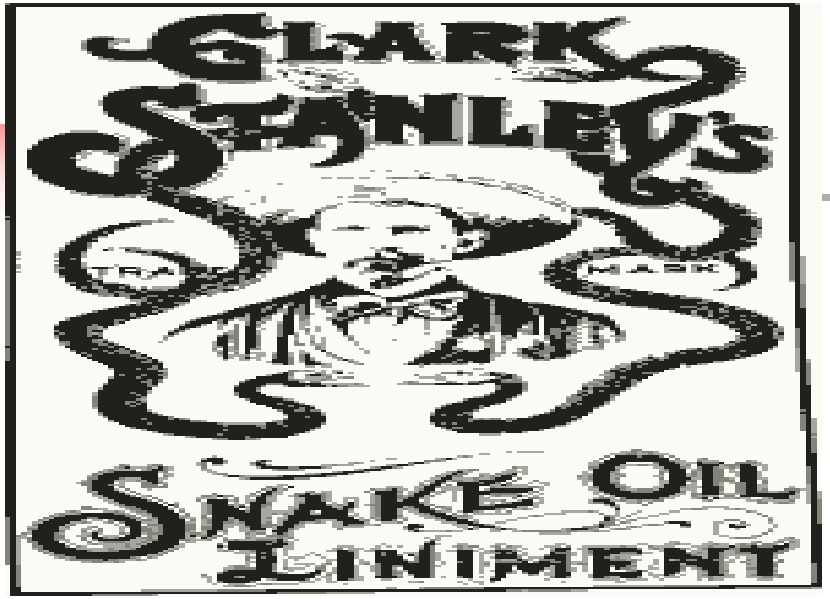
↓

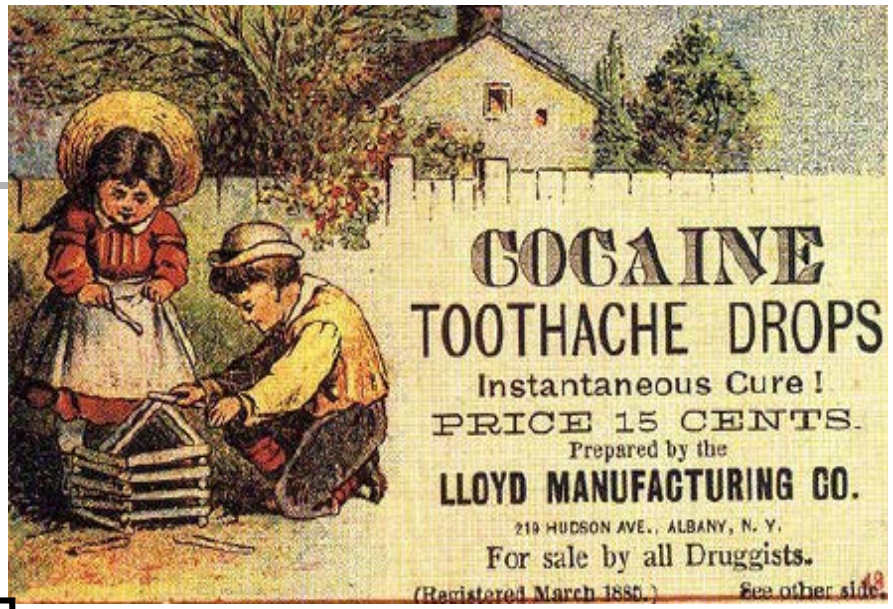
FDA publishes guidances ('recommendations') on its website
explaining in greater detail how to follow their regulations

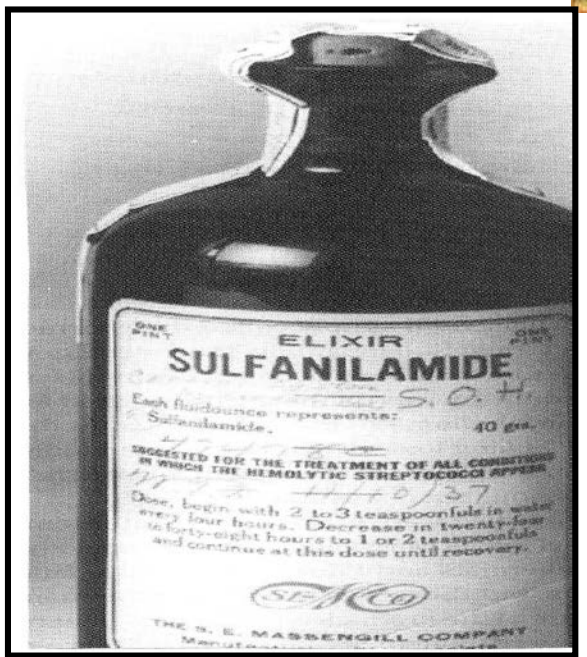
Food, Drug & Cosmetic (FD&C) Act

Public Health Service (PHS) Act

Prior to 1938 Buyer beware!







Elixir of Sulfanilamide

107 die (mostly children) in 1937

Antibacterial syrup was formulated with diethylene glycol (antifreeze)

No drug safety testing was required! Medicine was perfectly legal to sell!

Pulled off the market because of mislabeling (elixir requires alcohol)

1938 Food Drug & Cosmetics (FD&C) Act

Drug defined as ***'an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease'***

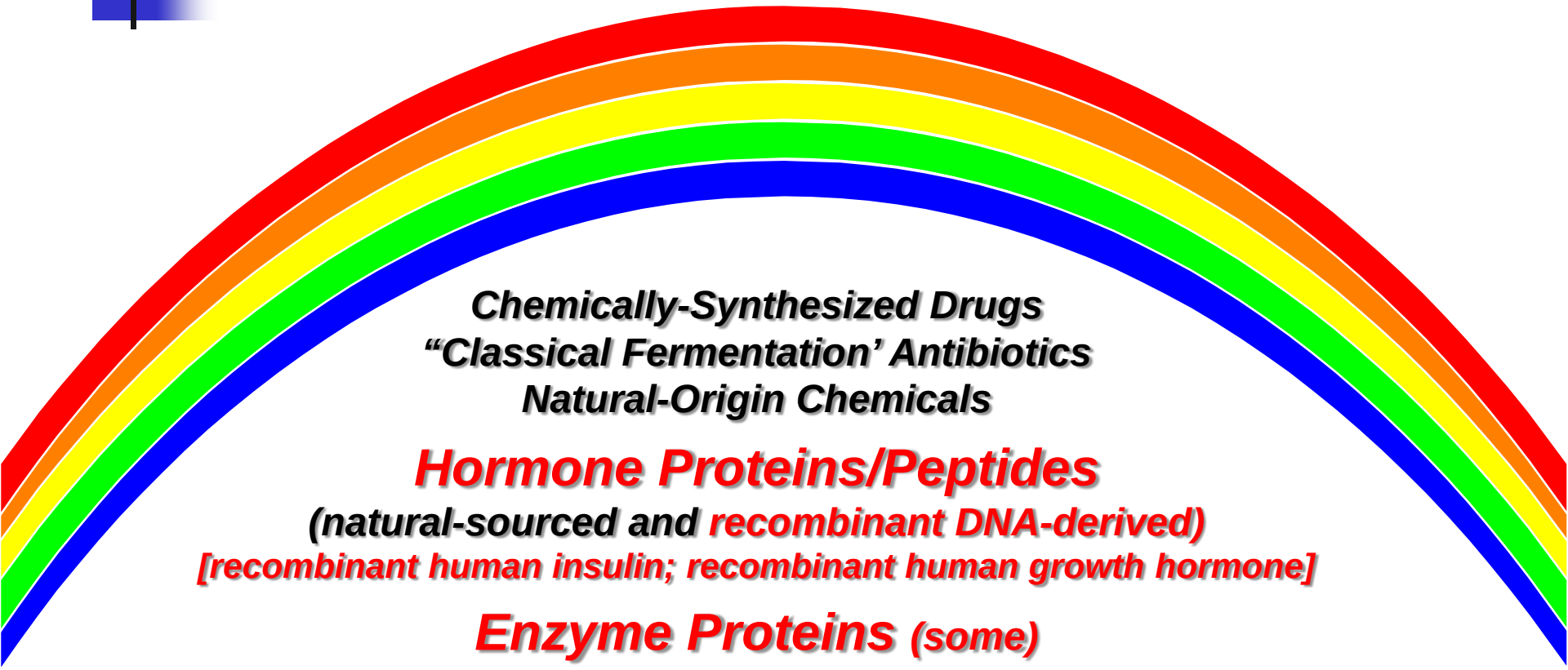
FD&C Act: New Drug Application (NDA) Pathway

Investigational New Drug (IND)
21 CFR 312
[human clinical studies]

→

New Drug Application (NDA)
21 CFR 314
[marketed products]

Some BIOPHARMACEUTICALS Under the NDA Pathway Regulated by the FD&C Act



Chemically-Synthesized Drugs
"Classical Fermentation' Antibiotics
Natural-Origin Chemicals

Hormone Proteins/Peptides

(natural-sourced and recombinant DNA-derived)
[recombinant human insulin; recombinant human growth hormone]

Enzyme Proteins (some)

(natural-sourced and recombinant DNA-derived)
[recombinant glucerases; recombinant hyaluronidases]

Major amendment to FD&C Act in 1984 allowing abbreviated pathways to the marketplace (Drug Price Competition and Patent Restoration Act)

New Drug Application [505(b)(1) NDA]
[innovator establishes statistical efficacy and safety]

New Drug Application [505(b)(2) NDA]
[manufacturer establishes comparative efficacy and safety]

used for biopharmaceuticals under FD&C Act

Abbreviated New Drug Application [505(j) NDA]
[manufacturer shows bioequivalence; for chemical generics]

Case Example: Recombinant Insulin Glargine

Lantus NDA 505(b)(1) Originator

Approved in 2000: > 4000 patients

Proof of clinical efficacy and safety

Basaglar NDA 505(b)(2) 'Follow-On Protein'

Approved in 2015: 535 patients

Comparative clinical efficacy and safety

1944 Public Health Service (PHS) Act

Biological product defined as 'a virus, therapeutic serum, toxin, antitoxin or analogous product or asphenamine'

Added in 1970: 'vaccine, blood, blood component or derivative, allergenic products'

Added in 2009: 'protein (except any chemically synthesized polypeptide)'

PHS Act: Biologic License Application (BLA) Pathway

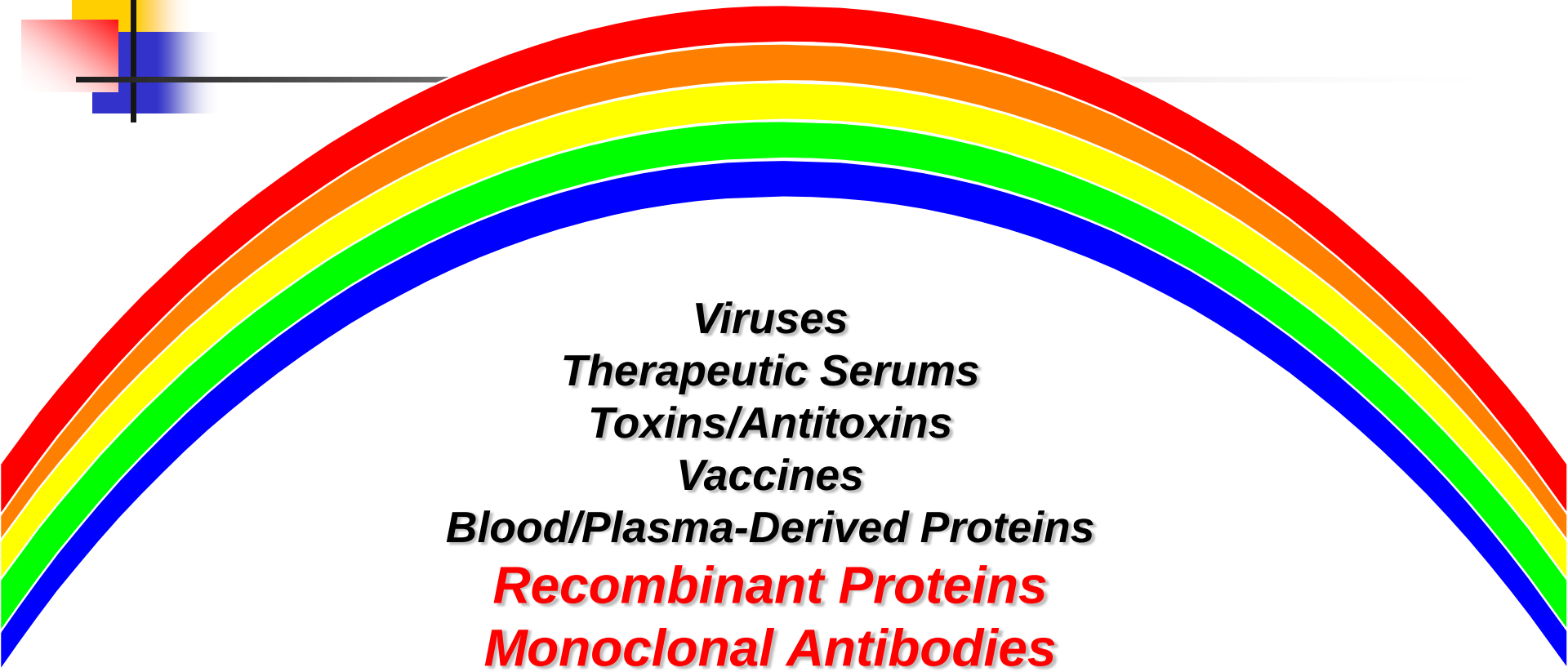
Investigational New Drug (IND)
21 CFR 312
[human clinical studies]

→

Biologics License Application (BLA)
21 CFR 600-680
[marketed products]

Note: same clinical development as FD&C Act!

Most BIOPHARMACEUTICALS Under the BLA Pathway Regulated by the PHS Act



Viruses
Therapeutic Serums
Toxins/Antitoxins
Vaccines
Blood/Plasma-Derived Proteins
Recombinant Proteins
Monoclonal Antibodies

+ 'Analogous Products'
(Gene Therapy,* Cellular Therapy*)

Major amendment to PHS Act in 2009 allowing abbreviated pathway to the marketplace (Biologics Price Competition and Innovation Act)

Biologic License Application [351(a) BLA]
[innovator establishes statistical efficacy and safety]

Biosimilar Biologic License Application [351(k) BLA]
[manufacturer establishes comparative efficacy and safety]

Case Example: Infliximab Monoclonal Antibody

Remicade **BLA 351(a)** **Originator**

Approved in 1998: > 5000 patients

Proof of clinical efficacy and safety

Inflectra **BLA 351(k)** **Biosimilar**

Approved in 2016: 606 patients

Comparative clinical efficacy and safety

Does it matter which FDA law (PHS or FD&C) regulates my biopharmaceutical?

No! ***Administrative Regulatory***

- *same 21 CFR 312 clinical study requirements*
- *same FDA 1571 form used for IND submissions*
- *same FDA 356h form for NDA/BLA submissions*

Yes! ***CMC Regulatory Compliance***

- *extra commercial testing requirements*
- *may require FDA commercial pre-release*
- *different commercial regulatory compliance procedures*
- *different marketing business impact*

1) Extra Commercial Testing Requirements

Extra PHS Act (BLA) Testing	Current Status
21 CFR 610.12 Bulk Sterility (in addition to final product sterility)	ELIMINATED in 2012 (now identical to FD&C Act)
21 CFR 610.11 General Safety Test (mice and guinea pig toxicity test)	ELIMINATED in 2015 (now identical to FD&C Act)
21 CFR 610.14 Labeled Final Container Identity Test	STILL IN EFFECT

The BLA submission does not contain information regarding identity testing of labeled ibalizumab drug product vials. 21 CFR 610.14 requires that identity testing be performed on each filled DP lot after all labeling operations have been completed. The identity test method for the labeled drug product should be appropriately validated for its intended use. Update your BLA with the following information:

- a description of the identity test method for the labelled drug product
- appropriate method validation, or if applicable, method transfer data
- revise FDA-356h form to include testing facility information
- revise Section 3.2.P.3.1 of Module 3 to include the testing facility information.

Trogarzo (Ibalizumab-uiyk) – FDA Approval History, Letters, Reviews and Related Documents – Administrative and Correspondence Documents – Meeting Minutes Mid-Cycle Communication (August 18, 2017)

2) May Require FDA Commercial Pre-Release

§ 610.2 Requests for samples and protocols; official release.

(a) *Licensed biological products regulated by CBER.* Samples of any lot of any licensed product together with the protocols showing results of applicable tests, may at any time be required to be sent to the Director, Center for Biologics Evaluation and Research (see mailing addresses in § 600.2 of this chapter). Upon notification by the Director, Center for Biologics Evaluation and Research, a manufacturer shall not distribute a lot of a product until the lot is released by the Director, Center for Biologics Evaluation and Research:

(b) *Licensed biological products regulated by CDER.* Samples of any lot of any licensed product together with the protocols showing results of applicable tests, may at any time be required to be sent to the Director, Center for Drug Evaluation and Research (see mailing addresses in § 600.2) for official release. Upon notification by the Director, Center for Drug Evaluation and Research, a manufacturer shall not distribute a lot of a biological product until the lot is released by the Director, Center for Drug Evaluation and Research: *Provided*, That the Director,

FD&C Act does not require this for NDA biologics!
Company QA solely determines release to inventory

FDA pre-release required for Vaccines

Cumulative 2017 Season

Manufacturer	Total Number of Lots Released by FDA
Afluria - Seqirus Pty. Ltd.	55
Afluria Quadrivalent - Seqirus Pty. Ltd.	1
Fluad – Seqirus, Inc.	8
Fluarix Quadrivalent – GlaxoSmithKline Biologicals	52
Flublok – Protein Sciences Corporation	6
Flublok Quadrivalent - Protein Sciences Corporation	0
Flucelvax Quadrivalent - Seqirus, Inc.	21
FluLaval Quadrivalent - ID Biomedical Corporation of Quebec	21
FluMist Quadrivalent - MedImmune, LLC	11
Fluvirin – Seqirus Vaccines Limited	33
Fluzone High Dose - Sanofi Pasteur, Inc.	27
Fluzone Quadrivalent - Sanofi Pasteur, Inc.	46

FDA pre-release may be required for Human Plasma-Derived Proteins

Fibryna – Fibrinogen (Human) (June 07, 2017)

Please submit final container samples of the product and each kit component in final containers together with protocols showing results of all applicable tests. You may not distribute any lots of product until you receive a notification of release from the Director, Center for Biologics Evaluation and Research (CBER).

Rebinyn – Coagulation Factor IX (Recombinant), PEGylated (May 31, 2017)

You are not currently required to submit samples or protocols of future lots of Coagulation Factor IX (Recombinant), GlycoPEGylated to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2(a). We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

stated in FDA market approval letter

FDA pre-release automatic waiver for Recombinant Proteins & Monoclonal Antibodies

granted in 1995

Fulphila – Peg-filgrastim-jmdb) Biosimilar (June 04, 2018)

***You are not currently required** to submit samples of future lots of Fulphila to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.*

Crysvita – Burosumab-twza (April 17, 2018)

***You are not currently required** to submit samples of future lots of CRYSVITA (burosumab-twza) to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.*

stated in FDA market approval letter

FDA pre-release required for Genetic Engineered Viruses

Spark Therapeutics, Inc.

December 19, 2017
BLA APPROVAL

LUXTURNA is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. Patients must have viable retinal cells as determined by the treating physician(s). (1)

FDA LOT RELEASE

You are required to submit lot release protocols for future lots of voretigene neparvovec-rzyl to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2(a). We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

stated in FDA market approval letter

FDA pre-release waivers for Genetic Engineered Cells

Kite Pharma,

YESCARTA.

BLA APPROVAL
October 18, 2017

You are not currently required to submit samples or protocols of future lots of axicabtagene ciloleucel to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2(a). We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

stated in FDA market approval letter

3) Different Commercial Regulatory Compliance Procedures

Reporting of Quality/Compliance concerns after a commercial batch has been released into the marketplace

FD&C Act

Field Alert Report (FAR)

FDA Form 3331

Within 3 days of QA awareness

PHS Act

Biological Product Deviation Report (BPDR)

FDA Form 3486

Within 45 days of QA awareness

4) Different Marketing Business Impact

"Market Exclusivity"
the period of time during which a generic/biosimilar company cannot market the same drug product as the innovator

FD&C Act

5 (7) years granted to innovator biologic manufacturer

PHS Act

12 years granted to innovator biologic manufacturer

Major change coming March 20, 2020!

(all proteins will be under requirements of the PHS Act)

FD&C Act

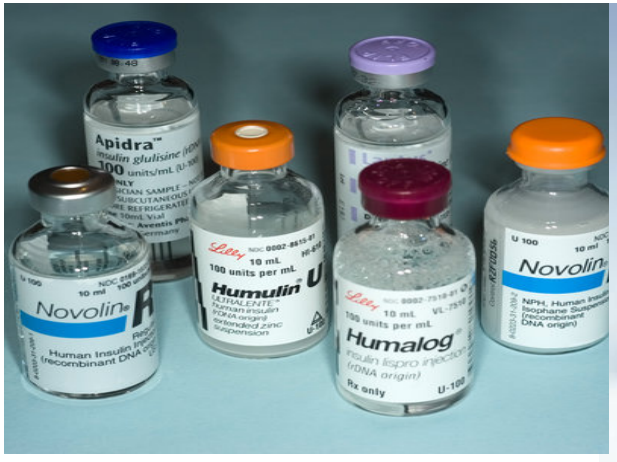
Biologic Hormones

Enzymes (some)

PHS Act

Biologic Hormones

Enzymes (some)



Implementation of the
"Deemed to be a License" Provision of
the Biologics Price Competition and
Innovation Act of 2009

DRAFT GUIDANCE March 2016

Two primary FDA Centers involved with biologic products

Center for Drug Evaluation and Research (CDER)

Center for Biologics Evaluation and Research (CBER)

So, if you have a biopharmaceutical, which FDA Center would you work with?

Prior to June 2003

CDER

FD&C Act

Natural Chemical Drugs
Synthesized Drugs
Antibiotics
Biologic Hormones
Biologic Enzymes *(some)*
Follow-on Proteins

CBER

PHS Act

Recombinant Proteins
Monoclonal Antibodies
Vaccines
Plasma-Derived Proteins
Gene Therapy Medicines
Analogous Products

After June 2003

CDER

FD&C Act

Natural Chemical Drugs
Synthesized Drugs
Antibiotics
Biologic Hormones
Biologic Enzymes (some)
Follow-on Proteins

PHS Act

Recombinant Proteins
Monoclonal Antibodies
(Biosimilars)

CBER

PHS Act

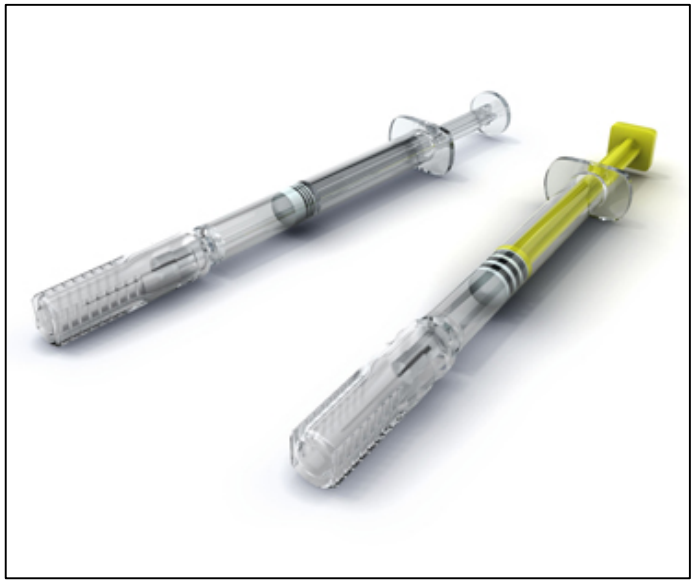
Vaccines
Plasma-Derived Proteins
Gene Therapy Medicines
Analogous Products

A 3rd FDA Center now frequently involved with biopharmaceutical products (typically a secondary consult for CDER/CBER)

U.S. Food and Drug Administration

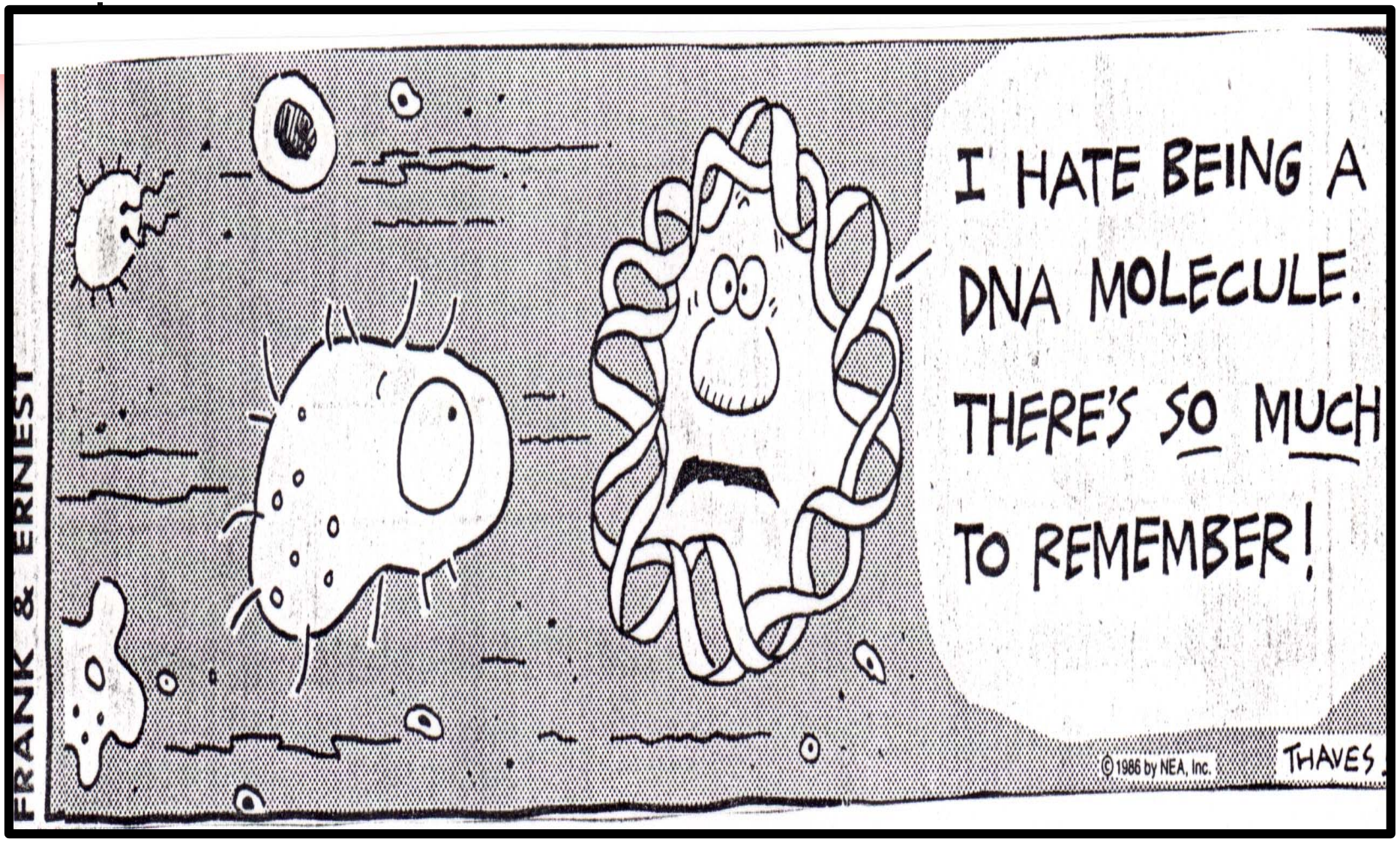
U.S. Department of Health and Human Services

Center for Devices and Radiological Health



Repatha® (evolocumab) *Pushtronex™* system
(on-body infusor with prefilled cartridge)

Are you confused yet?



European Union Pharmaceutical Law

***European Commission* (EC) passes:**

***Directive* – a legislative act that sets out a goal that all European Union countries must achieve; however it is up to each National Competent Authority (NCA) to decide how**

***Regulation* – a binding legislative act; must be applied in its entirety throughout the European Union**

↓

***European Medicines Agency* (EMA) publishes:**

requirements and guidelines ('recommendations') on its website explaining how it will implement the Regulations applicable to medicinal products

NCAs Regulate Clinical Trials For All Drugs and Biologics

DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

***Country-by-country* Clinical Trial Authorization (CTA) of the Investigational Medicinal Product Dossier (IMPD)**

28 Member States – each with a CMC opinion

REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

'fast and thorough assessment of the application by all Member States concerned and resulting in one single assessment outcome'

'submitted, reviewed, authorized' – single portal entry

coming into effect 2019?

EMA Regulates Marketed Products

REGULATION (EC) No 726/2004 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 31 March 2004

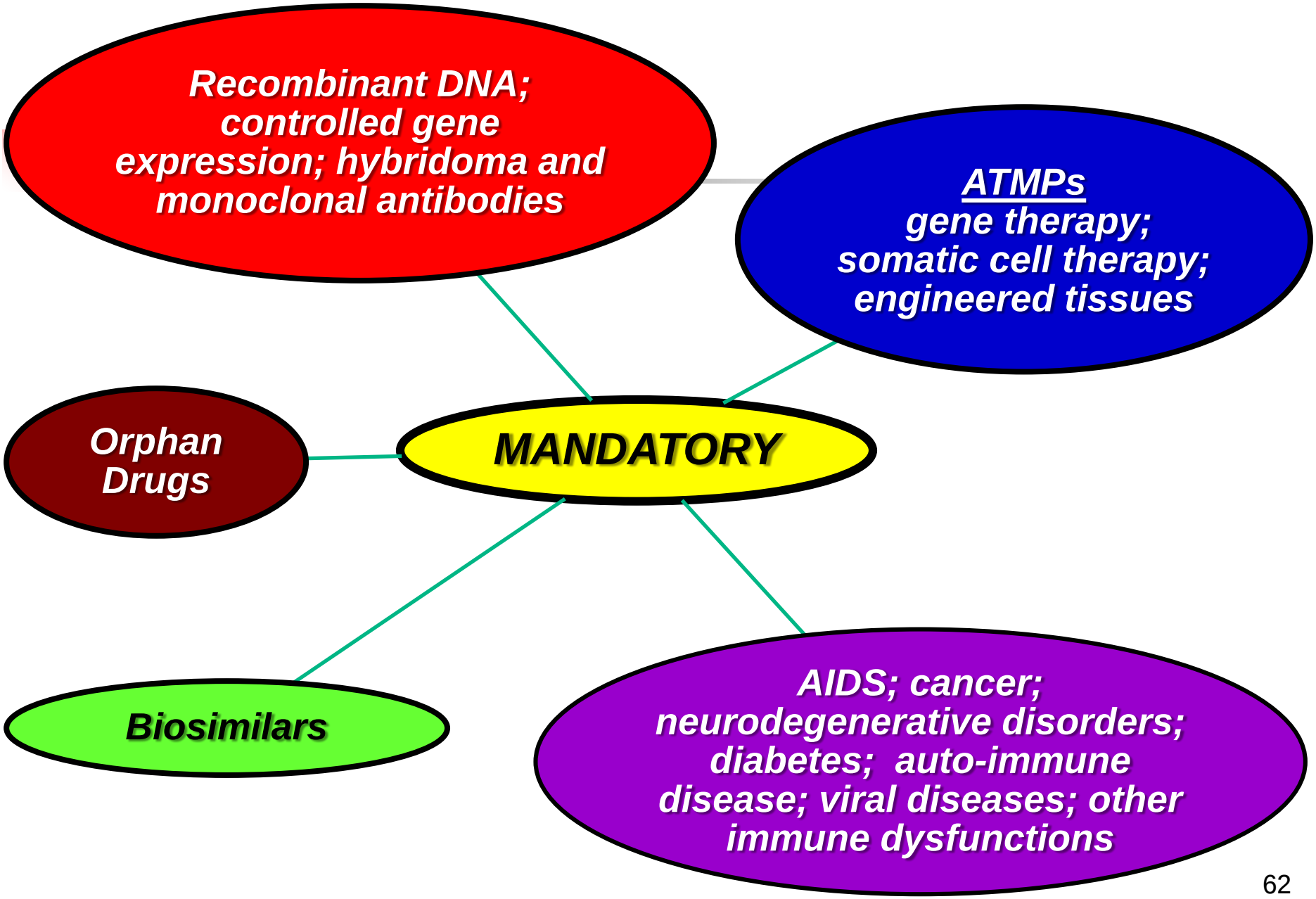
laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

EMA Centralized Procedure

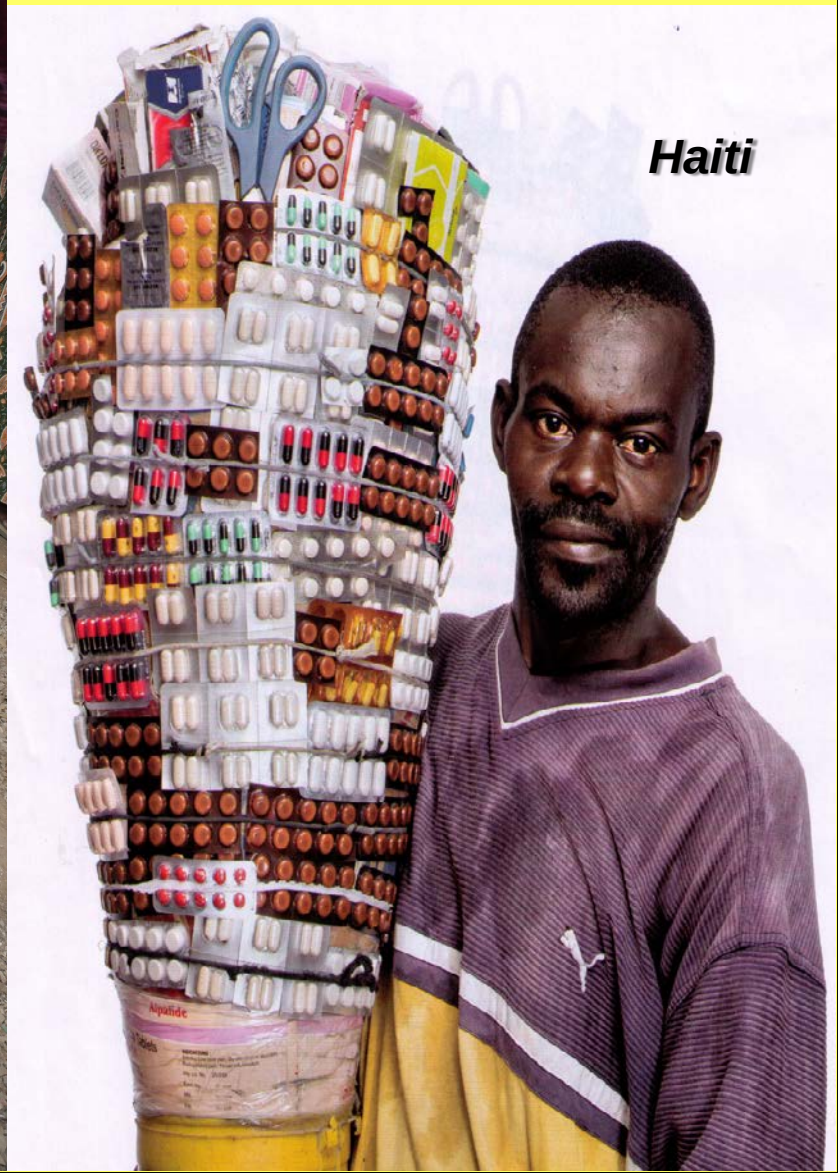
Market Authorization Application (MAA)

Mandatory for most Biologics →

(EU still uses a national authorization and a mutual recognition procedure)


Recombinant DNA; controlled gene expression; hybridoma and monoclonal antibodies
ATMPs
gene therapy; somatic cell therapy; engineered tissues
Orphan Drugs
MANDATORY
Biosimilars
AIDS; cancer; neurodegenerative disorders; diabetes; auto-immune disease; viral diseases; other immune dysfunctions

Other pharmaceutical regulation landscapes around the world!



Regulatory Authorities Know Biopharmaceuticals Are NOT Chemical Drugs!

The ways in which biological medicinal products are manufactured, controlled and administered make some particular precautions necessary.

Unlike conventional medicinal products, which are manufactured using chemical and physical techniques capable of a high degree of consistency, the manufacture of biological medicinal substances and products involves biological processes and materials, such as cultivation of cells or extraction of material from living organisms. These biological processes may display inherent variability, so that the range and nature of by-products may be variable.

A robust manufacturing process is therefore crucial and in-process controls take on a particular importance in the manufacture of biological active substances and medicinal products.

EU GMP Annex 2 Biological Manufacturing 2018

Biopharmaceuticals Are NOT Chemical Drugs!

Biopharmaceuticals differ from chemical drugs in 4 major areas that impact CMC regulatory compliance:

1) ***Synthesis of the product***
2) ***Impact of manufacturing process on the product***
3) ***Complexity of the product produced***
4) ***No bio-generics***

Biopharmaceuticals Differ From Chemical Drugs in 4 Major Areas That Impact CMC Regulatory Compliance

1 of 4: Synthesis of the Product

Chemical Drug	Biopharmaceutical
Product synthesized from non-living chemical reagents, under typically harsh conditions (e.g., organic solvents, high temps and/or pressures)	A living organism either produces the product or it is the product itself, cultured under mild aqueous tropical conditions

Challenge of use of living systems

Must be kept 'Alive'!

A living system must be kept alive, around the clock, 24/7

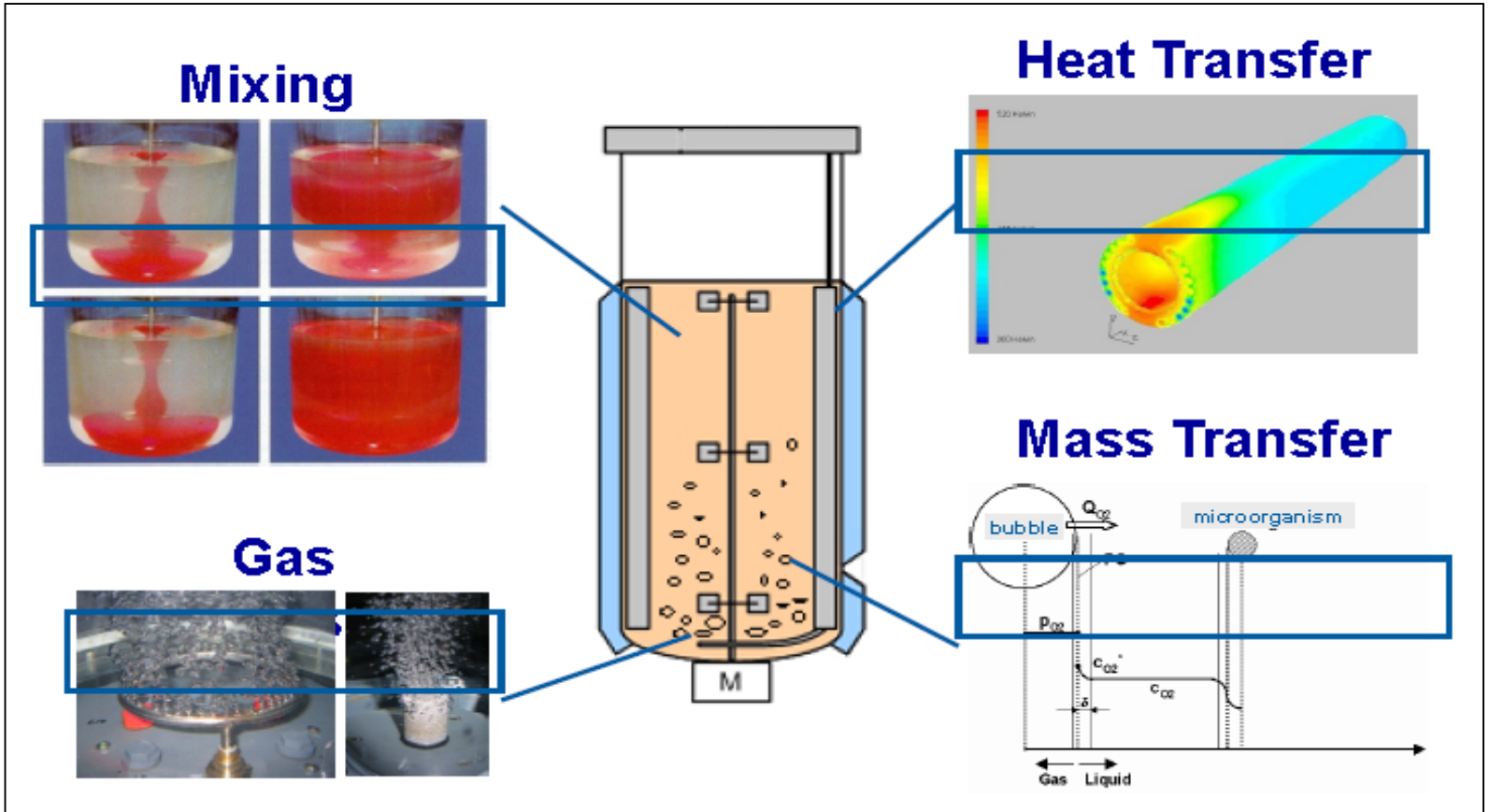
- ***For as long as needed ('life clock' can't be stopped)***
- ***Dead organisms do not produce biopharmaceuticals***

Cells and viruses 'hibernate' in liquid nitrogen

Challenge of use of living systems

Must be kept 'Happy'!

Control of the living system process is critical for production of the biopharmaceutical – process engineers earn their salary!

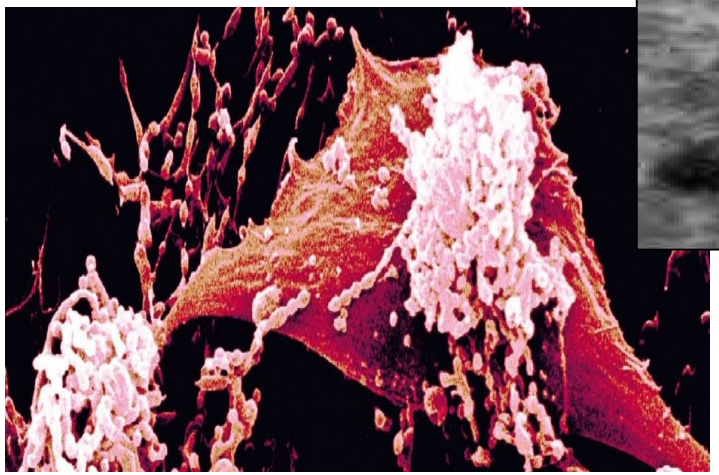


Challenge of use of living systems

Must be kept 'Healthy'!

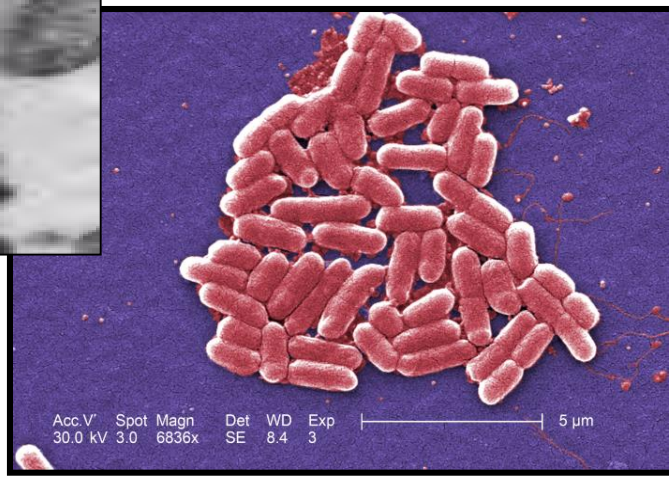
It's a nasty world facing the living system – 'adventitious agents'

Mycoplasmas

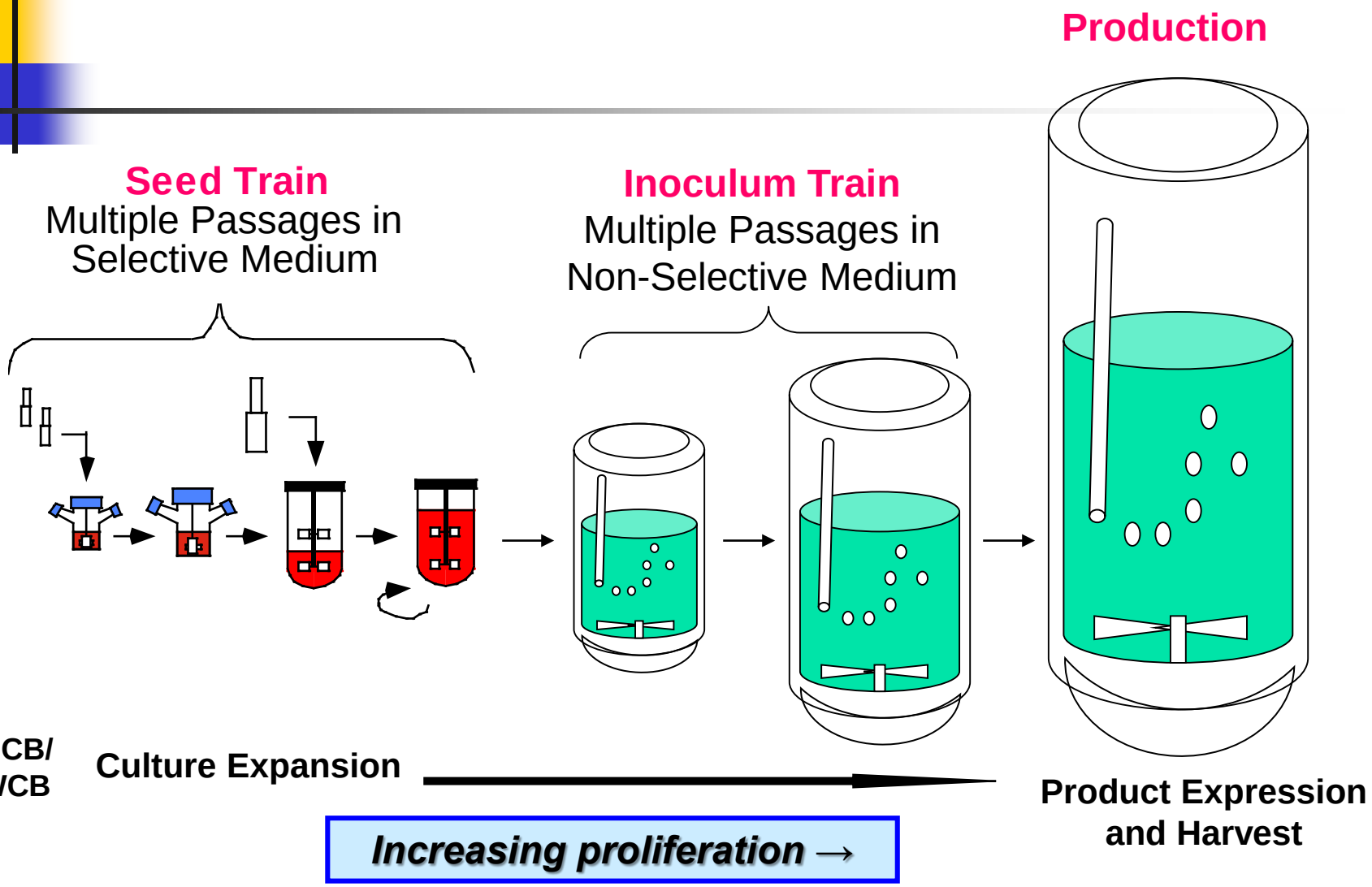


Viruses

Bacteria/Fungi



Once an adventitious agent contaminates a cell culture …



Biopharmaceuticals Differ From Chemical Drugs in 4 Major Areas That Impact CMC Regulatory Compliance

2 of 4: Impact of Manufacturing Process on Product

Chemical Drug	Biopharmaceutical
Product is independent of manufacturing process (explains why chemical generics are common)	Product is not completely independent of the manufacturing process (while 'process is no longer the product', the process may still significantly impact the biological product)

Chosen cell culture system can impact the manufacture of the recombinant protein or monoclonal antibody

primary, secondary, and tertiary structure potential impact

: Possible differences between the chosen expression system (i.e., host cell and the expression construct) of the proposed product and that of the reference product should be carefully considered because the type of expression system will affect the types of process- and product-related substances, impurities, and contaminants (including potential adventitious agents) that may be present in the protein product. For example, the expression system can have a significant effect on the types and extent of translational and posttranslational modifications that are imparted to the proposed product, which may introduce additional uncertainty into the demonstration that the proposed product is highly similar to the reference product.

FDA Guidance for Industry: Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product (April 2015)

Biosimilar manufacturers are keenly aware of possible differences!

Chosen manufacturing system can impact the manufacture of the cell-based biologic product

potential subtle impact during handling

CT products have unique complexities due to the dynamic nature of living cells. For example, cells may present a variety of molecules on their membranes and express a variety of factors. These molecules and factors may be affected by the microenvironment and change over time. Cells may differentiate in vivo into undesired cell types. Cells might also develop undesired autonomous functions

Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products

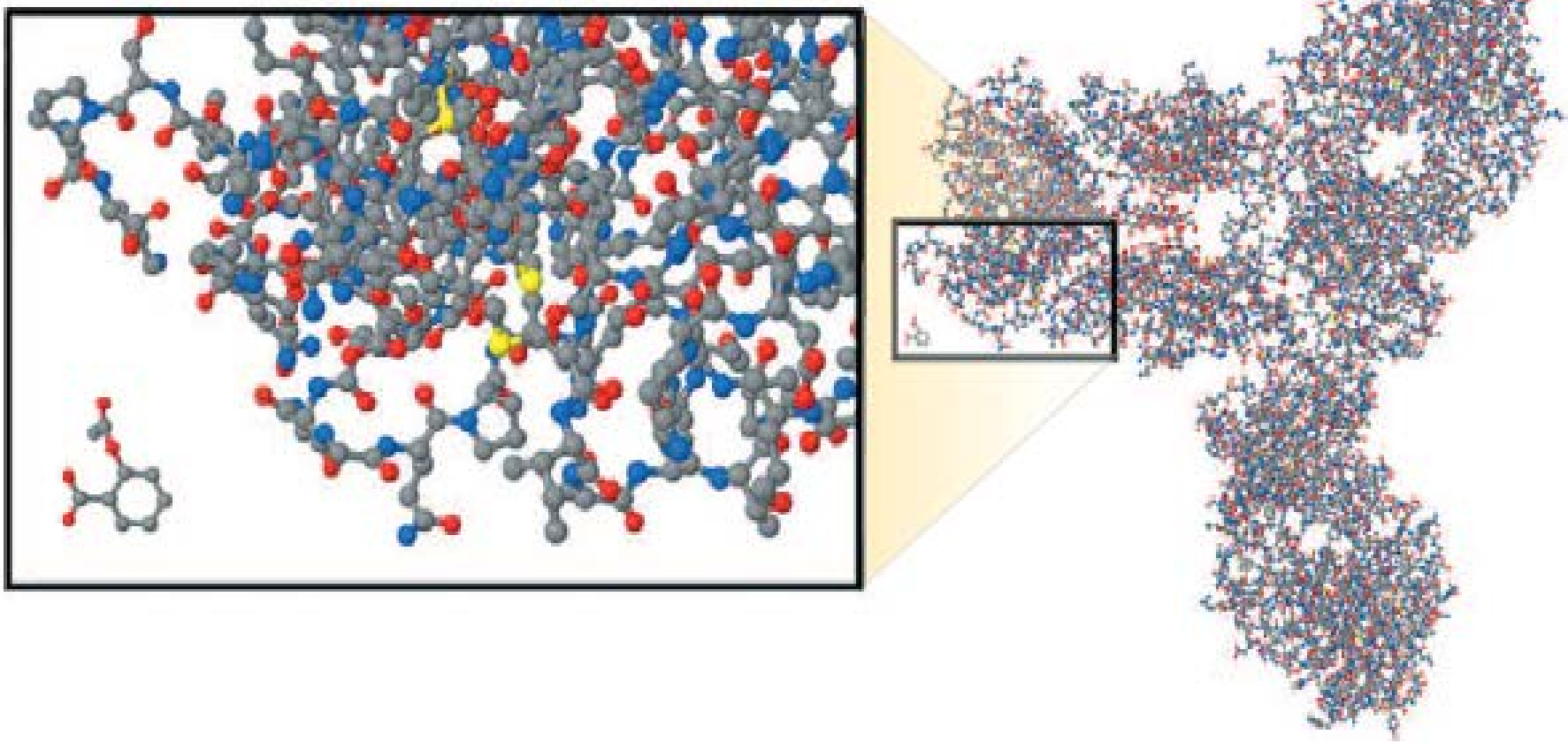
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
June 2015

Biopharmaceuticals Differ From Chemical Drugs in 4 Major Areas That Impact CMC Regulatory Compliance

3 of 4: Complexity of the Product Produced

Chemical Drug	Biopharmaceutical
Chemical products can be simple or more complex, but they do not have numerous molecular species involved	Biopharmaceuticals are by their nature very complex, having numerous molecular variants (if protein or virus) or surface markers (if a living cell)

Typical perception of size of a chemical drug vs a biopharmaceutical



Comparison between a Biologic Monoclonal Antibody and an Aspirin Molecule.

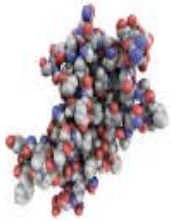
But chemical drugs can be large!

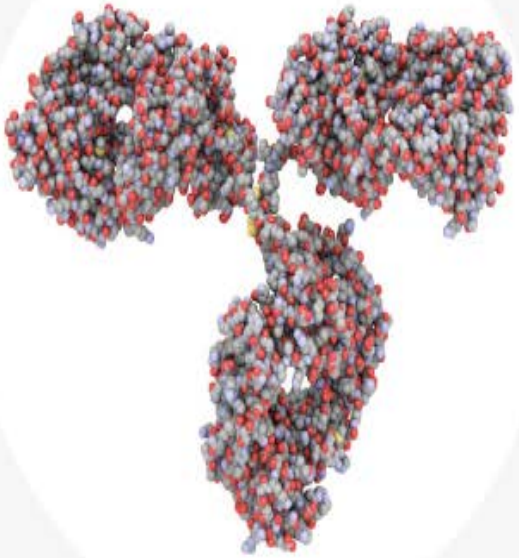
ONPATTRO

Alnylam Pharmaceuticals,

siRNA
chemical drug

MW 14,300 daltons





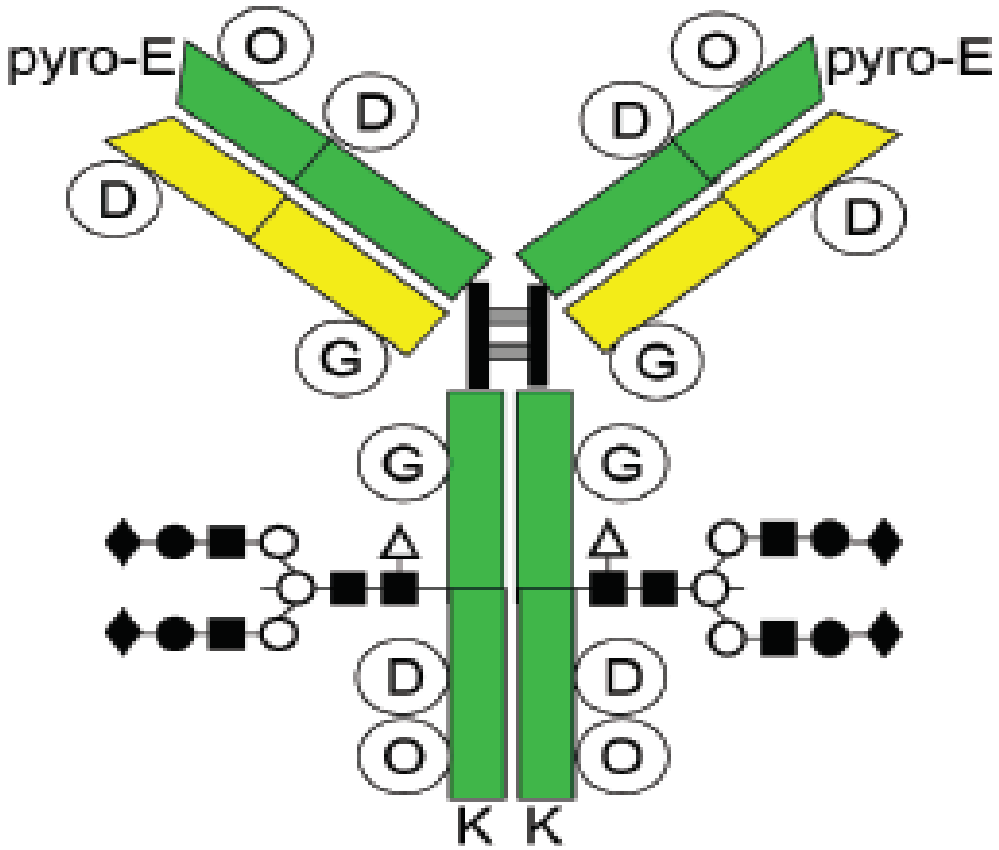
Insulin
5,808 daltons

Growth hormone
22,000 daltons

Monoclonal antibody
150,000 daltons

si – small, interfering (for gene silencing)

But chemical drugs are not as complex (molecular variants) as recombinant proteins or monoclonal antibodies!



Total variants
$(9600)^2 \approx 10^8$

Pyro-Glu (2)

Deamidation (3 x 2)

Methionine oxidation (2 x 2)

Glycation (2 x 2)

High mannose, G0, G1, G1, G2 (5)

Sialylation (5)

C-term Lys (2)

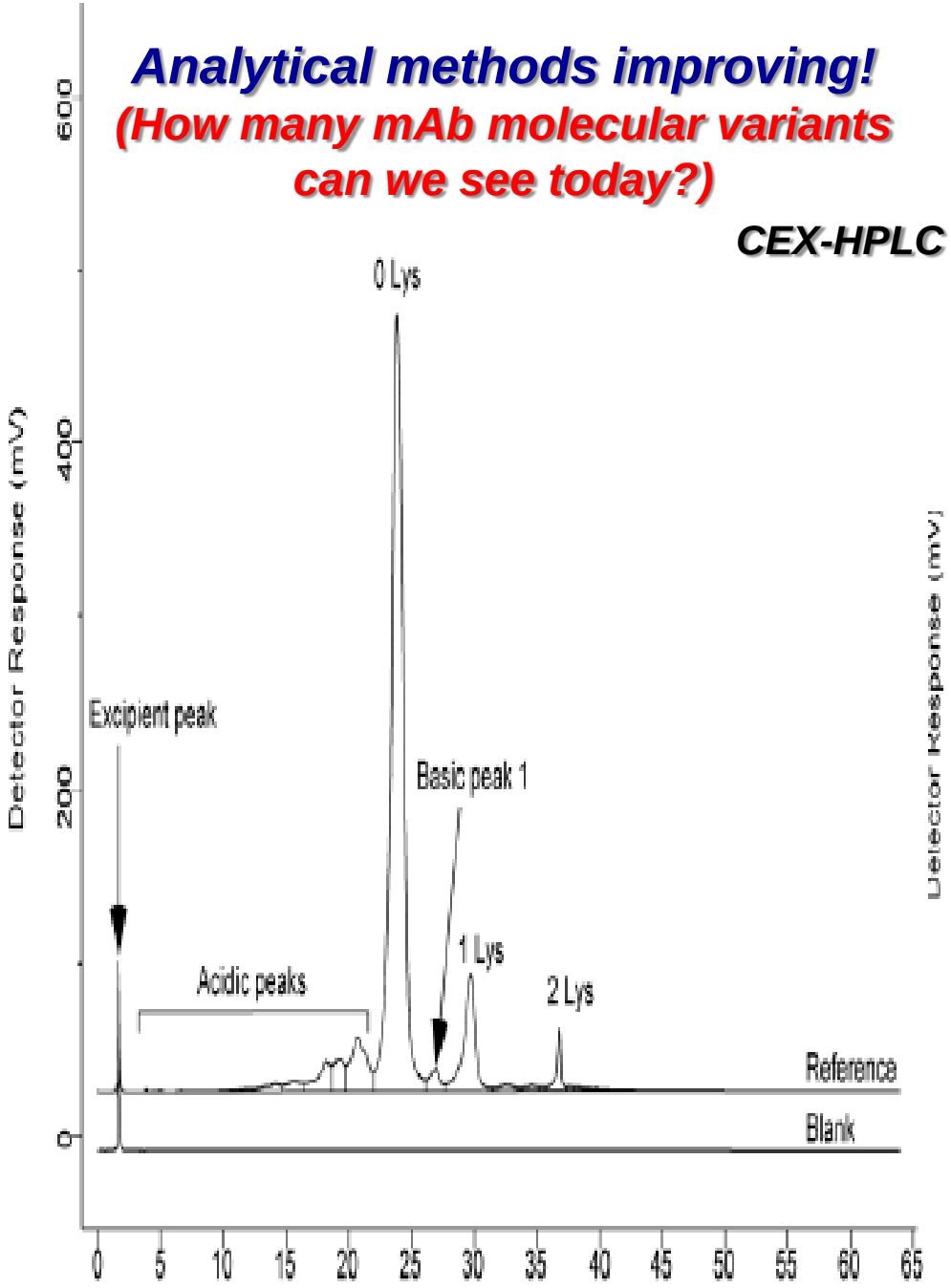
2 x 6 x 4 x 4 x 5 x 5 x 2 = 9600

Kozlowski and Swann, Current and Future Issues in the Manufacturing and Development of Monoclonal Antibodies; Advanced Drug Delivery Reviews, 58 (5-6), 7 Aug 2006, pp 707-722

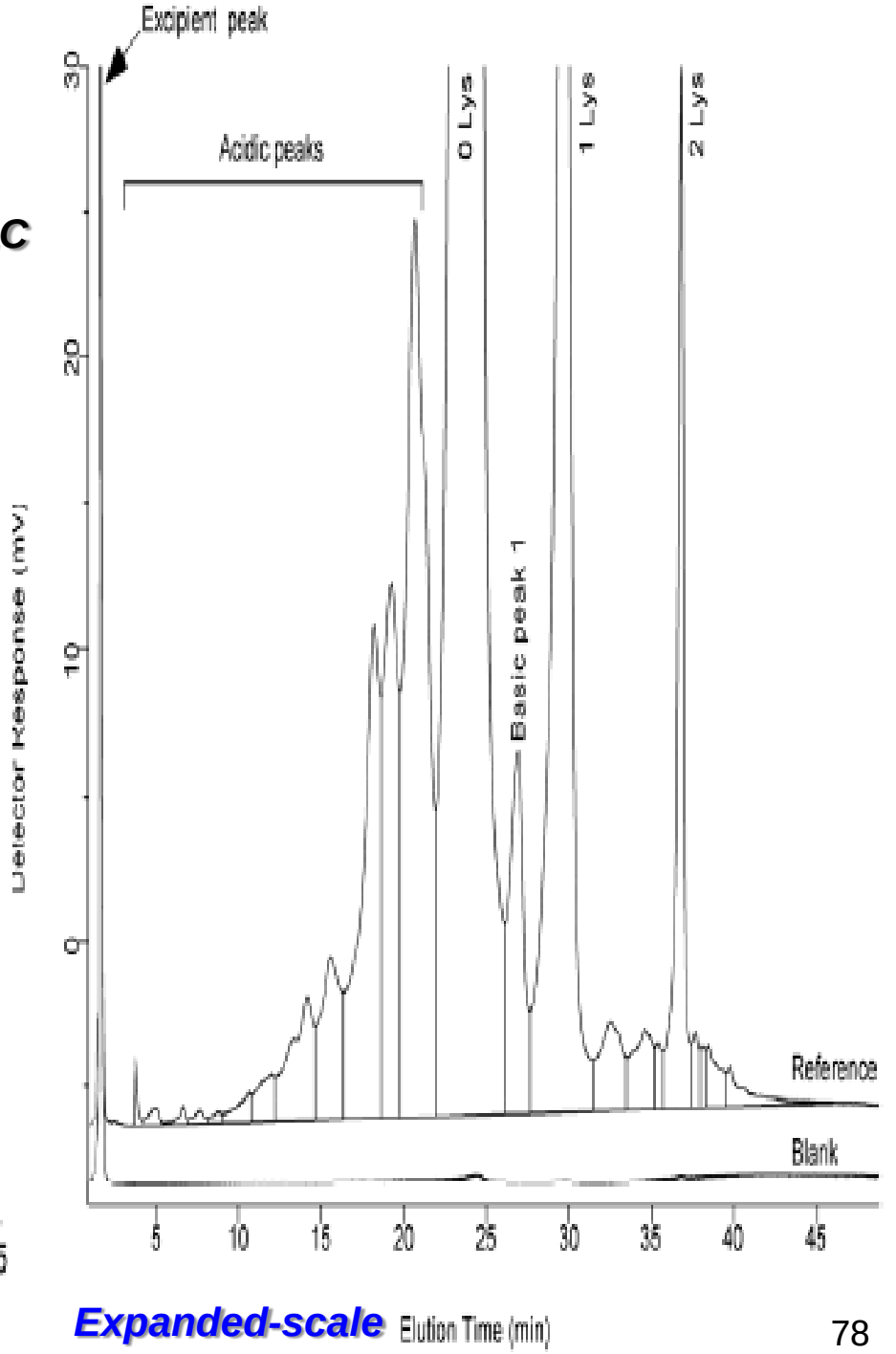
Analytical methods improving!

(How many mAb molecular variants can we see today?)

CEX-HPLC



Full-scale



Expanded-scale

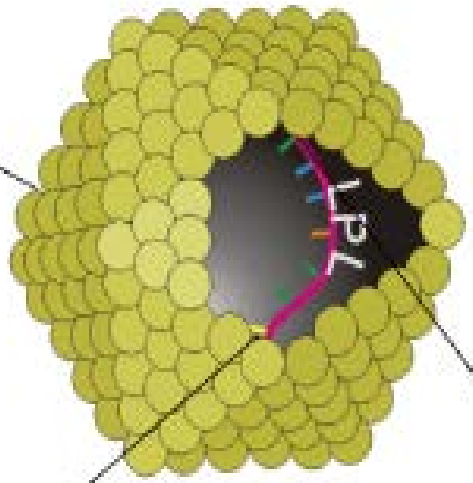
Further increasing in size and complexity are the genetic engineered living viruses for gene therapy

Genetically engineered viruses are living!

~ 25 nm

AAV1 capsid

protein shell + lipid encasing RNA or DNA

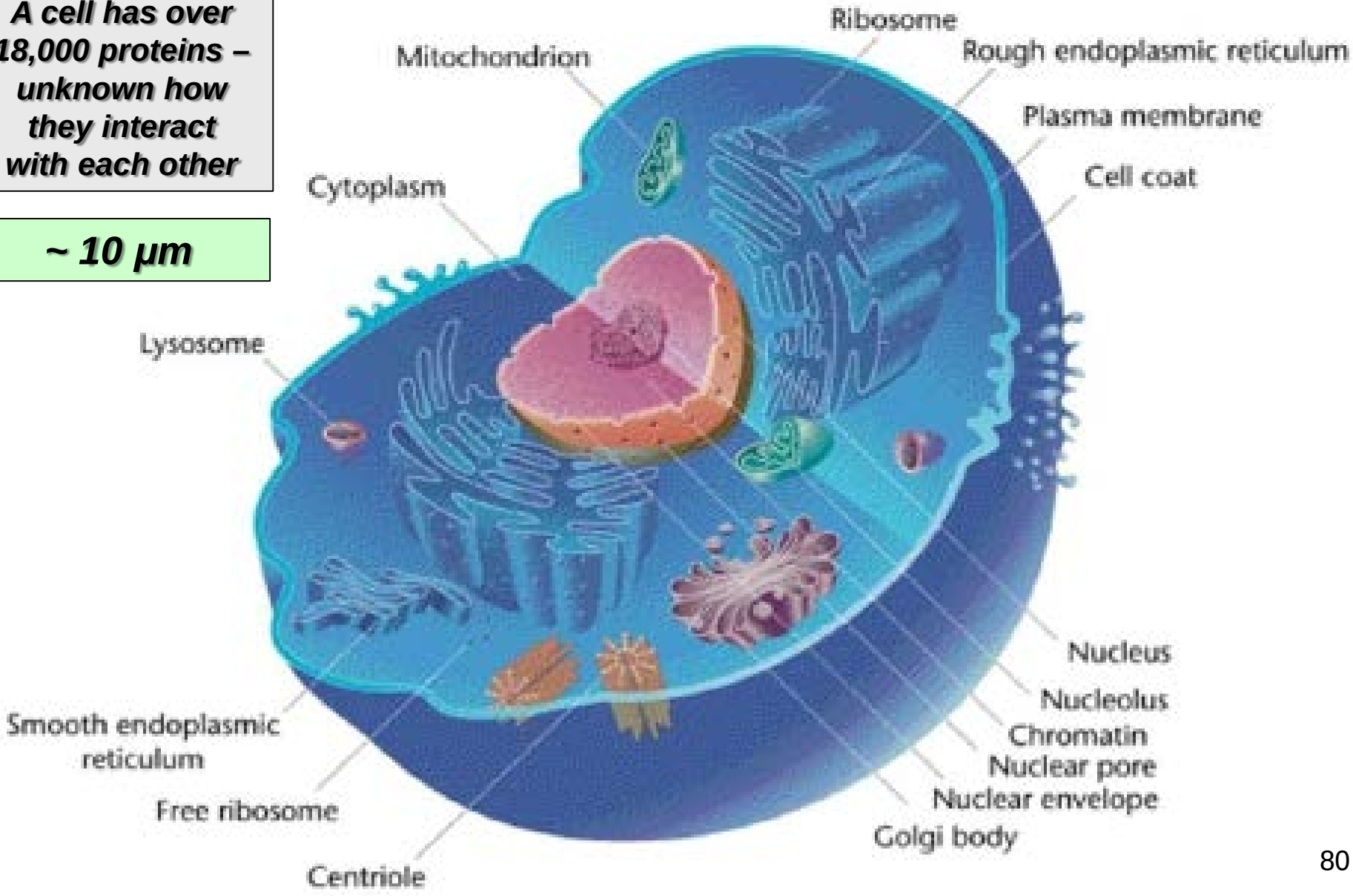


Glybera – adeno-associated viral vector designed to replace a deficient human LPL gene

Even more increasing in size and complexity are the genetic engineered living cells for gene therapy

A cell has over 18,000 proteins – unknown how they interact with each other

~ 10 µm



Biopharmaceuticals Differ From Chemical Drugs in 4 Major Areas That Impact CMC Regulatory Compliance

4 of 4: No Bio-Generics

Chemical Drug	Biopharmaceutical
Chemical Generic Exact structure between generic and innovator chemical drug CMC standard is 'equivalent'	**Biosimilar** Extensive CMC comparability between biosimilar and innovator biologic CMC standard is 'highly similar'

Are biosimilar medicines generic medicines of biological medicines?

Biosimilar medicines are not the same as generic medicines (a medicine which contains exactly the same molecule as an existing non-biological medicine, such as aspirin). This is because unlike nonbiological medicines, biological medicines cannot be exactly copied.

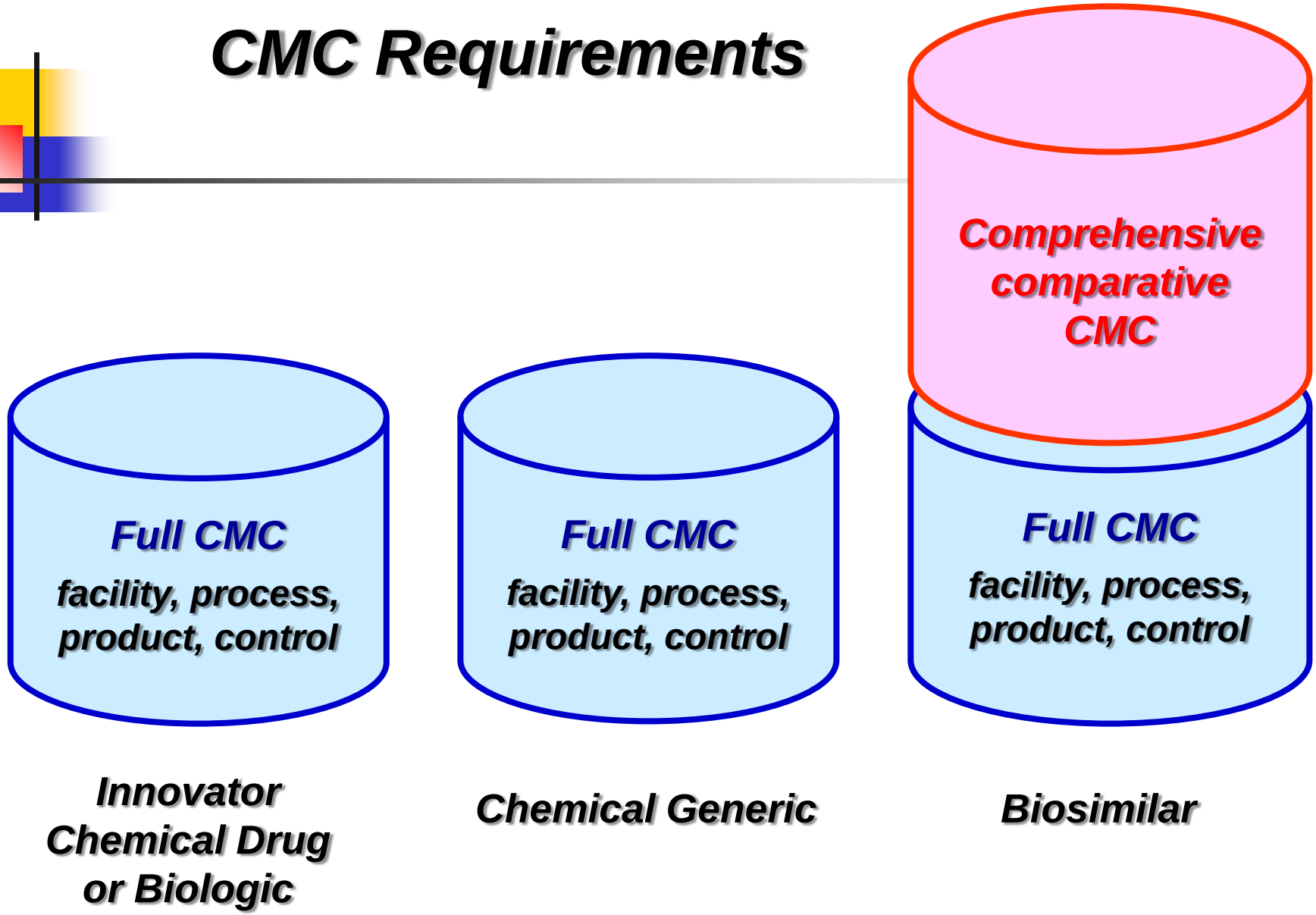
EMA/EC What I Need to Know About Biosimilar Medicines – Information for Patients (2017)

Are biosimilars different from generic drugs?

Biosimilars are not the same as generic drugs. Generic drugs are small molecules that are chemically synthesized and contain identical medicinal ingredients to their brand name reference products. Due to the size, complexity and natural variability of biologic drugs, and because drugs are made in living cells rather than with chemicals, a biosimilar and its reference biologic drug can be shown to be similar, but not identical.

Health Canada Biologics, Radiopharmaceuticals and Generic Therapies: Fact Sheet - Biosimilars

CMC Requirements



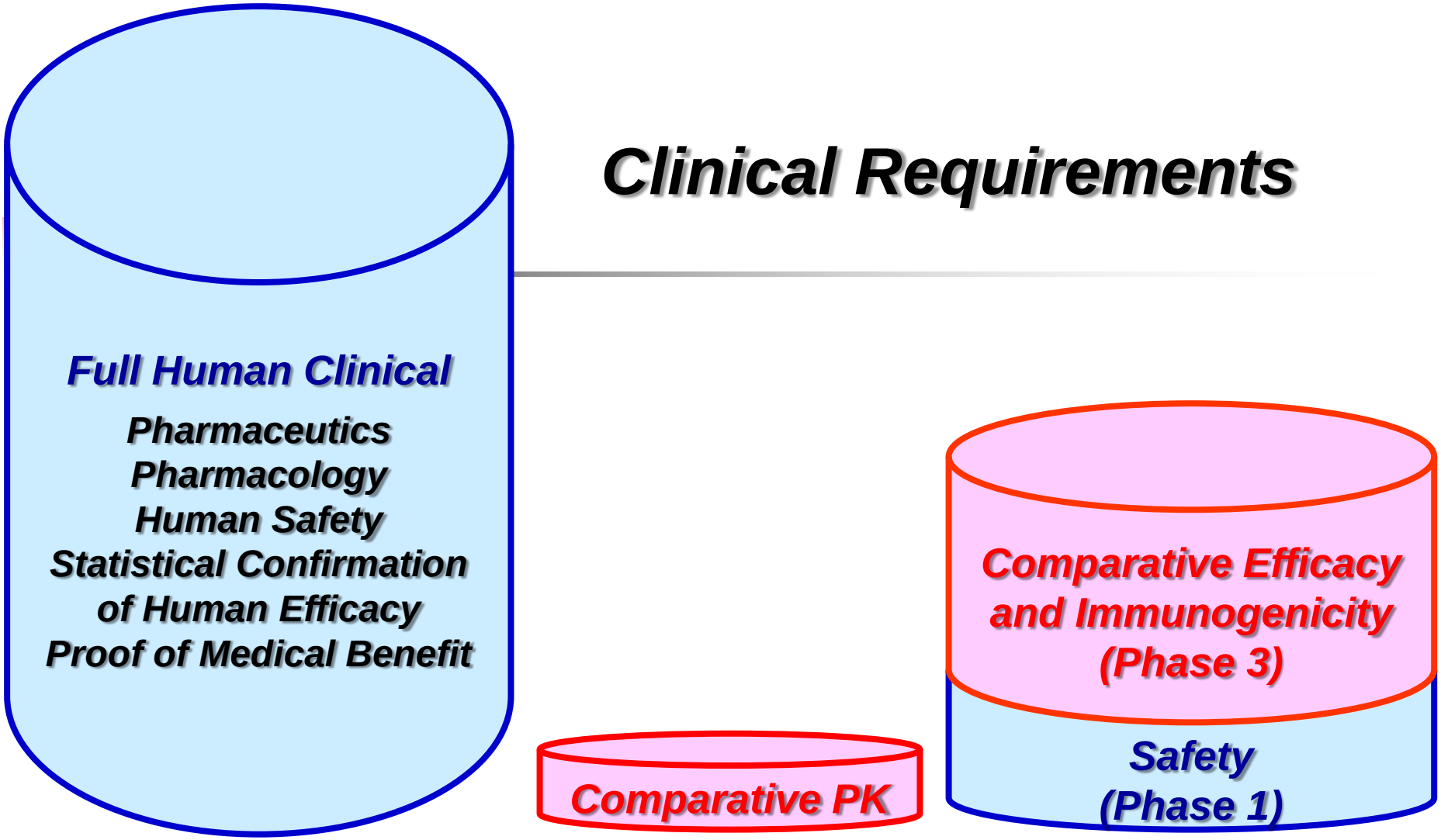
Nonclinical Requirements

Innovator
Chemical Drug
or Biologic

Chemical Generic

Biosimilar

Clinical Requirements



Innovator
Chemical Drug
or Biologic

Chemical Generic

Biosimilar

Biosimilars under development 2017	
Epoetin alfa	81
Interferons (alpha)	63
Insulin & analogs	61
Neupogen (filgrastim)	58
Rituxan (rituximab)	54
Herceptin (trastuzumab)	38
Humira (adalimumab)	35
Somatotropins	35
Avastin (bevacizumab)	33
Enbrel (etanercept)	31

Source: Biosimilarpipeline.com

Biosimilar competition is intense!

Innovator

Roche/Genentech

Biosimilars on Market

Mylan – Ogivri

Celltrion – Herzuma

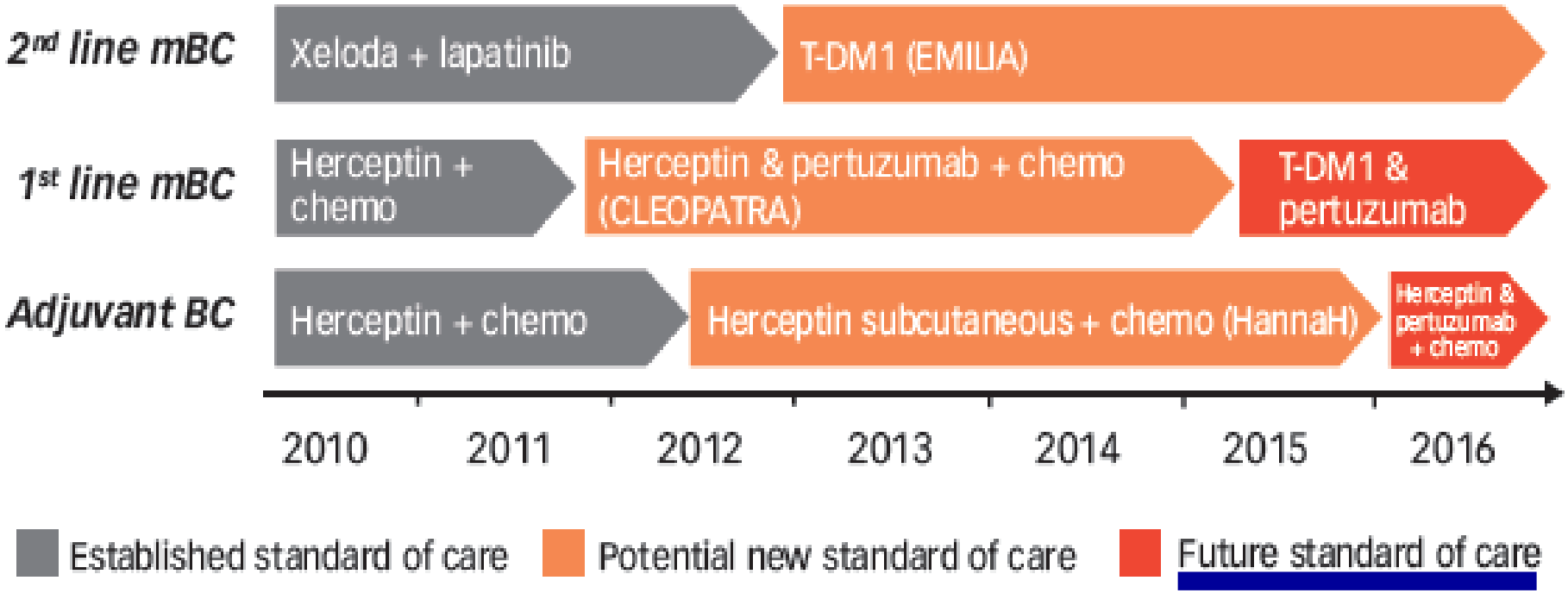
Sandoz - Ontruzant

Roche

"Biobetter"

Generation: 1st – Herceptin 2nd – Perjecta 3rd – Kadcyla (T-DM1)

Securing Growth for the HER2 Franchise



Building on the blockbuster Herceptin for metastatic breast cancer (mBC), Roche recently launched two follow-on agents: Kadcyla, an antibody-drug conjugate combining Herceptin and the cytotoxic chemotherapy, DM1; and Perjeta, to be used in conjunction with Herceptin or Kadcyla.

Source: Roche

PHARMACEUTICAL EXECUTIVE JUNE 2015

Biosimilars limited to recombinant proteins and monoclonal antibodies, for now!

Although this guidance applies specifically to therapeutic protein products, the general scientific principles may be informative for the development of other protein products, such as in vivo protein diagnostic products. If the reference product or the proposed product cannot be adequately characterized with state-of-the-art technology as recommended by this guidance, the application may not be appropriate for submission under section 351(k) of the PHS Act.

FDA Guidance for Industry: Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product (April 2015)

In principle, the concept of similar biological medicinal product is applicable to any biological product. However, in practice, the success of such a development approach will depend on the ability to characterise the product and therefore to demonstrate the similar nature of the concerned products.

EMA Procedural Advice for Users of the Centralised Procedure for Similar Biological Medcinal Products Applications (May 2017)

INN-xxxx

Bioqualifiers used by FDA, <u>not</u> EMA

Innovator chemical drug → Chemical generic

same INN

Innovator biopharmaceutical → Biosimilar

different INN bioqualifier

Humira
adalimumab

Cyltezo
adalimumab-adbm

Amjevita
adalimumab-atto

Interchangeability

(by pharmacy or insurance company)

Innovator chemical drug → Chemical generic

automatic interchangeable

Innovator biopharmaceutical → Biosimilar

must be specifically approved for interchangeable

FDA must approve – interchangeable a higher standard than biosimilarity

EMA approves biosimilarity and leaves interchangeable to National Competent Authorities

Summary - QUICK QUIZ

Biopharmaceuticals differ from chemical drugs in what 4 major areas that impact CMC regulatory compliance?

1. ***Use of L_____ S_____***
2. ***Impact of the M_____ P_____***
3. ***C_____ of the biologic molecule***
4. ***No B___-G_____***