CMC Regulatory Compliance Strategy For Biopharmaceuticals

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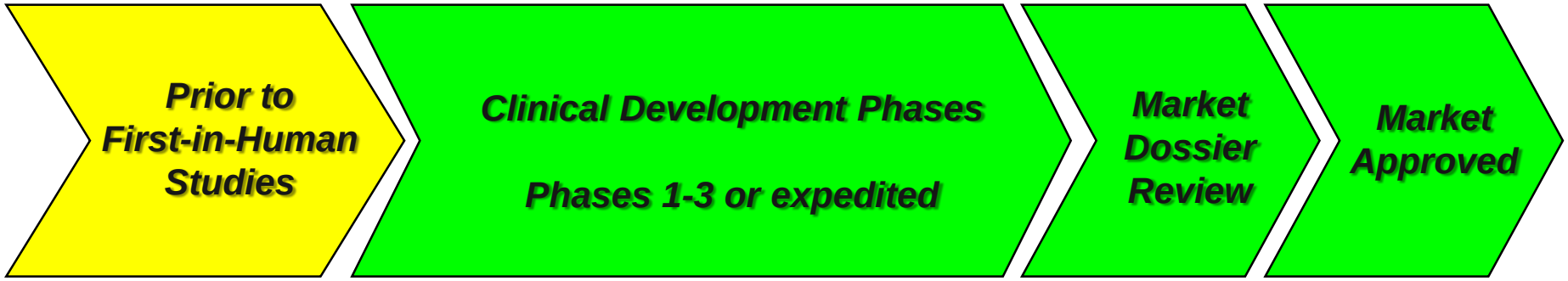
CMC Regulatory Compliance Strategy For Biopharmaceuticals

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 Biopharmaceuticals 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*

Note: many of the principles to be discussed are applicable or adaptable to other biologics – vaccines, natural proteins, cell therapy, etc.

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 Biopharmaceuticals 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 either non-living (protein-based) or living (virus-/cell-based)*

Biologic/Biological: Consensus Definition

(EMA, FDA, HC, WHO, …)

Definition of biological medicinal product

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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.

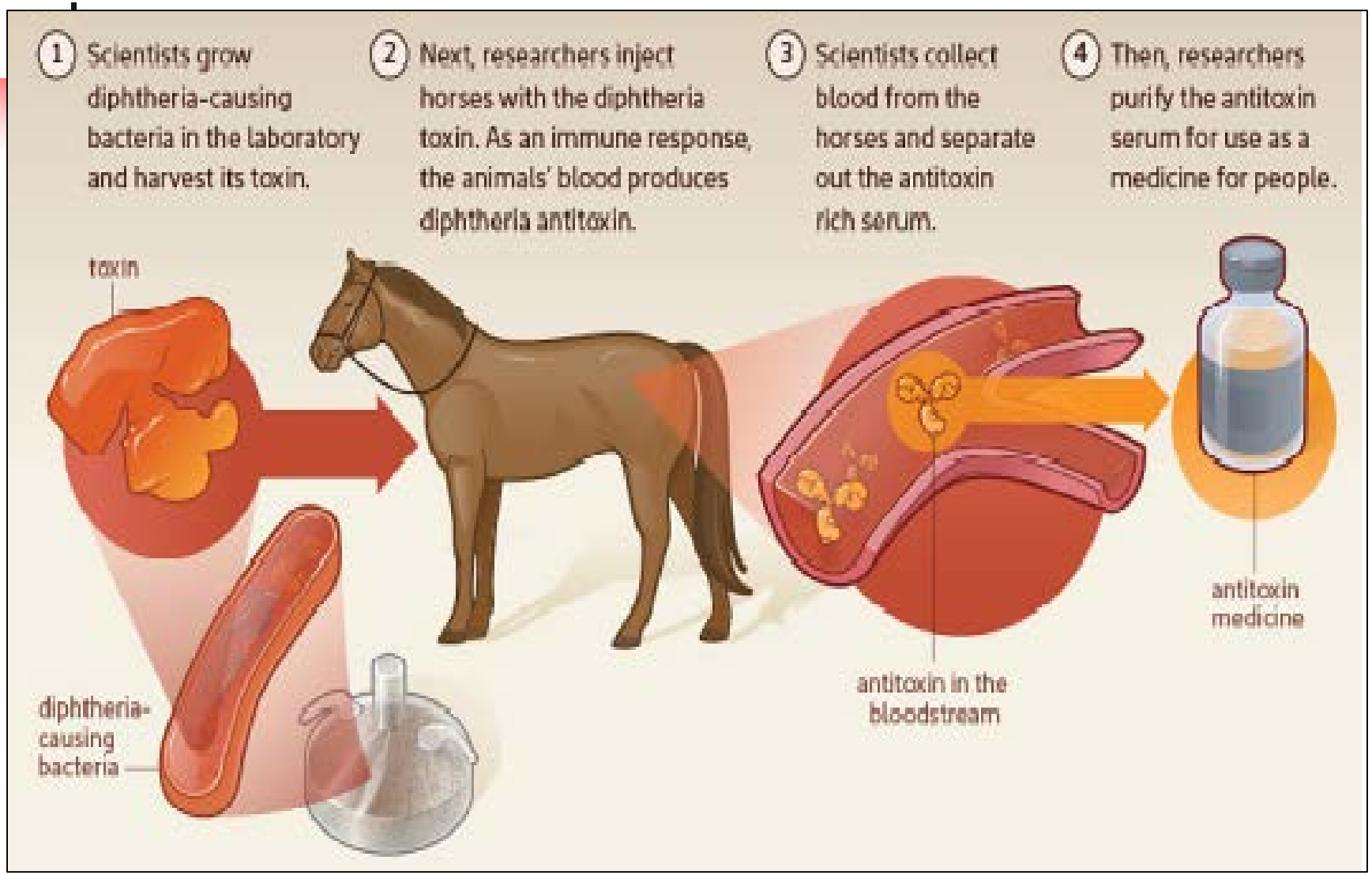
3 components

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

Biologics before Genetic Engineering

- ***Immune Serums (Anti-toxins)***
- ***Vaccines***
- ***Human Plasma-Derived proteins***
- ***Animal-Derived Protein Hormones***

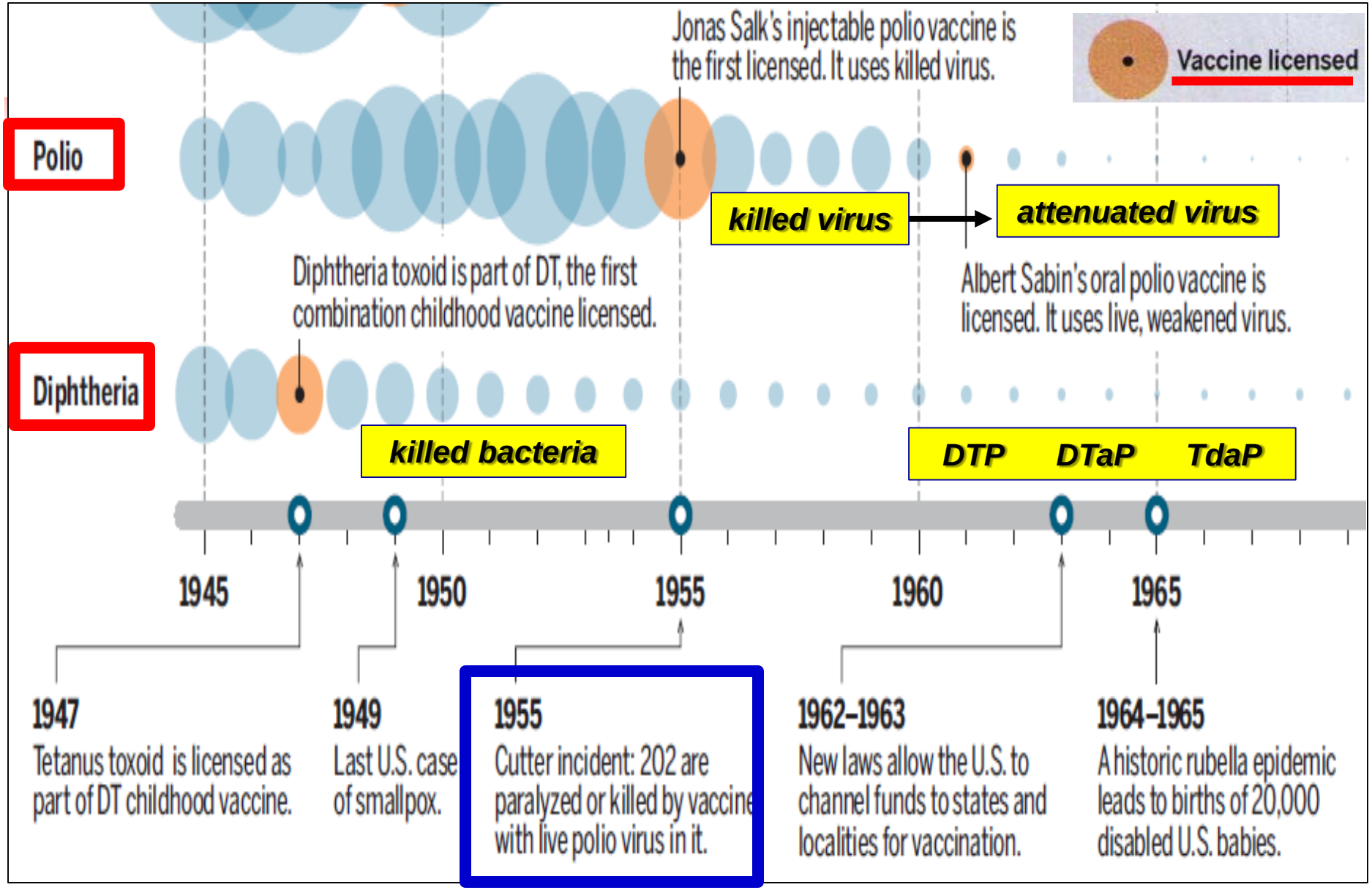
Immune Serums (Anti-toxins) since 1920's



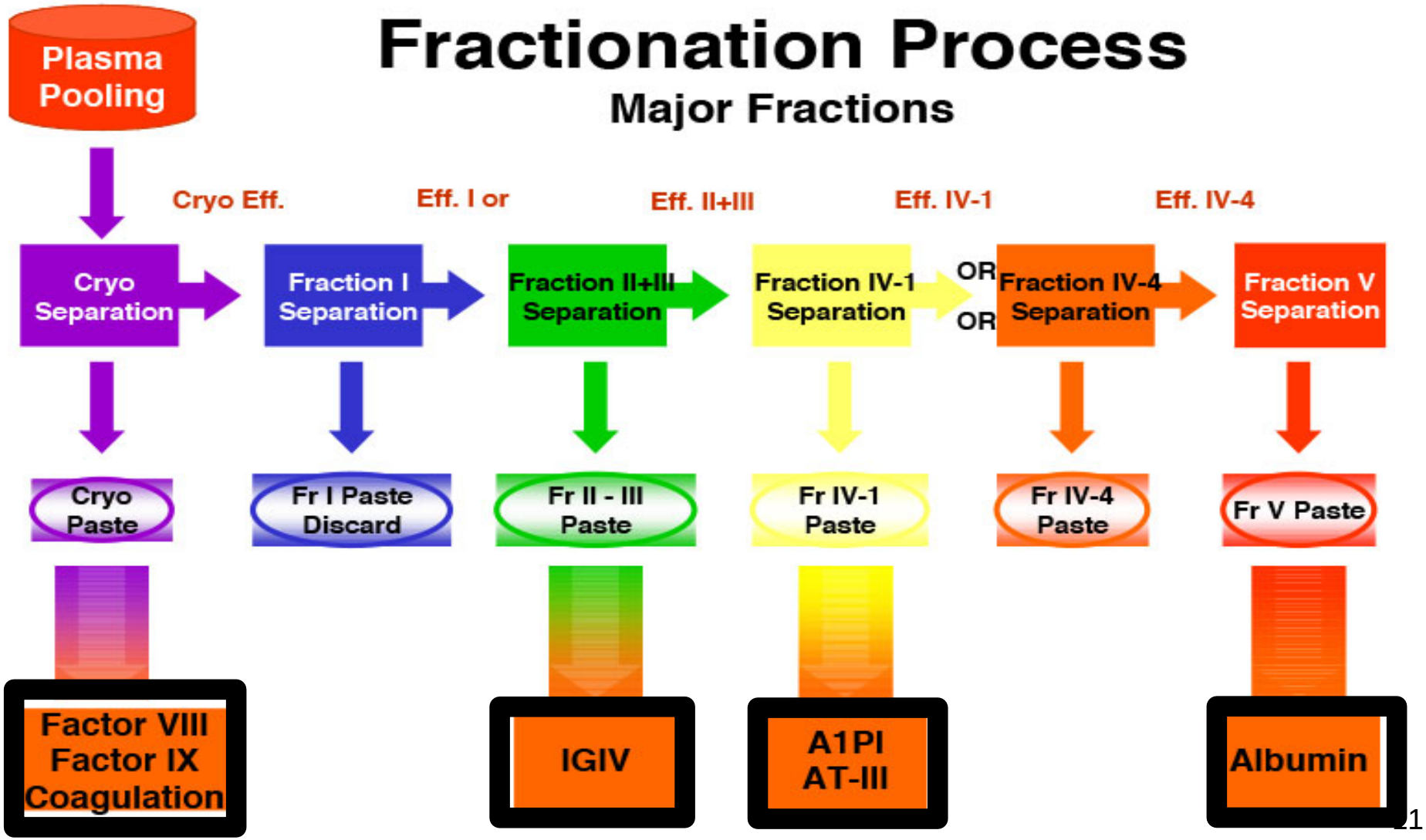
Iditarod Alaska Dog Relay 1925 – Anchorage to Nome to save children dying of diphtheria

Vaccines since 1940's

SCIENCE
28 APRIL 2017 • VOL 356 ISSUE 6336



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



Protein hormones since 1930's

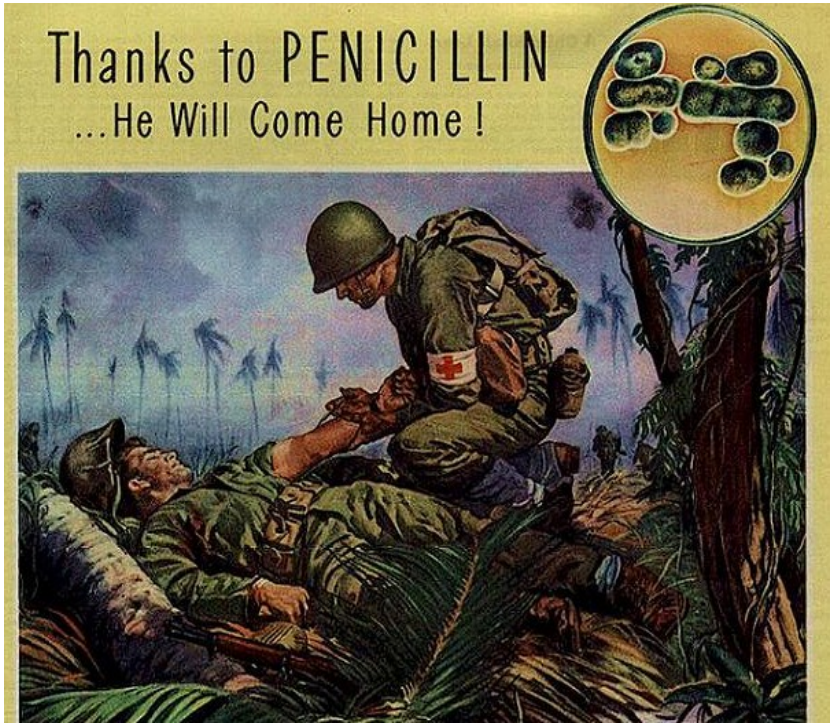
Extraction of 2 tons of pig pancreases to isolate 8 oz of insulin

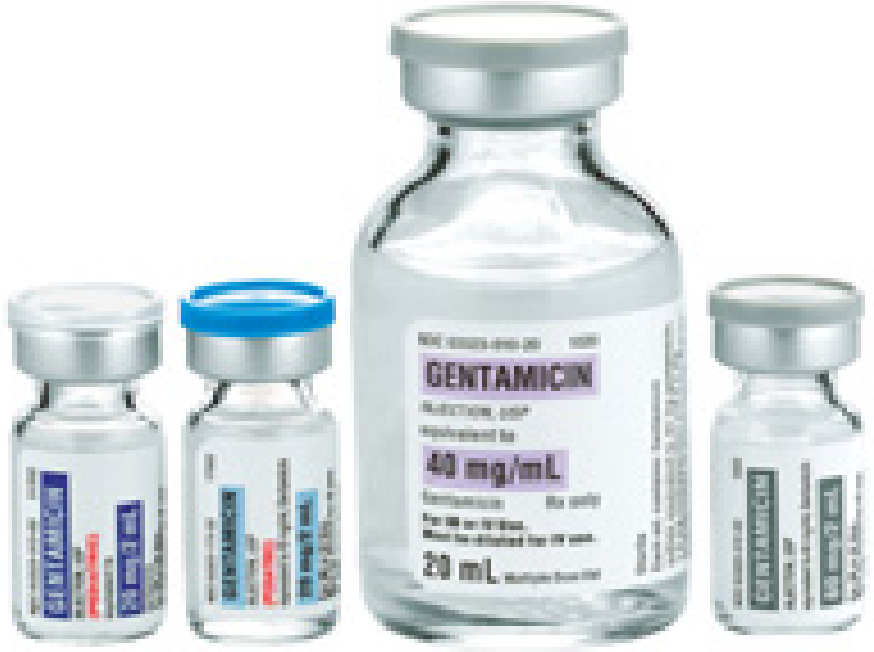
Eli Lilly
porcine insulin
final product

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

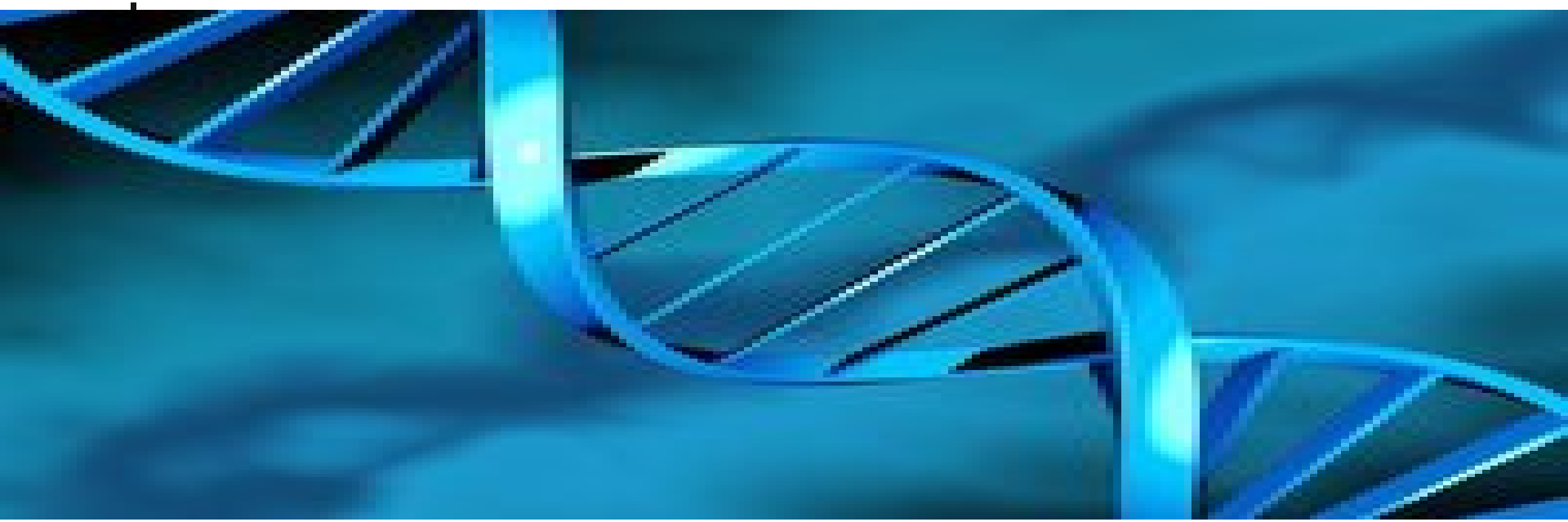
('biologic' meets all 3 components)

Antibiotics are 'chemical drugs'
from living microorganism fermentations
(penicillin, cephalosporin, tetracycline, gentamicin, ...)





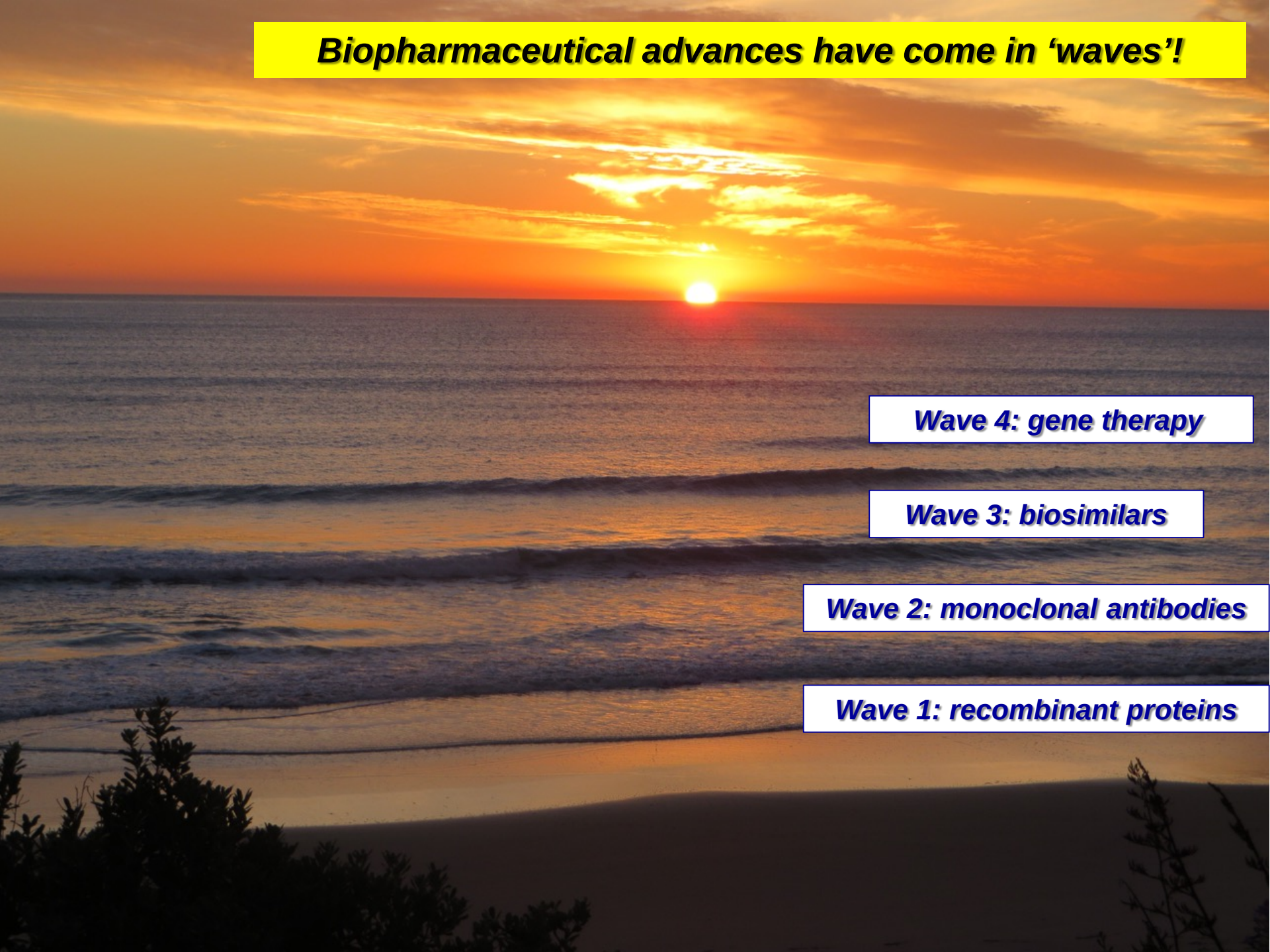
Biologics after Genetic Engineering



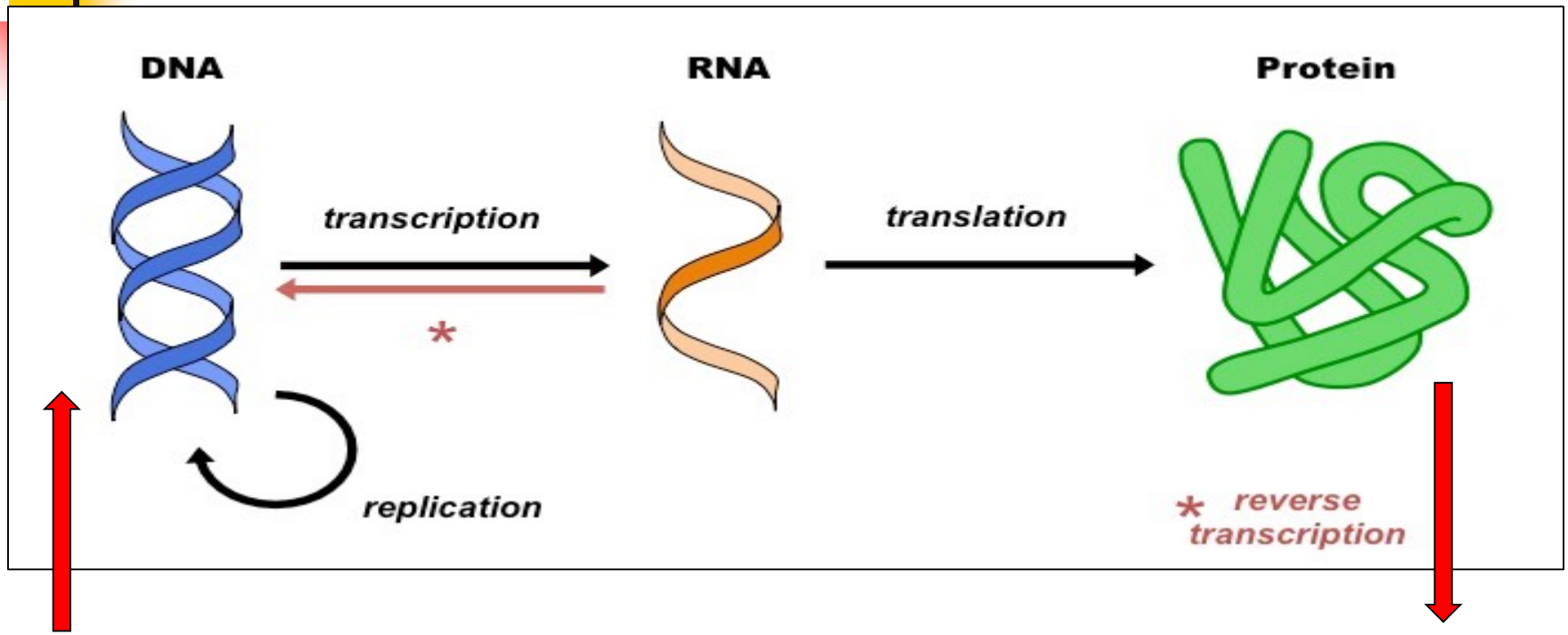
"Biopharmaceuticals"

***3* components**

- *Derived from a genetically engineered living system*
- *Challenging manufacturing process*
- *Complex molecule*


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

WAVES 1, 2 and 3



Foreign DNA inserted into a living microorganism (e.g., E. coli, CHO) that can then produce the specific protein/mAb

Recombinant protein/mAb isolated, purified, formulated for human administration

WAVE 1

Recombinant proteins

1982 1st recombinant protein

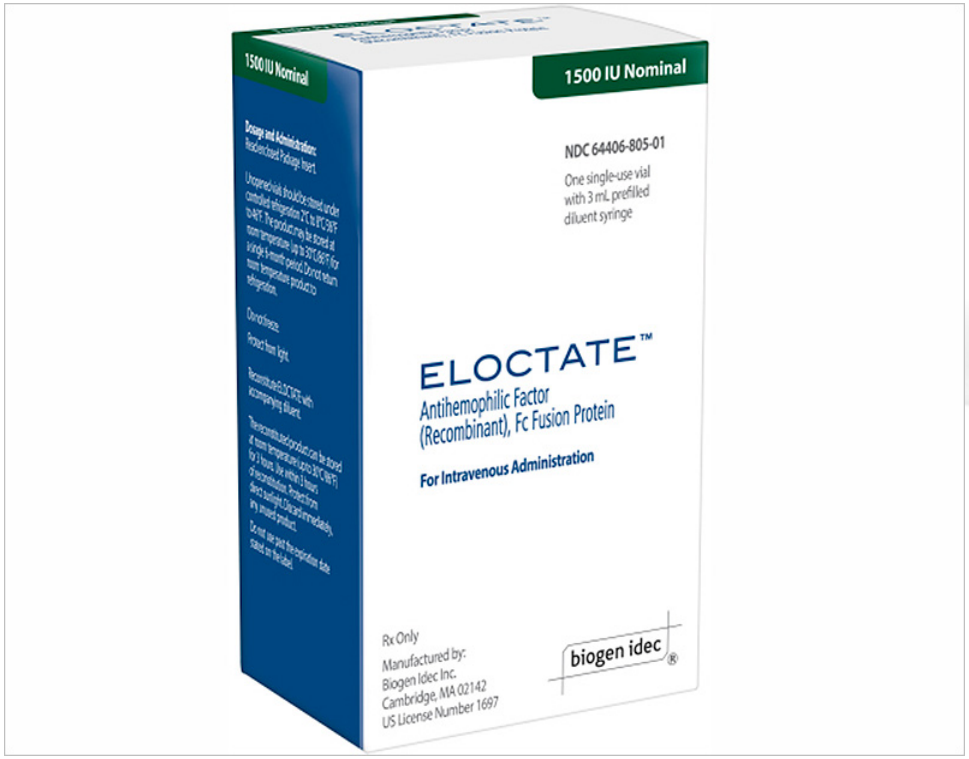
Global human insulin market in 2018: > $30 billion

TODAY

- ***Over 100 recombinant protein approved medicines***
- ***Enbrel (recombinant etanercept fusion protein)***
  3rd best selling medicine in the world

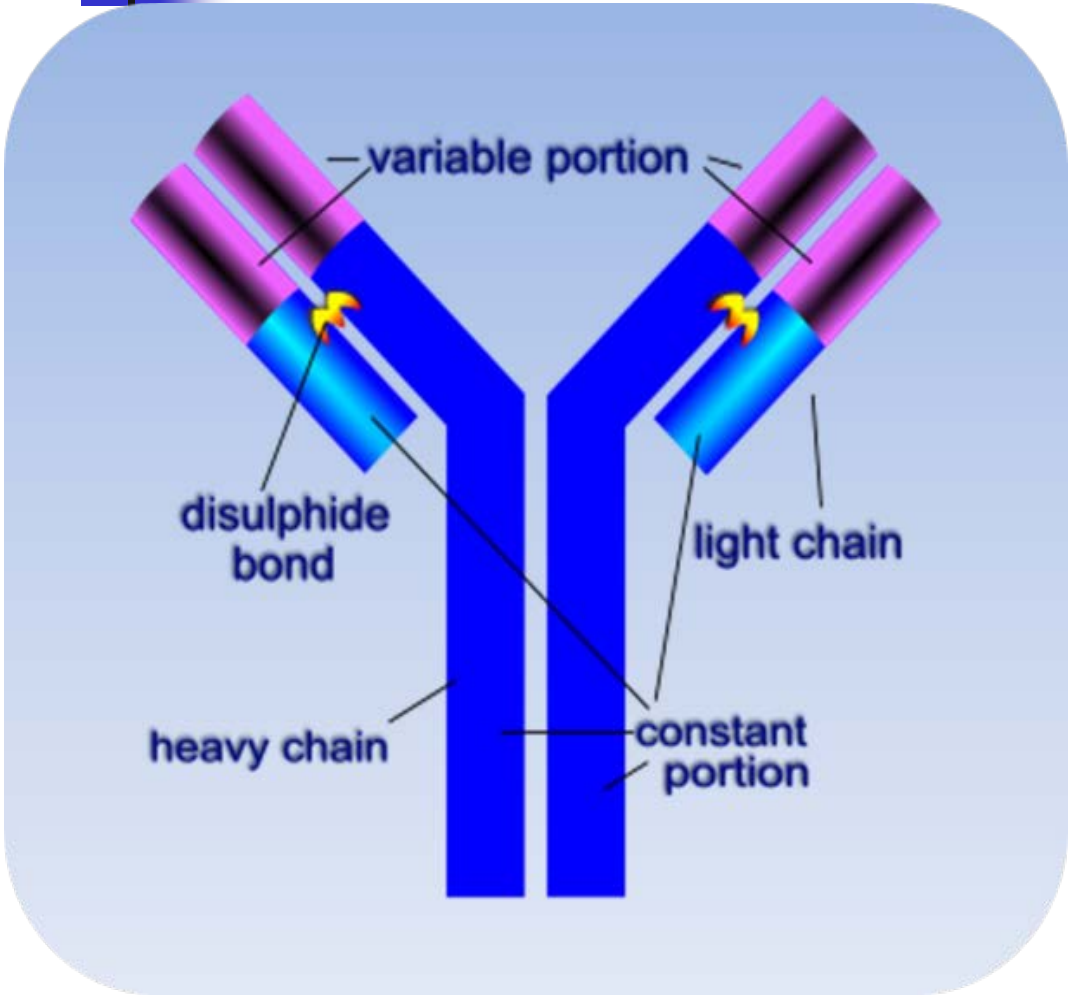
www.nature.com/nrd 232 | APRIL 2018 | VOLUME 17

Recombinant proteins also used as vaccines and human plasma-derived proteins



Factor VIII

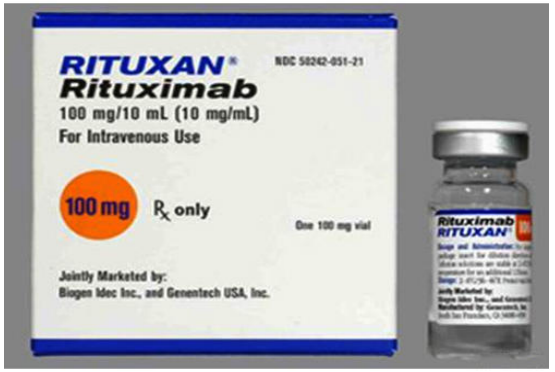
WAVE 2
Monoclonal antibodies



The recombinant protein is a 'clonal' immunoglobulin that binds to a <u>specific</u> site to either block or initiate a cellular interaction to treat medical symptoms

1986 1st monoclonal antibody (murine)

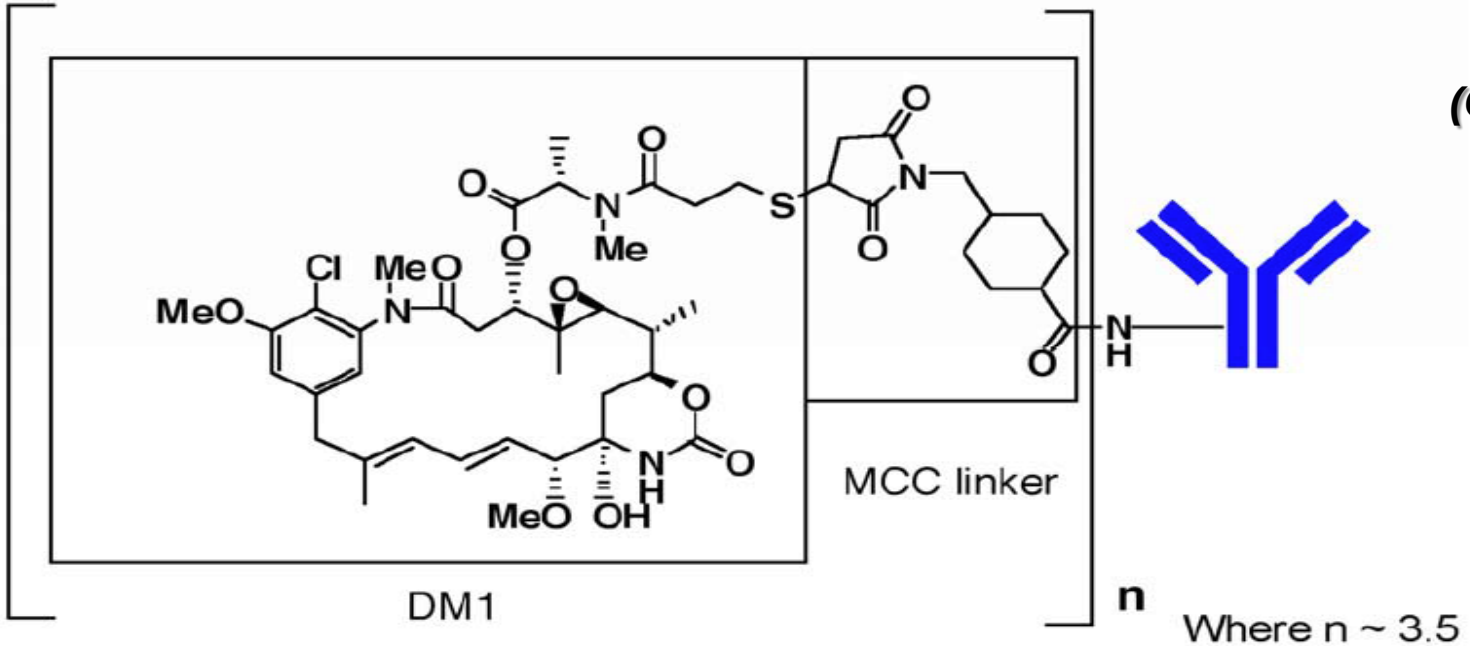
1997 1st commercially successful monoclonal antibody (chimeric)



TODAY

- Murine → chimeric (part murine/part human) → fully human
- Over 100 monoclonal antibody approved medicines
- Humira (adalimumab)
  1st best selling drug in the world (> $16 billion)

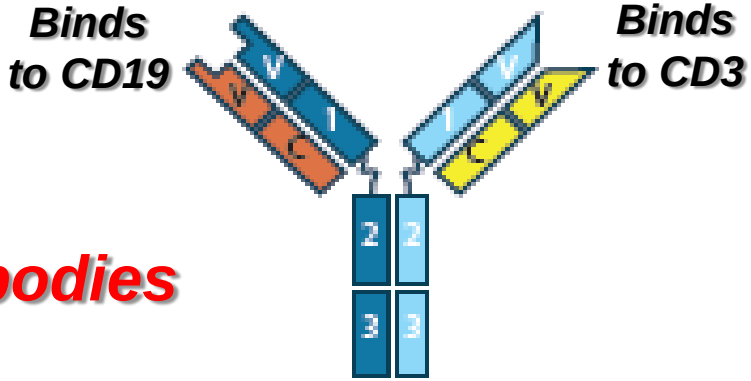
Antibody Drug Conjugates (ADCs)



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

Currently, due to scientific limitations, regulatory authorities are limiting biosimilars to recombinant proteins and monoclonal antibodies

Biosimilars in Europe since 2006; in USA since 2015

Must be 'highly similar' to innovator's biopharmaceutical

Biosimilars to
Recombinant Proteins

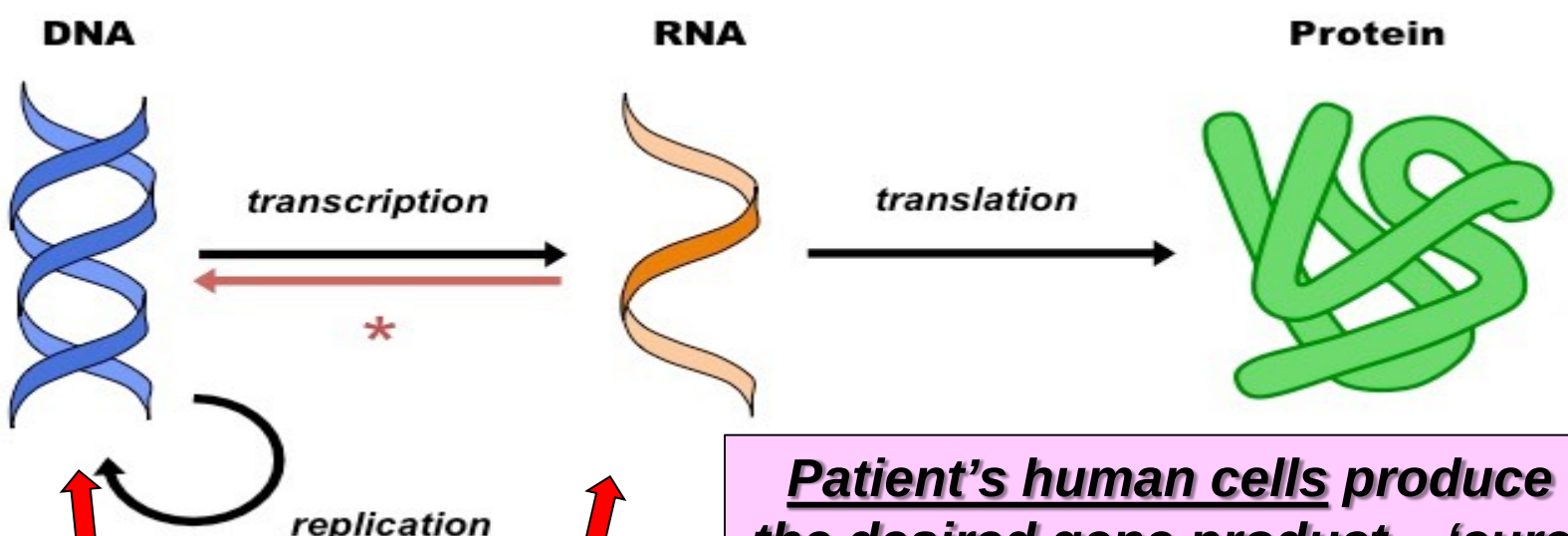
- Erythropoietin (EPO)
- G-Colony Stimulating Factor (G-CSF)
- TNF-α/Fc Fusion Protein (Enbrel)
- Pegylated-G-CSF (Neulasta)
- Human Insulin (HI)*
- Human Growth Hormone (HGH)*
- Follicle Stimulating Hormone (FSH)*
- Parathyroid Hormone (PTH)*

Biosimilars to
Monoclonal Antibodies

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

** Follow-on proteins in USA*

WAVE 4



Patient's human cells produce the desired gene product – 'cure'

Transfer of new genetic capability into or manipulation of existing genetic capability in living human cells

(ongoing debate about the amplitude of this upcoming 4th wave)

Amplitude opinion by the Regulatory Authorities

FDA

We anticipate that by 2020 we will be receiving more than 200 INDs per year, building upon our total of more than 800 active cell-based or directly administered gene therapy INDs currently on file with the FDA. And by 2025, we predict that the FDA will be approving 10 to 20 cell and gene therapy products a year based on an assessment of the current pipeline and clinical success rates of these products.

FDA Press Release January 15, 2019 – Statement from FDA Commissioner Scott Gottlieb, M.D. and Peter Marks, M.D., Ph.D., Director of CBER

EMA

PRIME is meant for the most promising medicines and EMA focuses its attention on medicines that can demonstrate a major therapeutic advantage. On average, only 20% of applications are accepted into the scheme. Within PRIME, Advanced Therapies Medicinal Products (ATMPs) are of special relevance, making up close to 40% of the medicines admitted to the scheme. This reflects the potential for this type of therapy to address unmet medical needs.

Annual Report 2017

The European Medicines Agency's contribution to science, medicines and health in 2017

1003

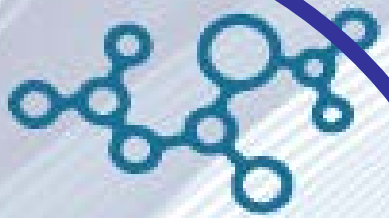
Clinical trials underway worldwide by end of Q3 2018

Ph. I: 330
Ph. II: 580
Ph. III: 93

Number of Clinical Trials Utilizing Specific RM/AT Technology: Q3 2018

Gene Therapy

Total: 351
Ph. I: 114
Ph. II: 204
Ph. III: 33



Gene-Modified Cell Therapy

Total: 328
Ph. I: 145
Ph. II: 168
Ph. III: 15

Cell Therapy

Total: 283
Ph. I: 61
Ph. II: 189
Ph. III: 33

Tissue Engineering

Total: 41
Ph. I: 10
Ph. II: 19
Ph. III: 12

Alliance for Regenerative Medicine

Q3 2018

US Food and Drug Administration (FDA)

Cellular and Gene Therapy Products (CGTPs)

- *Gene Therapy*
- *Cellular Therapy*
- *Tissue-Product*

(RMAT – Regenerative Medicine Advanced Therapy)

(OTAT – Office of Tissues and Advanced Therapies)

European Medicines Agency (EMA)

Advanced Therapy Medicinal Products (ATMPs)

- *Gene Therapy*
- *Somatic Cell Therapy*
- *Tissue Engineered*

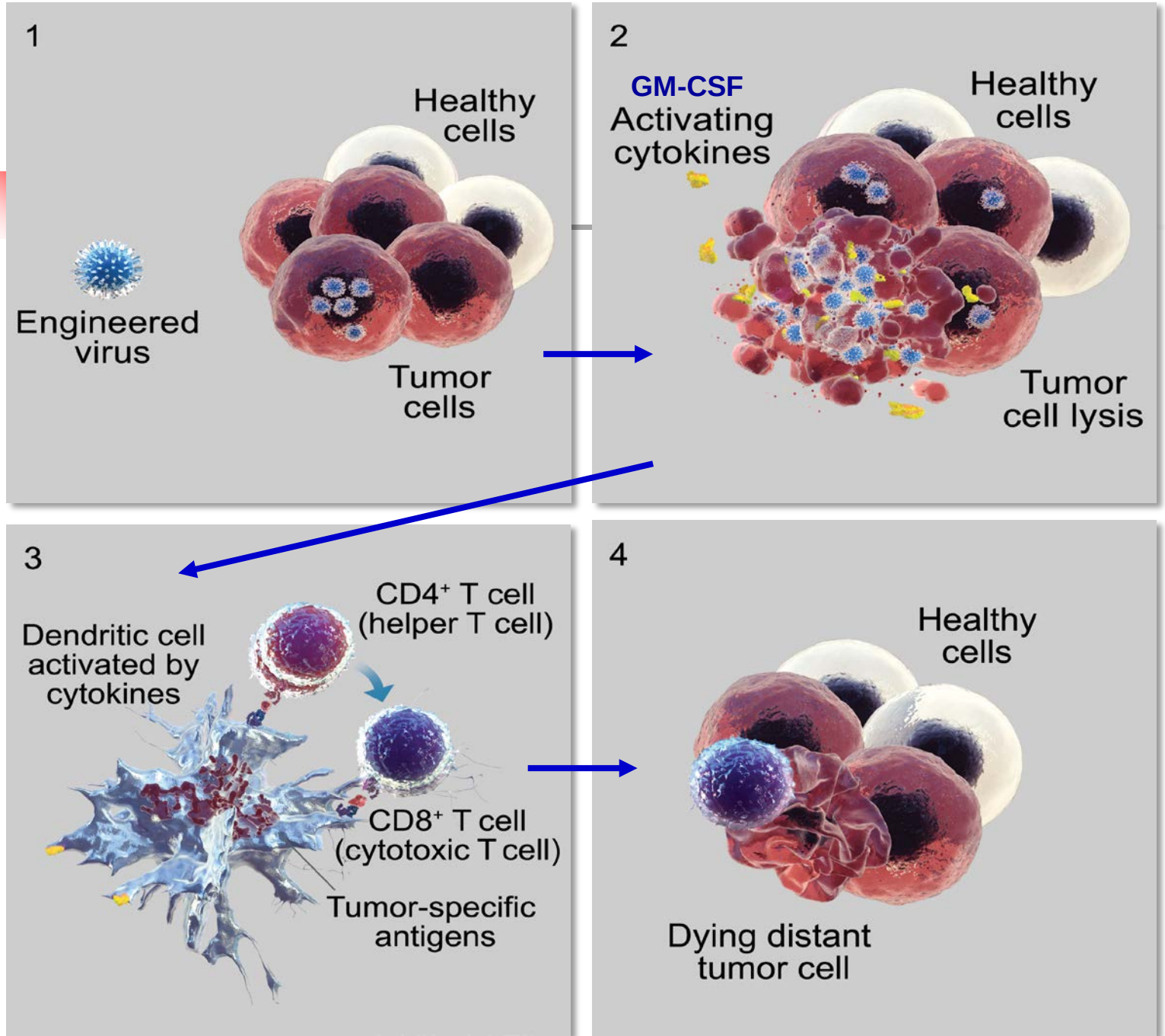
(CAT – Committee for Advanced Therapies)

Oncolytic virus – in vivo

Amgen IMLYGIC

genetically engineered HSV virus (with GM-CSF gene)

to treat melanoma FDA/EMA approved 2015



Local effect

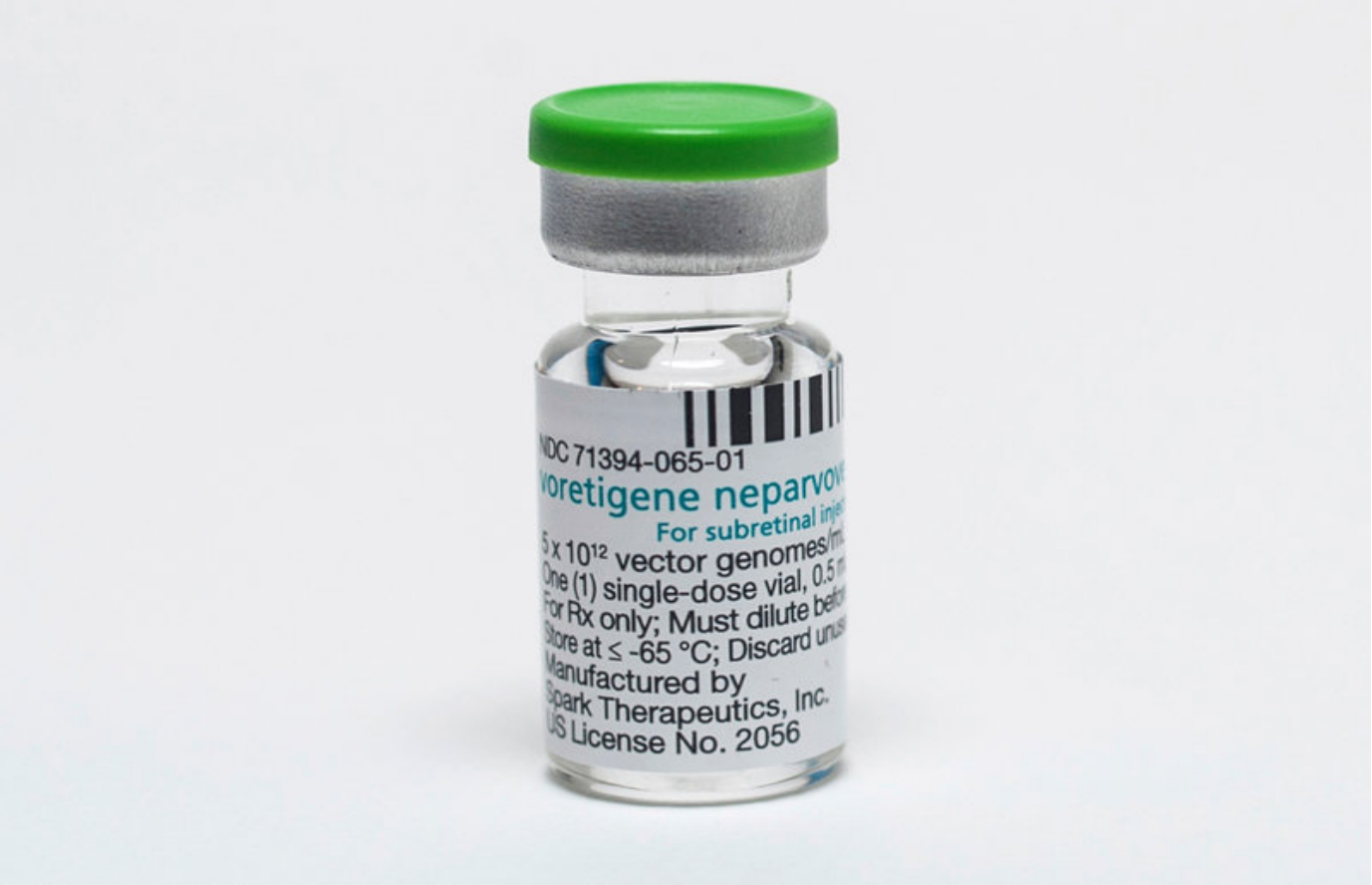
Systemic effect

Gene therapy – in vivo

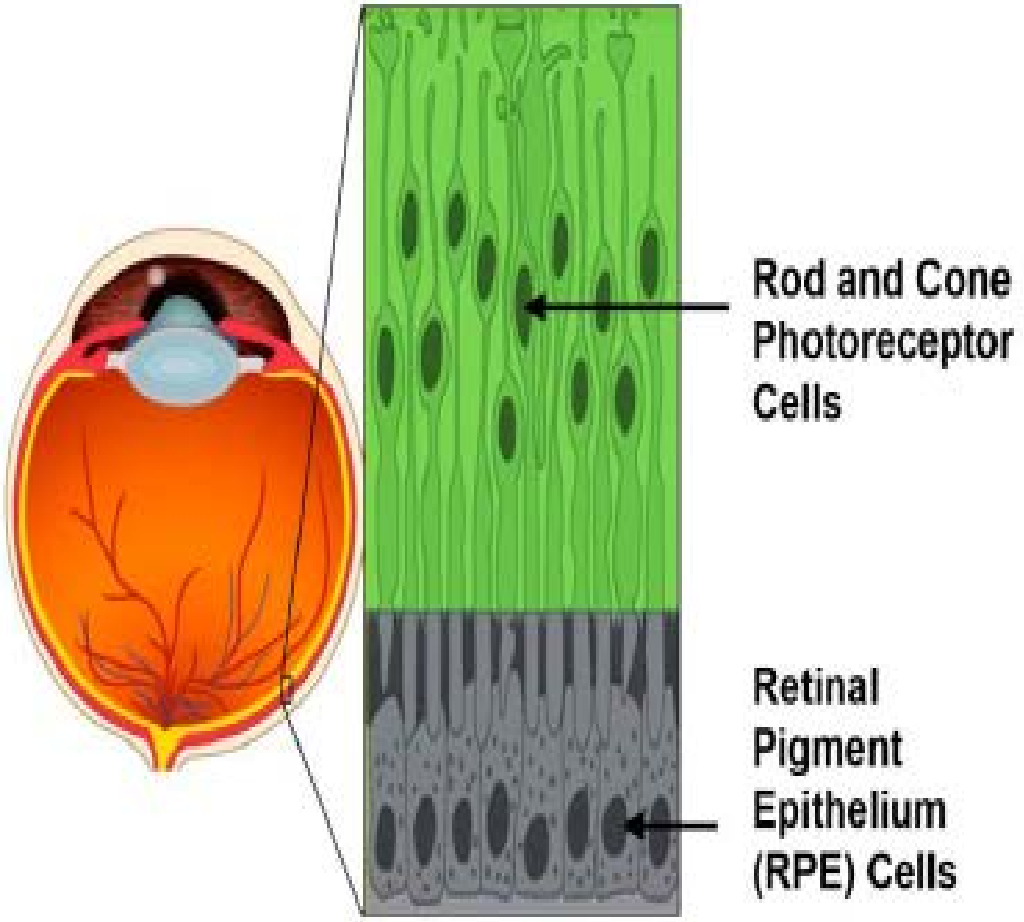
Spark Therapeutics LUXTERNA

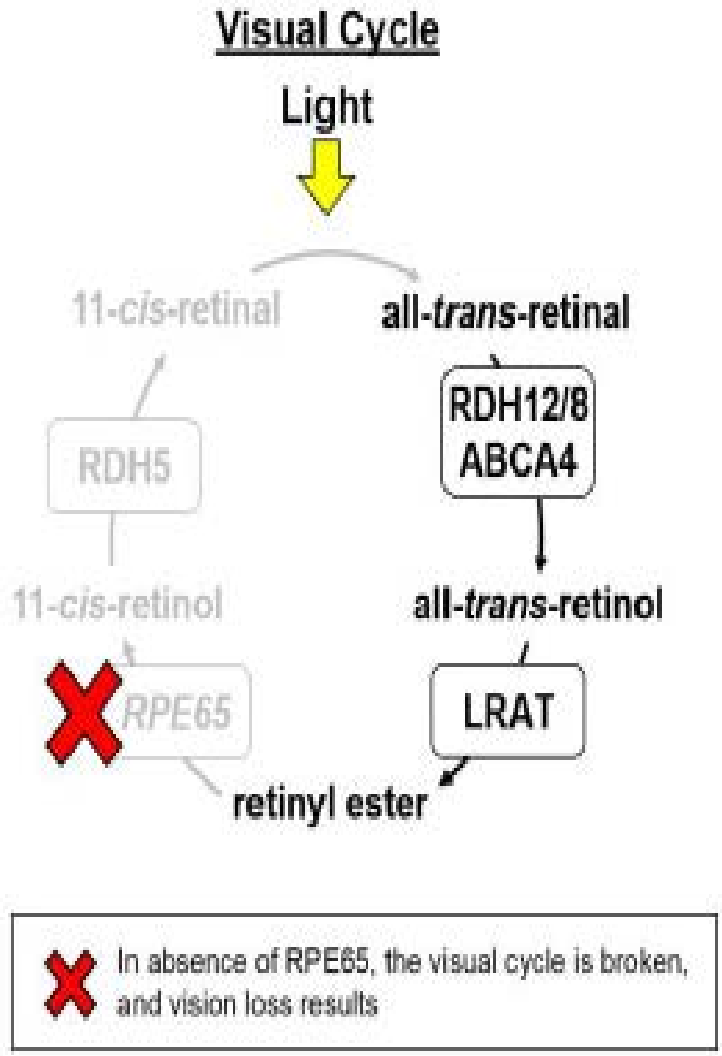
adeno-associated virus vector (with RPE65 gene)

to treat vision loss FDA/EMA approved 2017/2018



RPE65 gene produces a protein necessary in the cycle for vision





Direct injection of live virus into eye to replace defective gene

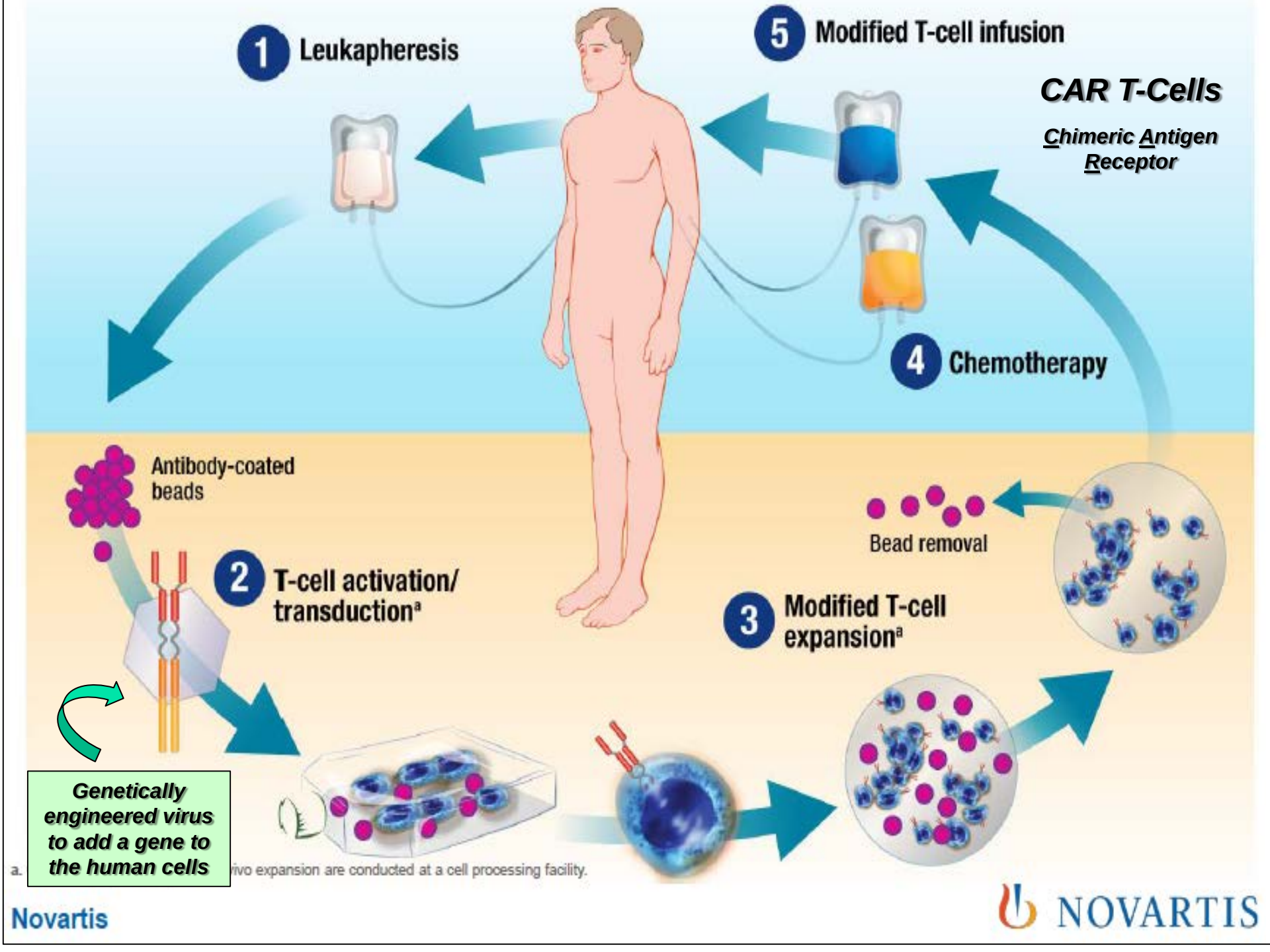
Gene therapy – ex vivo

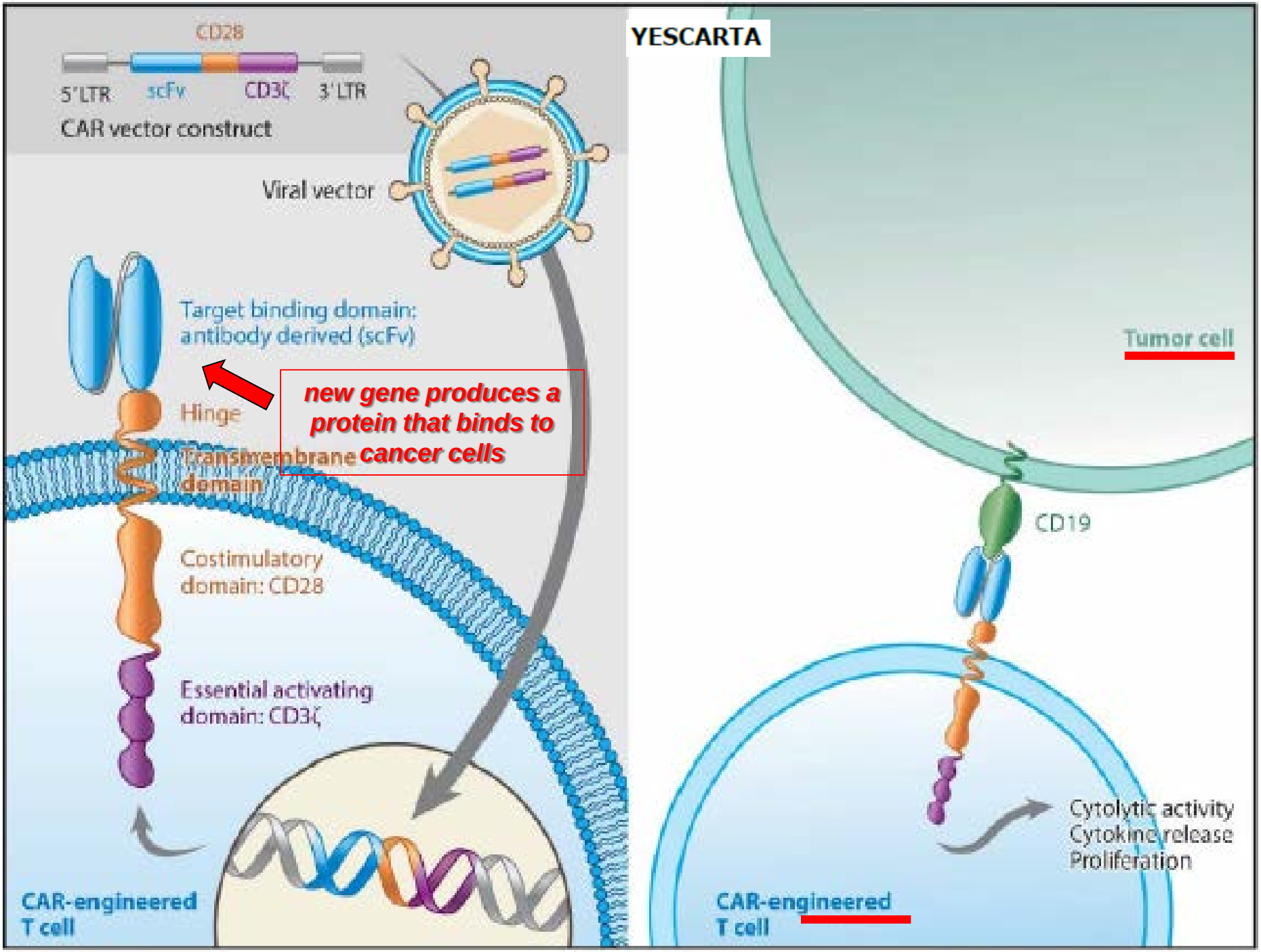
Novartis KYMRIAH

Gilead/Kite YESCARTA

Autologous genetically modified (CAR – chimeric antigen receptor) T cells to treat acute lymphoblastic leukemia (ALL)

FDA/EMA approved 2017/2018


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 to add a gene to the human cells
a. ivo expansion are conducted at a cell processing facility.
Novartis
NOVARTIS


CD28
5'LTR
scFv
CD3ζ
3'LTR
CAR vector construct
Viral vector
YESCARTA
Target binding domain: antibody derived (scFv)
new gene produces a protein that binds to cancer cells
Hinge
Transmembrane domain
Costimulatory domain: CD28
Essential activating domain: CD3ζ
Tumor cell
CD19
Cytolytic activity
Cytokine release
Proliferation
CAR-engineered T cell
CAR-engineered T cell

Whenever a new biopharmaceutical type makes it commercially …

… some will start saying 'the sky is falling'!

Cell and Gene Therapies: Industry Faces Potential Capacity Shortages

GEN
Genetic Engineering & Biotechnology News
November 15, 2017

Gene Therapy Hits a Peculiar Roadblock: A Virus Shortage

The New York Times
NOV. 27, 2017

We may soon have our first $1 million drug. Who will pay for it? And how?

PBS NEWS HOUR
Oct 15, 2017

… and there always will be 'rogue ventures'!

➢ Self injection of gene therapies (YouTube)

Why I injected myself with an untested gene therapy - BBC News
www.bbc.com/news/world-us-canada-41990981
Nov 21, 2017 - The moment Tristan Roberts became the first human to **inject** an untested, experimental **gene therapy** into his stomach fat, he was sitting on a …

A biotech CEO explains why he injected himself with a DIY herpes …
https://www.technologyreview.com/.../a-biotech-ceo-explains-why-he-injected-himsel...
Feb 5, 2018 - Traywick's stunt is the latest example of **self-injection** by biohackers who, despite … Biohackers Disregard FDA Warning on DIY **Gene Therapy**.

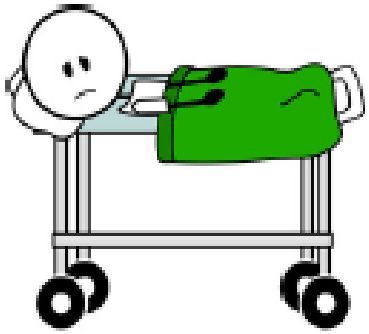
➢ Stem cell 'false promises'

American CryoStem Corporation **WARNING LETTER** January 3, 2018

… your firm receives and processes adipose tissue, a structural tissue, for autologous use … your firm isolates cellular components from the adipose tissue, thereby processing the adipose tissue into Stromal Vascular Fraction (SVF). The SVF is then expanded through cell culture to produce your product ATCELL™. American CryoStem then ships the autologous product back to physicians to treat patients for a variety of diseases or conditions by various routes of administration, including intravenously, intrathecally (i.e., injection or infusion into the central nervous system) and by aerosol inhalation

… records reveal that ATCELL™ is intended to treat a variety of diseases and conditions, including, but not limited to, anoxic brain injury, Parkinson's disease, amyotrophic lateral sclerosis (ALS), stroke, and multiple sclerosis.

… always a learning curve!



vein to vein, 2-3 weeks

Black Box In

1 batch = 1 patient

Black Box Out

Cell culturing manufacturing process

Substantial manipulation of cells → Cellular Therapy
(if genetic engineering involved → Gene Therapy)

Industry knows how to handle cells!

Pharmaceutical

Chemical Drug

- Chemical Synthesis
- Natural Sourced

Generics

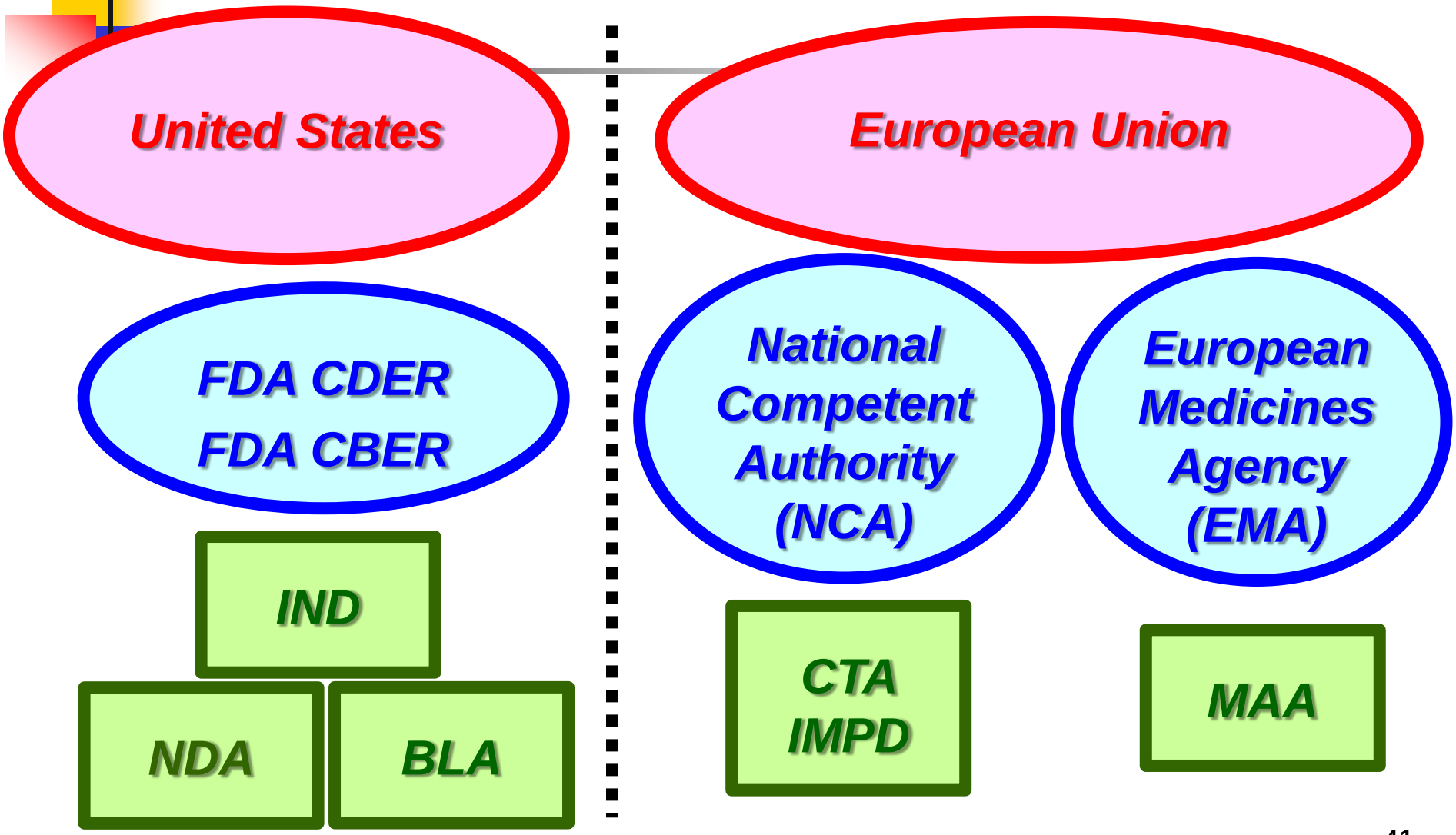
Biologic/ Biological

- **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)

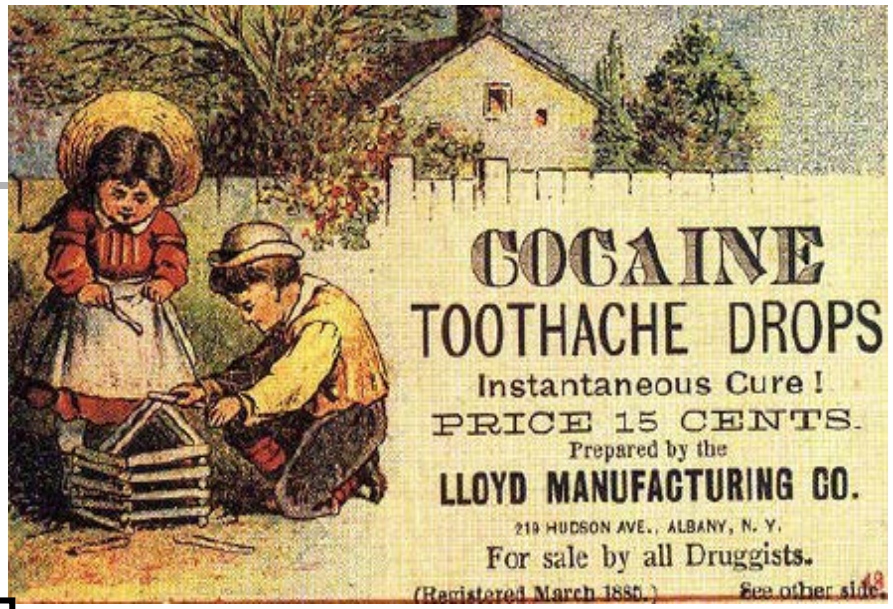
↓

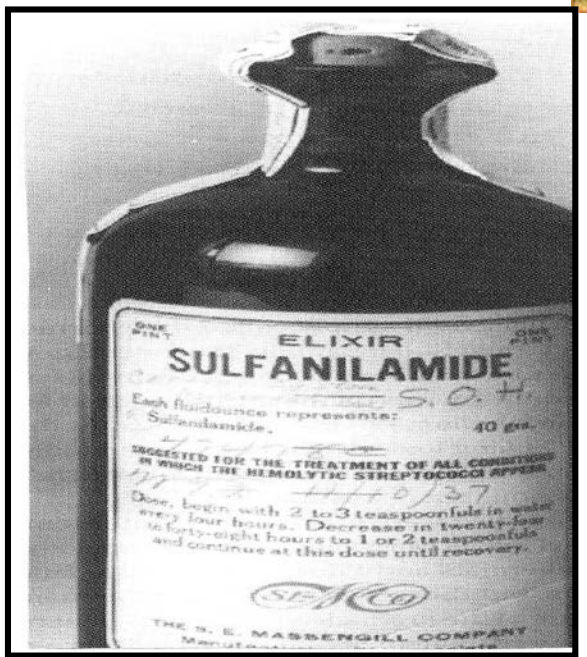
FDA publishes guidances ('recommendations') on its website
explaining in greater detail how to follow their regulations

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 cheaper, sweet, 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'***

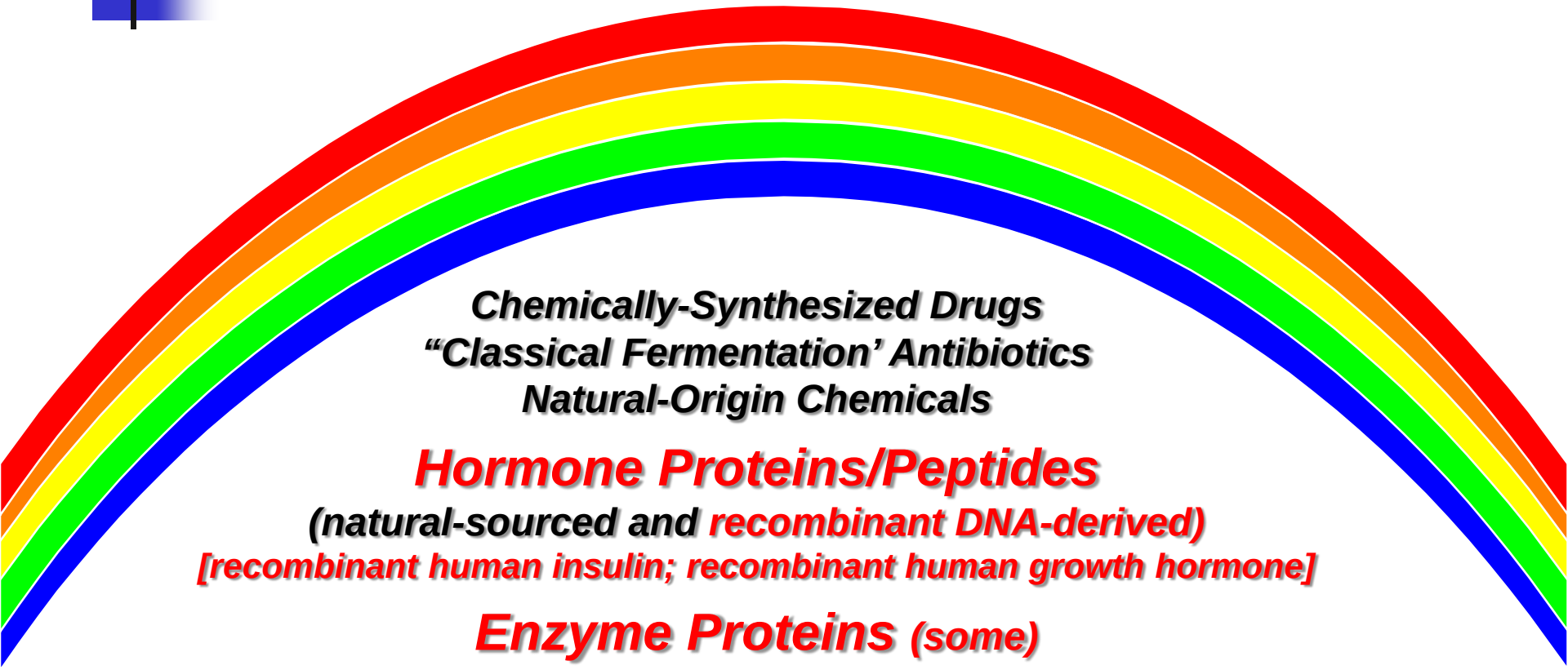
FD&C Act: New Drug Application (NDA) Pathway

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

→

New Drug Application (NDA)
21 CFR 314 + 21 CFR 211
[marketed products]

Some BIOPHARMACEUTICALS
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

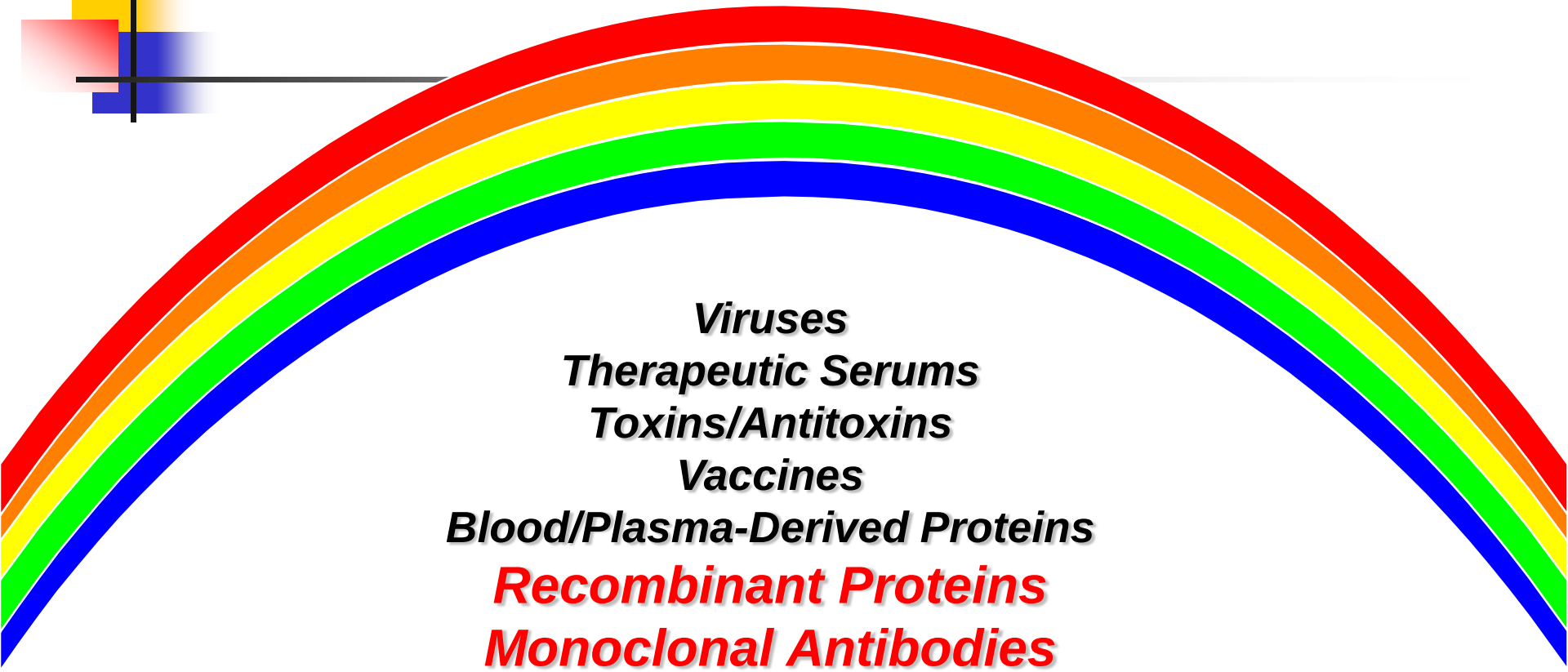
Investigational New Drug (IND)
21 CFR 312
[human clinical studies]

→

Biologics License Application (BLA)
21 CFR 600-680 + 21 CFR 211
[marketed products]

Note: same clinical development as FD&C Act!

Most BIOPHARMACEUTICALS
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***

1. *extra commercial testing requirements*
2. *may require FDA commercial pre-release*
3. *different commercial regulatory compliance procedures*
4. *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 (content 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 biopharmaceuticals!
Company QA solely determines release to inventory

Example: FDA pre-release required for Vaccines

illustrated by influenza vaccines

Cumulative 2018-2019 Season

Manufacturer	Total Number of Lots Released by FDA
Afluria Seqirus Pty. Ltd.	6
Afluria Quadrivalent Seqirus Pty. Ltd.	56
Fluad Seqirus, Inc.	26
Fluarix Quadrivalent GlaxoSmithKline Biologicals	39
Flucelvax Quadrivalent Seqirus, Inc.	46
Flublok Quadrivalent Protein Sciences Corporation	36
FluLaval Quadrivalent ID Biomedical Corporation of Quebec	36
FluMist Quadrivalent MedImmune, LLC	9
Fluzone High Dose Sanofi Pasteur, Inc.	29
Fluzone Quadrivalent Sanofi Pasteur, Inc.	37

FDA pre-release 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).

Albuminex – Albumin, Human-kjda (June 19, 2018)

Please submit final container samples of the product 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).

stated in FDA market approval letter

Vaccine and human plasma-derived protein manufacturers can request a waiver after a 'significant' period of time and/or number of batches

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

granted in 1995

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.*

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.*

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 23, 2020!

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

FD&C Act

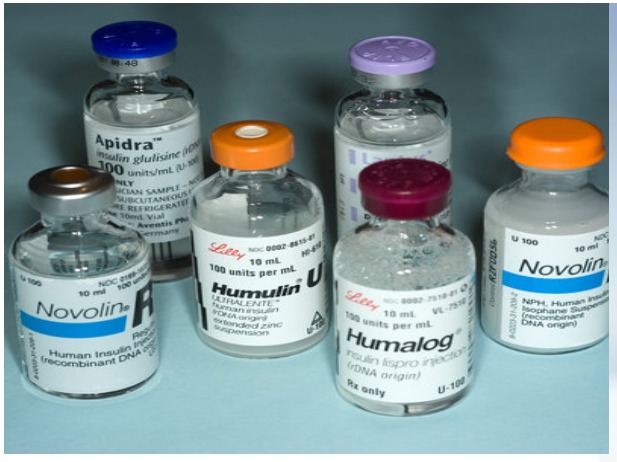
Biologic Hormones

Enzymes (some)

PHS Act

Biologic Hormones

Enzymes (some)



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

December 2018

March 23, 2020 regulatory challenges

Monday, March 23, 2020, during hours in which FDA is open for business	Approved NDAs for biological products	FDA intends to send a letter to each holder of an approved NDA for a biological product that advises that the approved NDA has been deemed to be a BLA by operation of the statute, and no longer exists as an NDA. FDA intends to update the Orange Book to remove biological product listings.
Monday, March 23, 2020, 11:59 pm (EDT)	Pending 505(b)(1) applications and pending 505(b)(2) applications that do not rely, to any extent, on FDA's finding of safety and/or effectiveness for a listed drug that is a biological product	Deadline for any pending 505(b)(1) application or any pending 505(b)(2) application of this type to be approved under the FD&C Act. An NDA approved on March 23, 2020, will be deemed to be a BLA immediately after approval under the FD&C Act.

- ***NDAs under review will be given a Complete Response Letter***
- ***NDAs moved over do not get 12 yr BLA market exclusivity***
- ***Must now follow PHS Act CMC requirements***

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

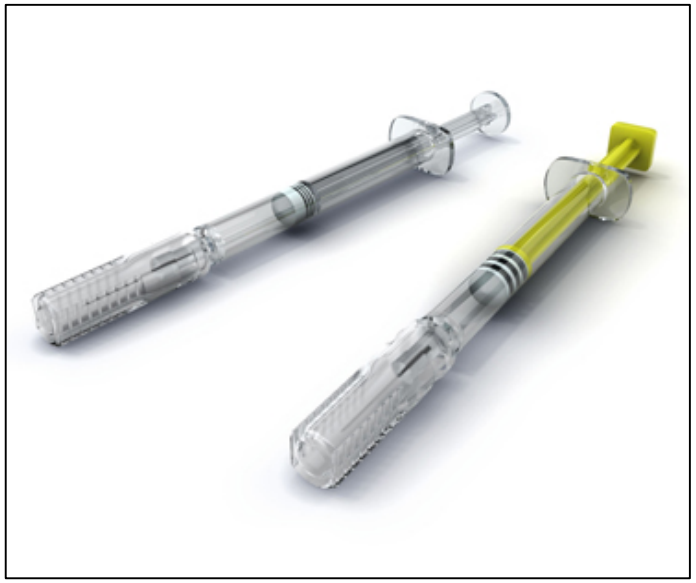
Why did this change make sense?

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

U.S. Food and Drug Administration

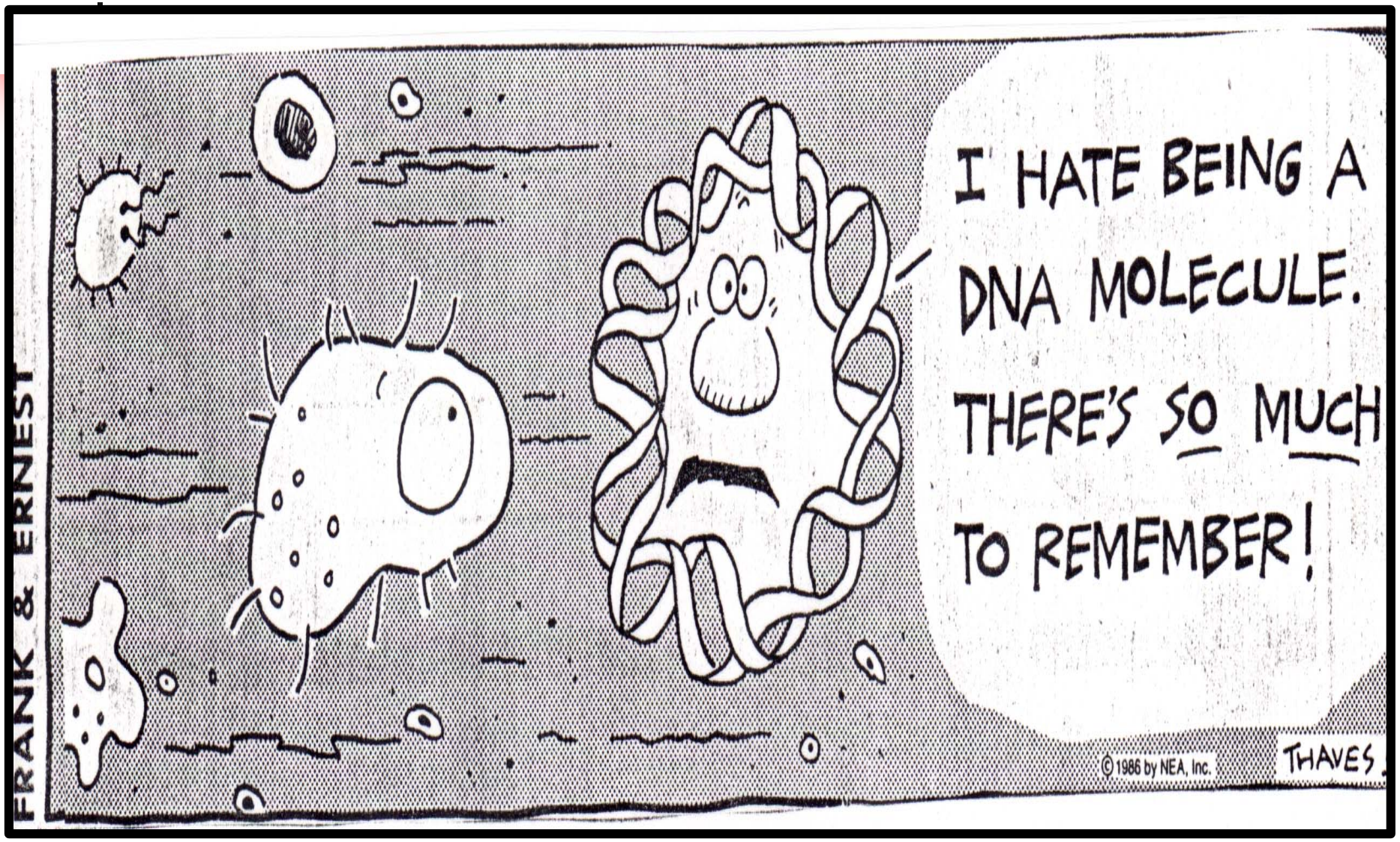
U.S. Department of Health and Human Services

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

coming into effect 2020?

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

EMA Regulates Marketed Products

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

of 31 March 2004

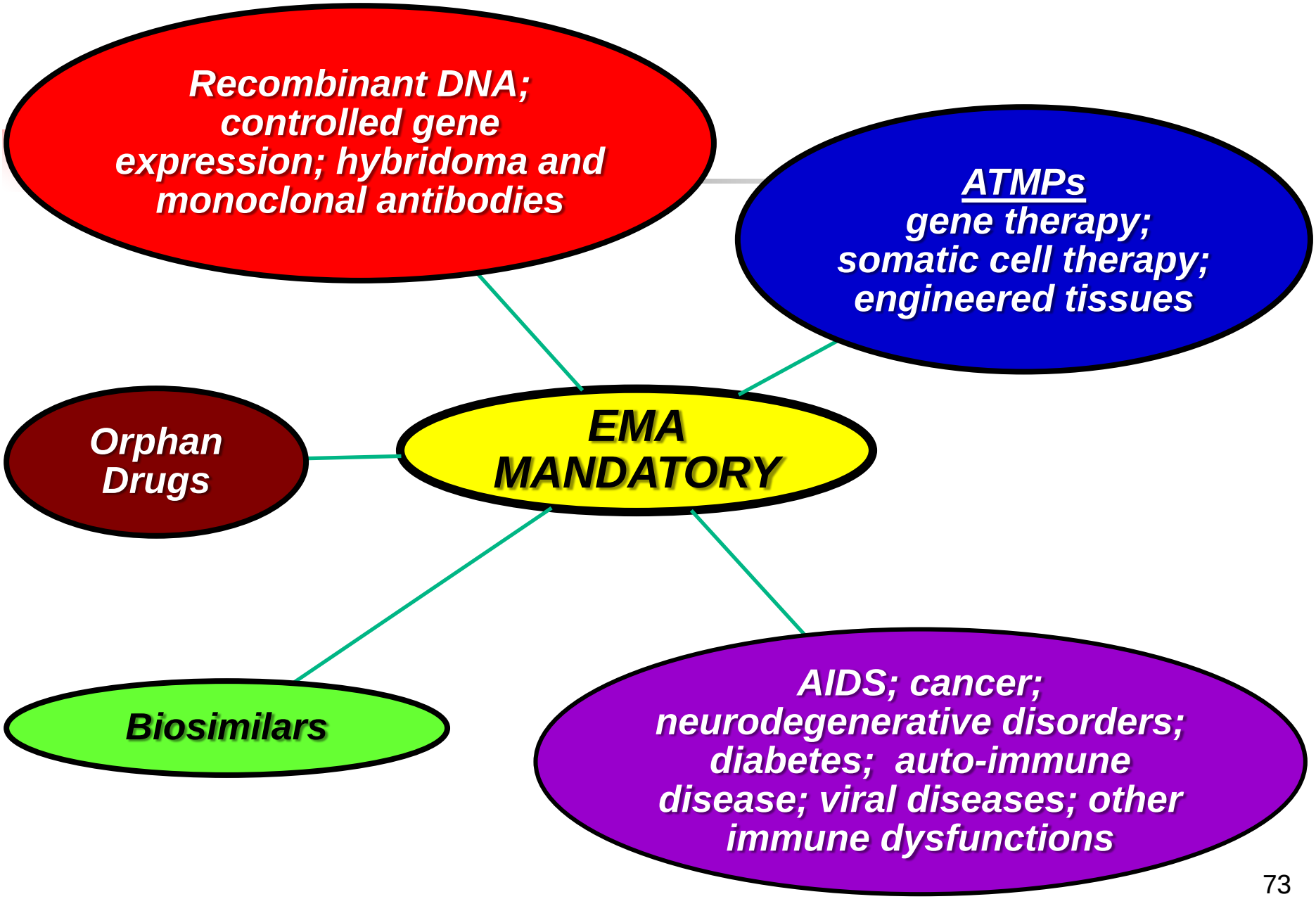
laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

EMA Centralized Procedure

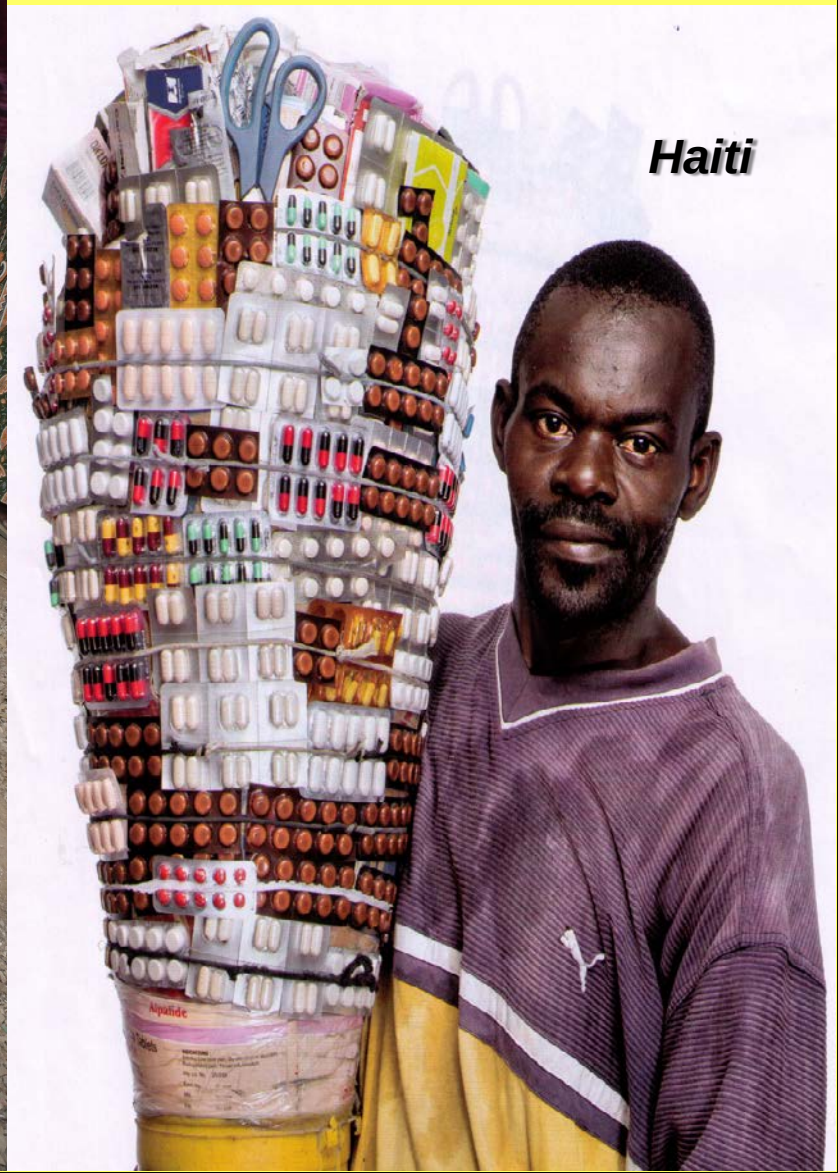
Market Authorization Application (MAA)

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
EMA MANDATORY
Biosimilars
AIDS; cancer; neurodegenerative disorders; diabetes; auto-immune disease; viral diseases; other immune dysfunctions

Other pharmaceutical regulation landscapes around the world!



Biopharmaceuticals are NOT like Chemical Drugs

Regulatory Authorities know this very well!

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.

EU GMP Annex 2 Biological Manufacturing 2018

ICH has 2 separate guidelines – one for chemical drugs, one for biopharmaceuticals

Specifications:	***ICH 6A***	***ICH 6B***
Stability:	***ICH Q1A***	***ICH Q5C***

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

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 CMC Regulatory Compliance Areas

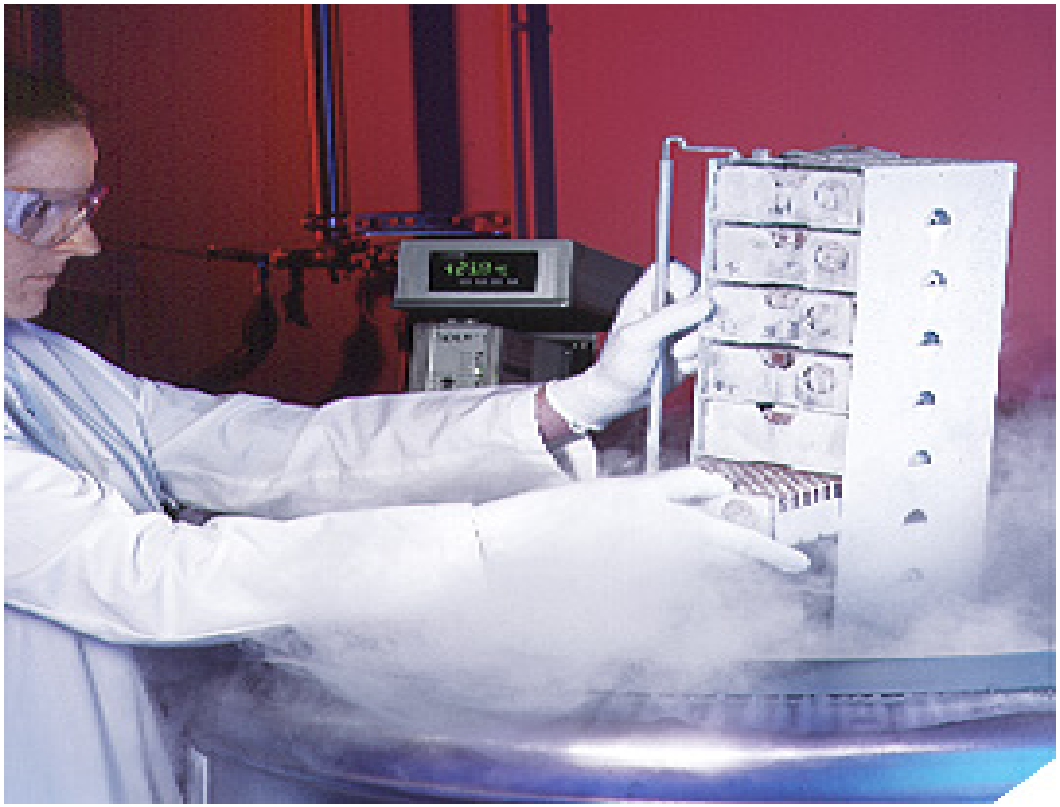
1 of 4: Synthesis of the product

Chemical Drug	*Biopharmaceutical*
Product synthesized from non-living chemical reagents *Produced under typically harsh conditions* *(e.g., organic solvents, high temp, high pressure)*	*Product synthesized by a living organism* *(or the product can be the genetically engineered living organism itself)* *Produced under mild, aqueous, tropical conditions*

Challenge of use of living organisms

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



Living systems 'hibernate' under liquid nitrogen temperature (-196°C)

but apoptosis

Challenge of use of living organisms

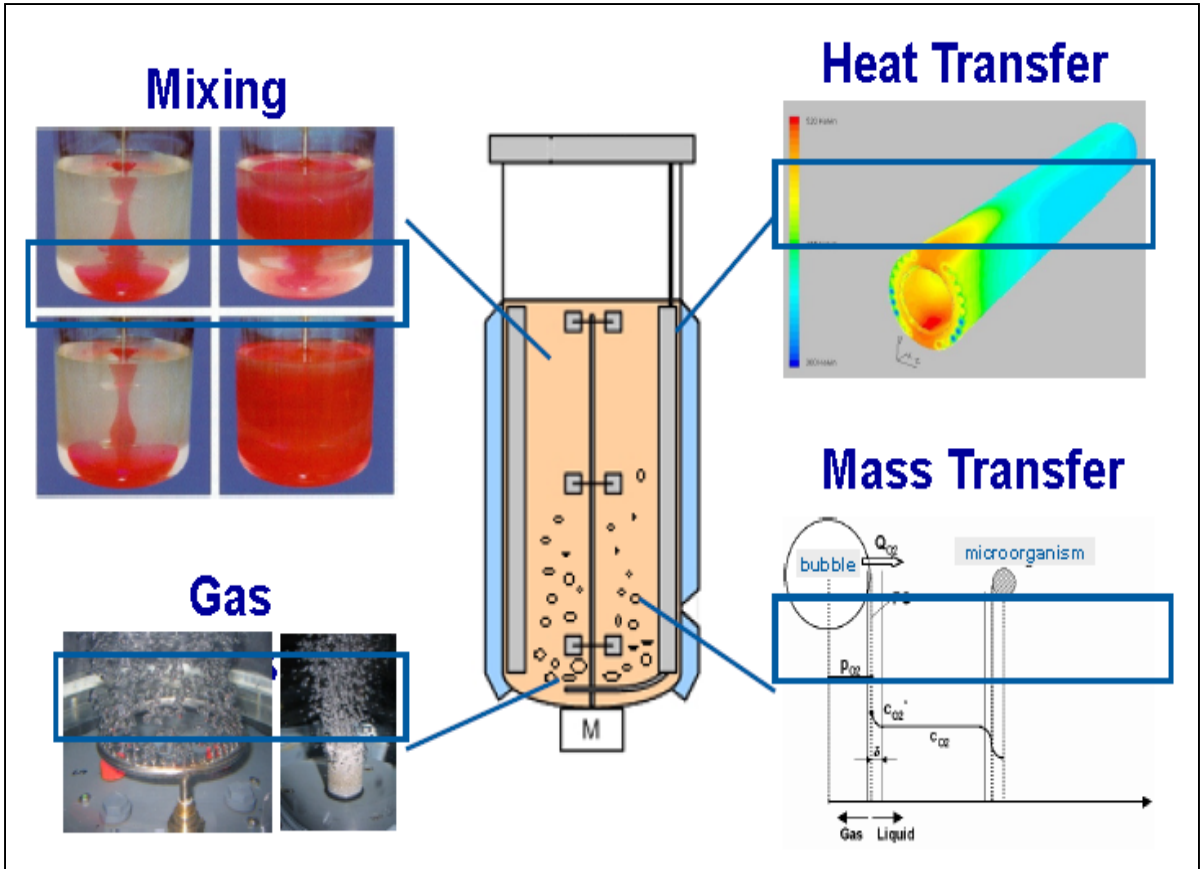
Must be kept 'Happy'!

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

hardy bacterial cells vs fragile mammalian cells

nutrients waste products

CO_2 O_2 levels



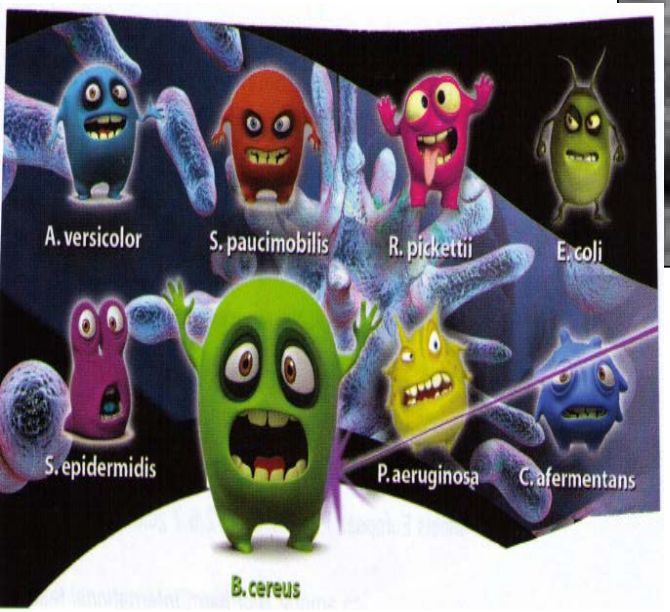
rapidly growing bacterial cells vs slow growing mammalian cells

Challenge of use of living organisms

Must be kept 'Healthy'!

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

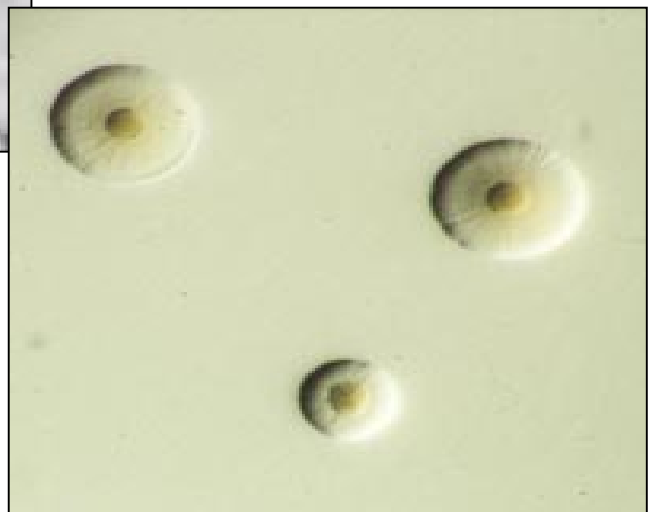
Bacteria/Fungi



Virus

Mouse Minute Virus (MMV)
Vesivirus

Mycoplasma



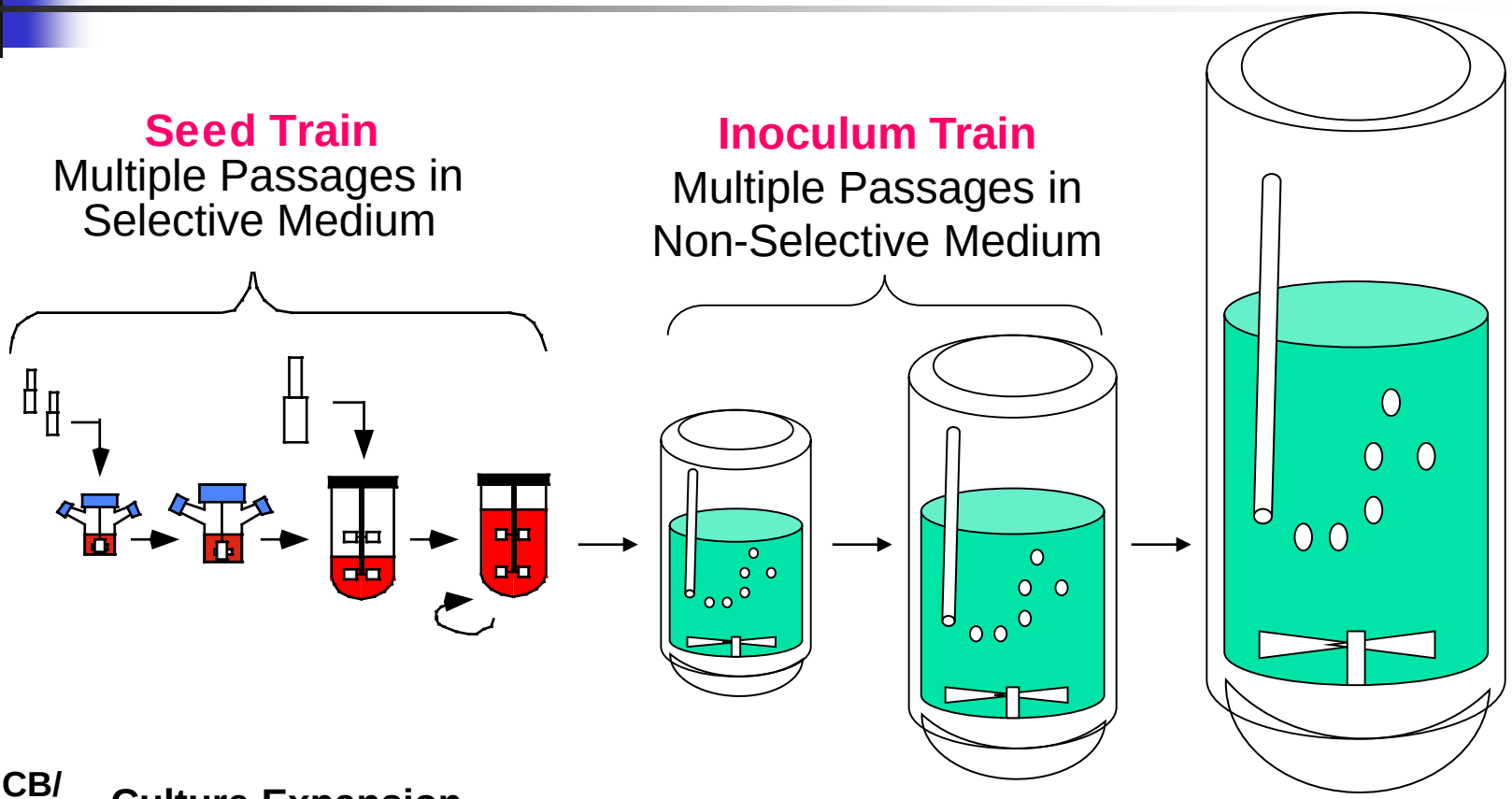
***Once* an adventitious agent contaminates a cell culture …**

Increasing proliferation →

Production

Seed Train
Multiple Passages in
Selective Medium

Inoculum Train
Multiple Passages in
Non-Selective Medium



MCB/ WCB **Culture Expansion**

Product Expression and Harvest

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

2 of 4: Impact of the manufacturing process on product

Chemical Drug	*Biopharmaceutical*
Product can be independent of the manufacturing process *(basis for generic chemical drug industry)*	*Product is not independent of the manufacturing process* *(Past: 'process is the product', Present: 'the process may or may not impact the product')*

Manufacturing process can impact the produced biopharmaceutical

Biosimilar manufacturers are keenly aware of possible differences!

Therapeutic protein products can be produced in microbial cells (prokaryotic or eukaryotic), cell lines (e.g., mammalian, avian, insect, plant), or tissues derived from animals or plants. It is expected that the expression construct for a proposed product will encode the same primary amino acid sequence as its reference product. However, minor modifications, such as N- or C-terminal truncations (e.g., the heterogeneity of C-terminal lysine of a monoclonal antibody) that are not expected to change the product performance, may be justified and should be explained by the sponsor. 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)

Manufacturing process can impact the produced biopharmaceutical

Gene therapy manufacturers are keenly aware of possible differences!

The genetic modification of the cells is a manufacturing step that is affected by a variety of inputs and therefore its control is critical. Genetic modification efficiency may depend on different factors such as target cell features (primary cells or cell lines, adherent or in suspension, dividing or quiescent), features of the cell culture (culture system such as flasks or bags, cell seeding density or concentration), type and amount of vector and/or modifying enzyme, transfection reagent, time of incubation and culture media components.

Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells

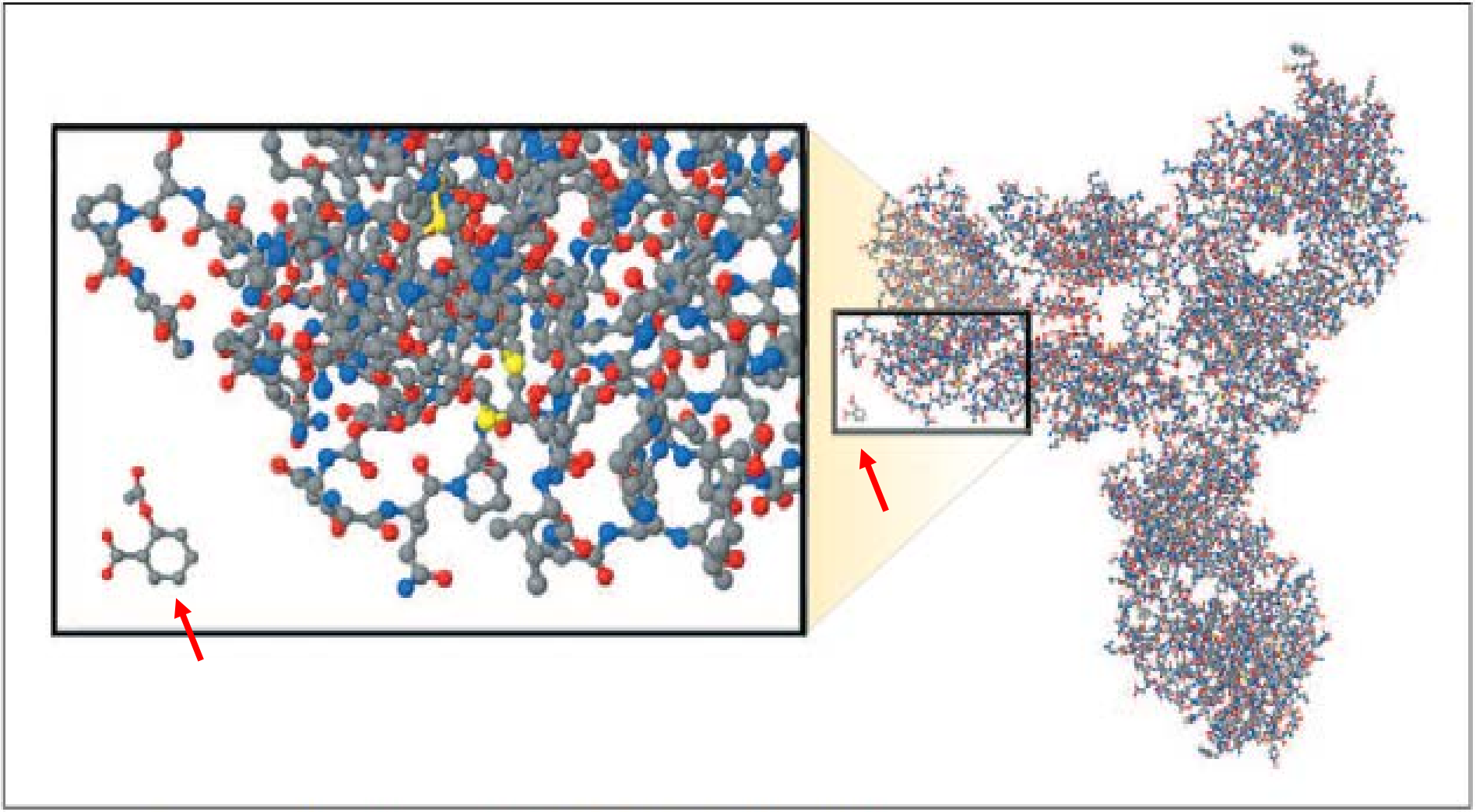
26 July 2018
EMA/CAT/GTWP/671639/2008 Rev. 1

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

3 of 4: Complexity of the product produced

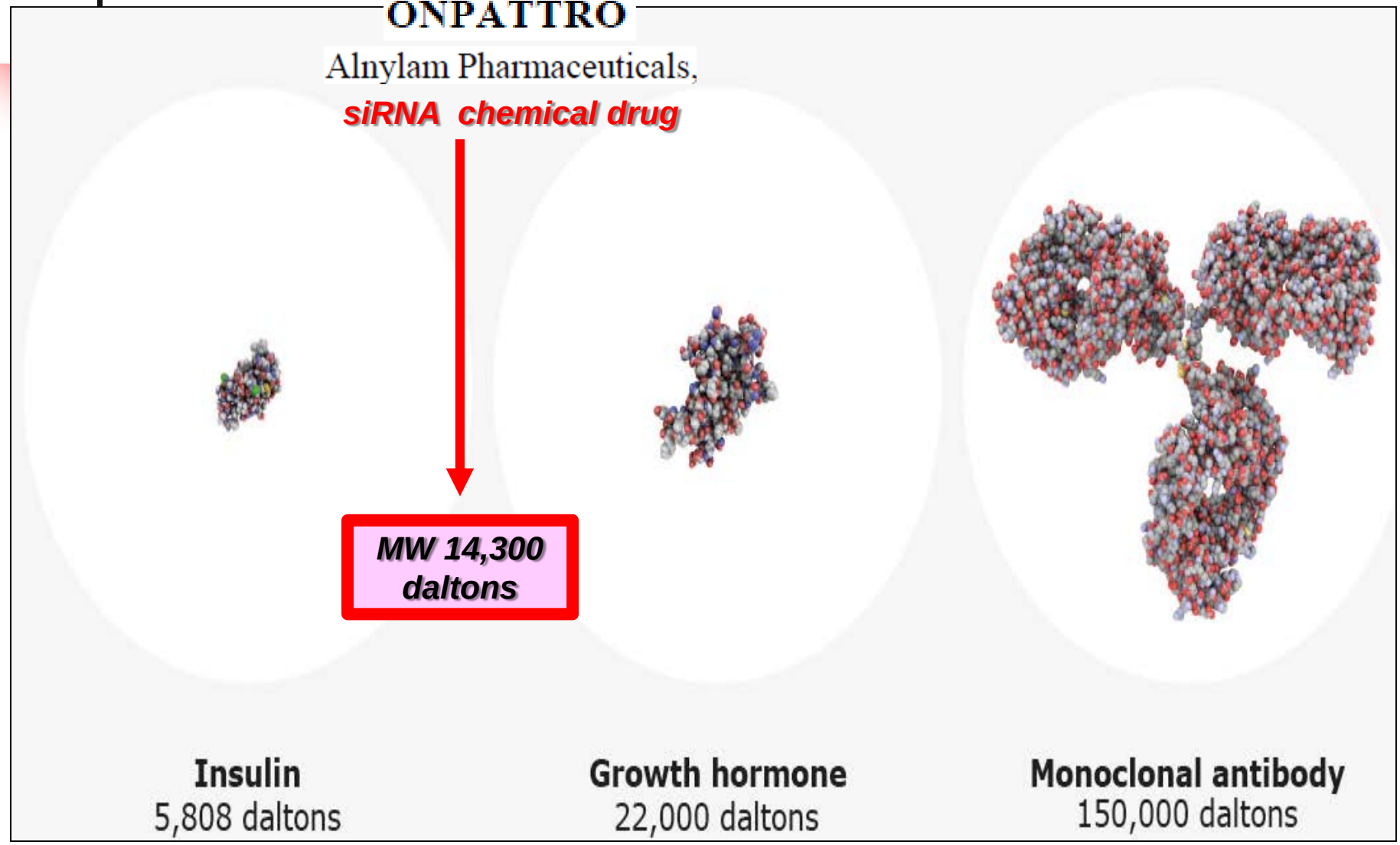
Chemical Drug	Biopharmaceutical
Chemical products can be simple or a bit complex may have a few molecular species present (typically stereoisomers, functional group changes)	Biopharmaceuticals are by their nature very complex will have numerous molecular species present (e.g., molecular variants, higher order structures, etc.)

Typical perception of size of a chemical drug vs a biopharmaceutical



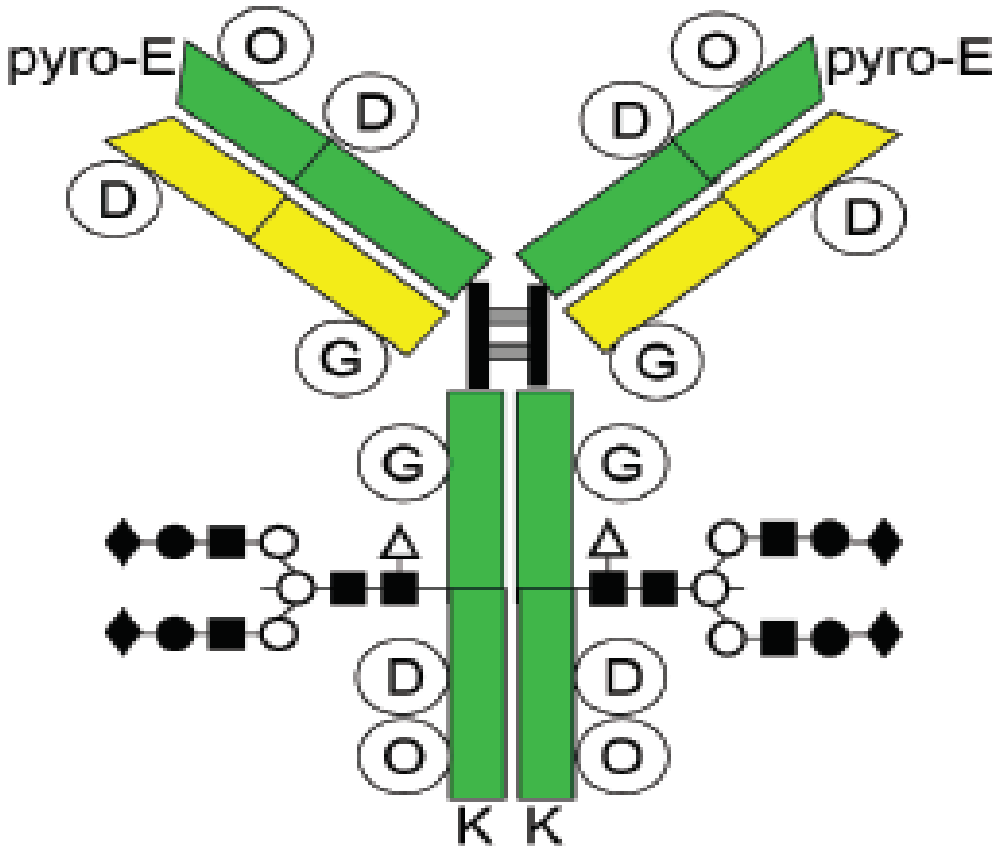
Comparison between a Biologic Monoclonal Antibody and an Aspirin Molecule.

***But* chemical drugs can also be somewhat large!**



si – small, interfering (for gene silencing)

But chemical drugs are neither as large nor as complex 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)

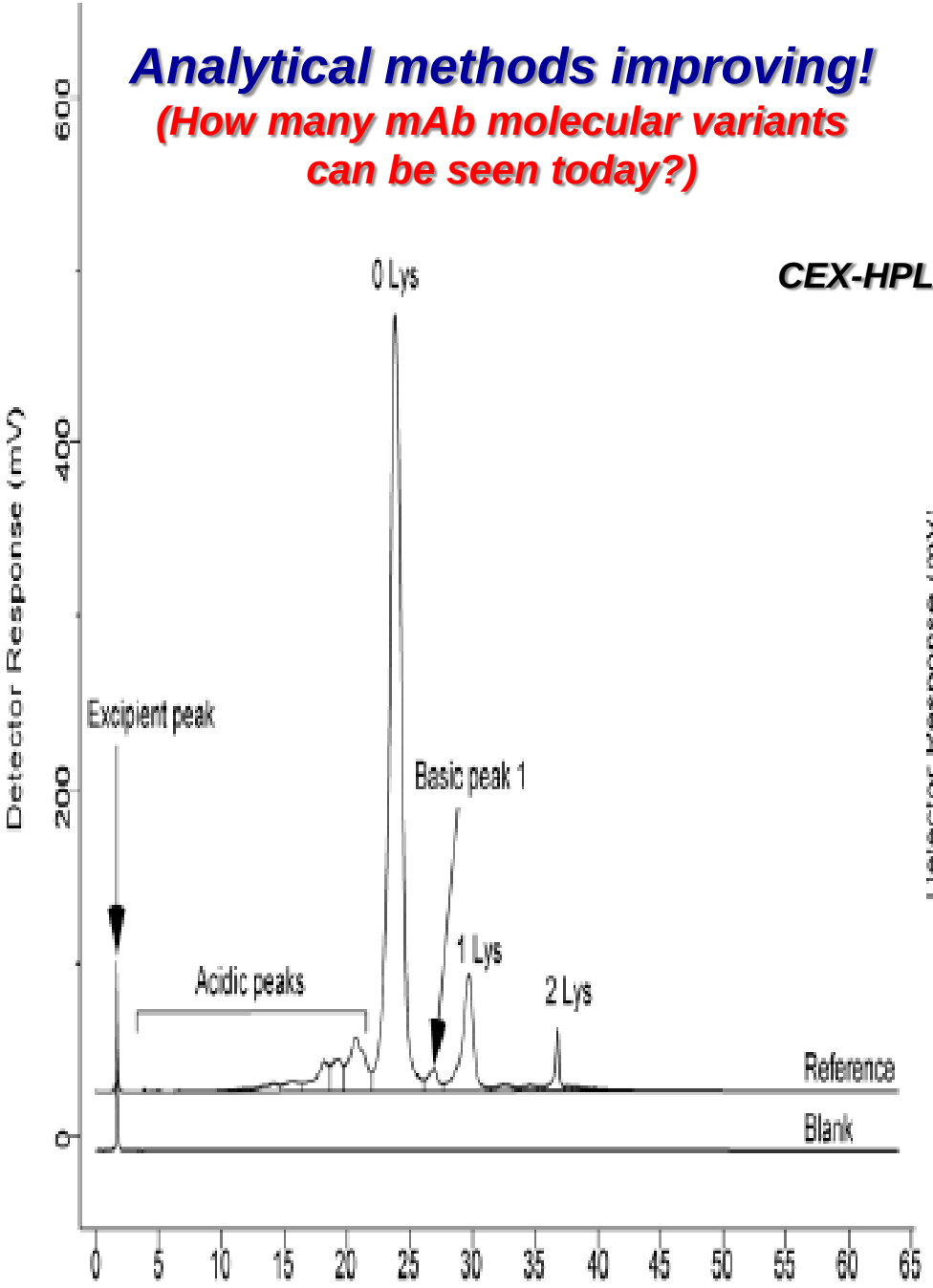
2 x 6 x 4 x 4 x 5 x 5 x 2 = 9600

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

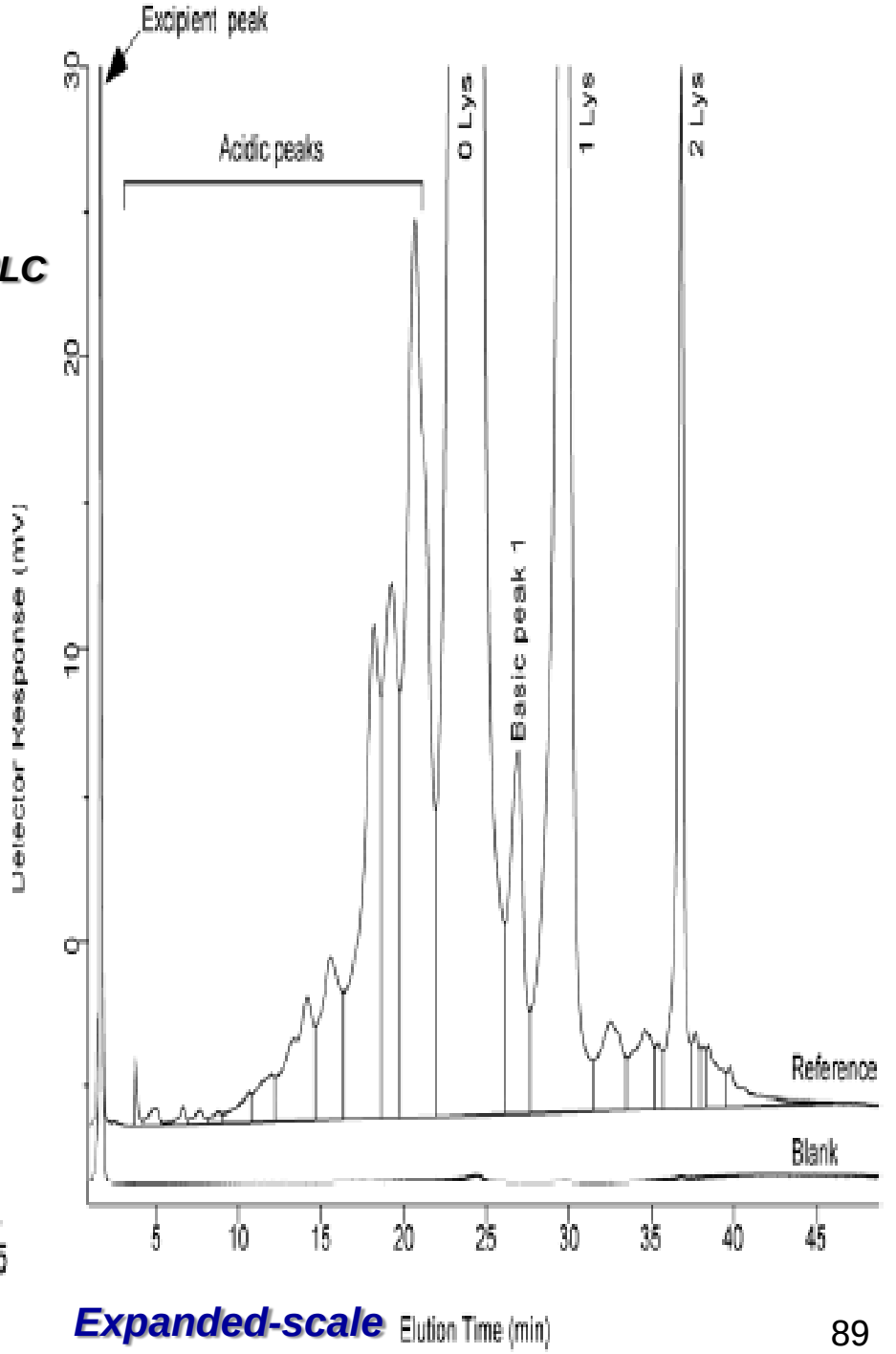
Analytical methods improving!

(How many mAb molecular variants can be seen today?)

CEX-HPLC



Full-scale

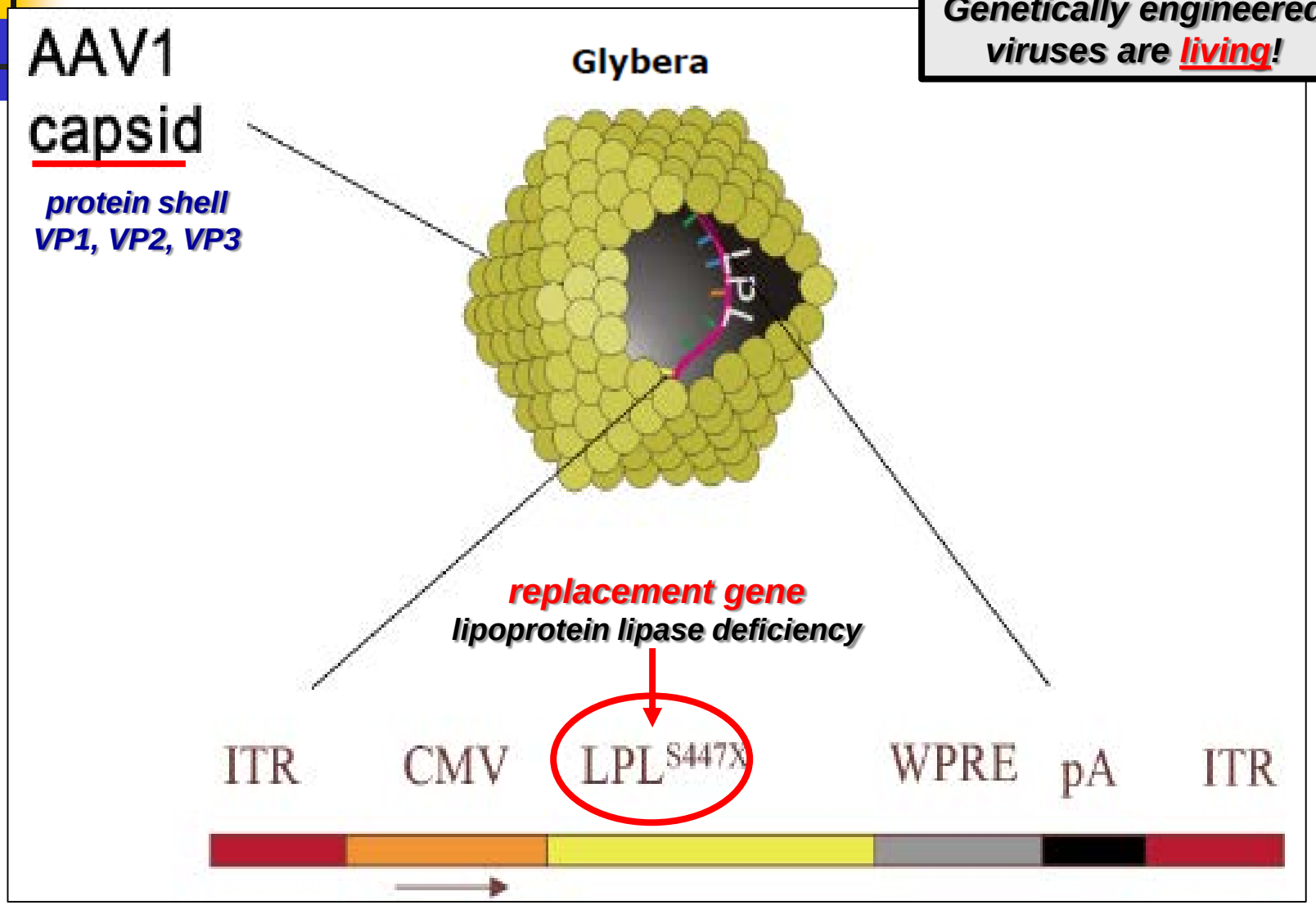


Expanded-scale

Further increasing in size and complexity

mAb (~10 nm) → genetically engineered living virus (~25 nm)

Genetically engineered viruses are living!

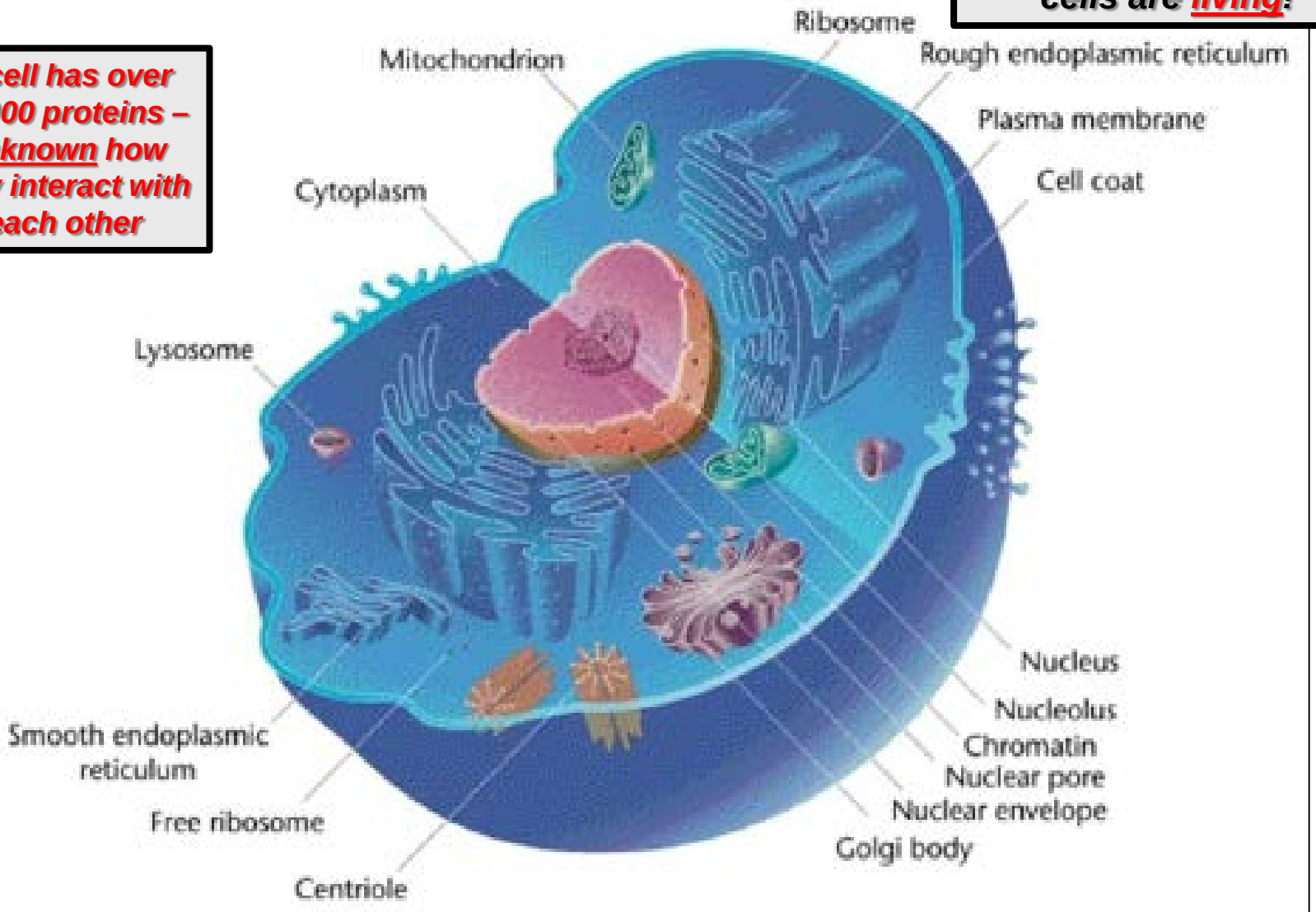


Hugh increase in size and complexity

mAb (~10 nm) → g.e. living virus (~25 nm) → g.e. living cell (~10 µm)

Genetically engineered cells are living!

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



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

4 of 4: No bio-generics

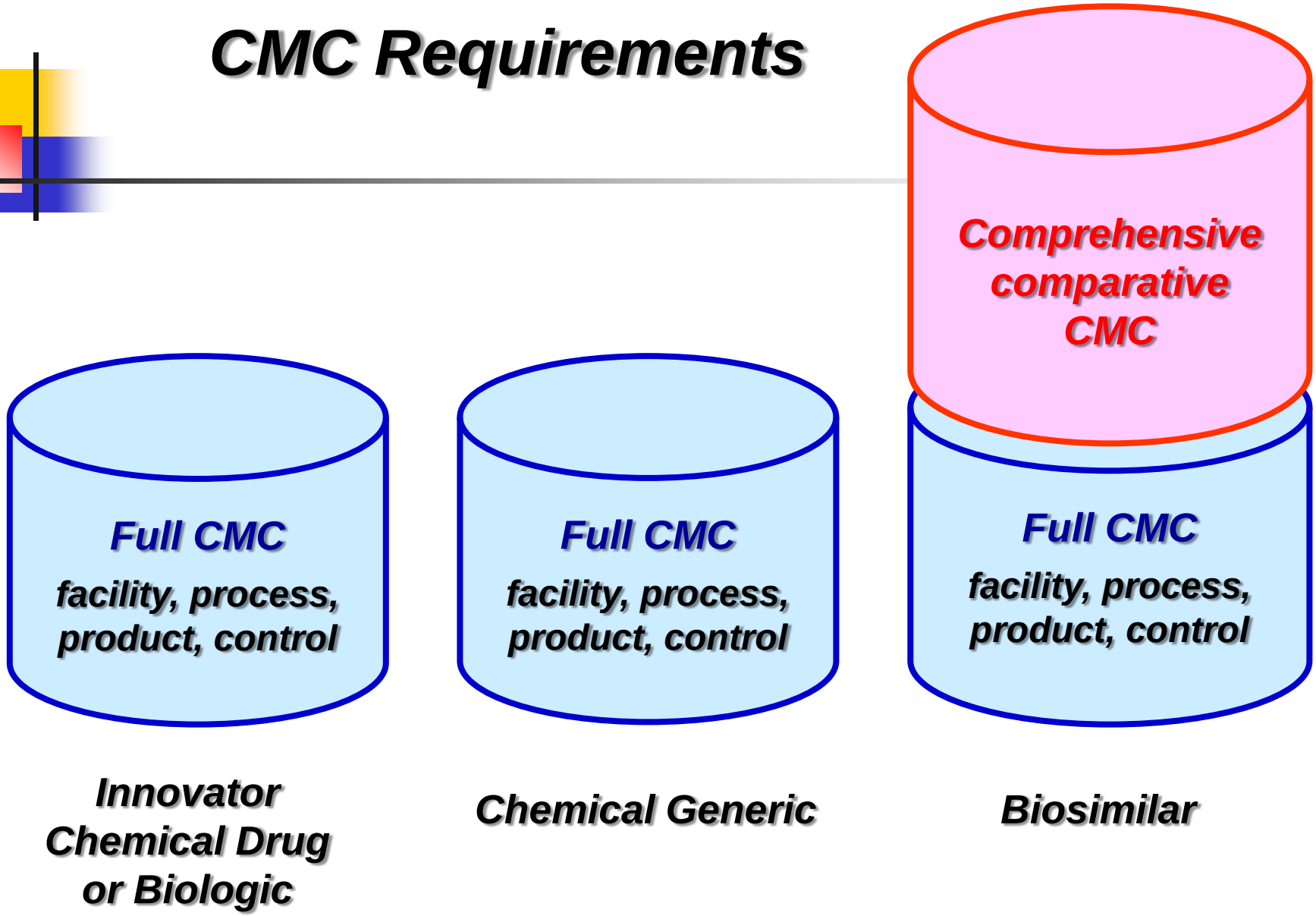
Chemical Drug	*Biopharmaceutical*
Generic	***Biosimilar***
Exact structure between generic and innovator chemical drug	***Extensive CMC comparability between biosimilar and innovator biopharmaceutical***
CMC standard is 'equivalent'	***CMC standard is 'highly similar'***

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)

CMC Requirements



For Biosimilars, if Step 1 comparability is not achieved, do not go to Step 2 or 3!

Step 3

Step 2

Step 1

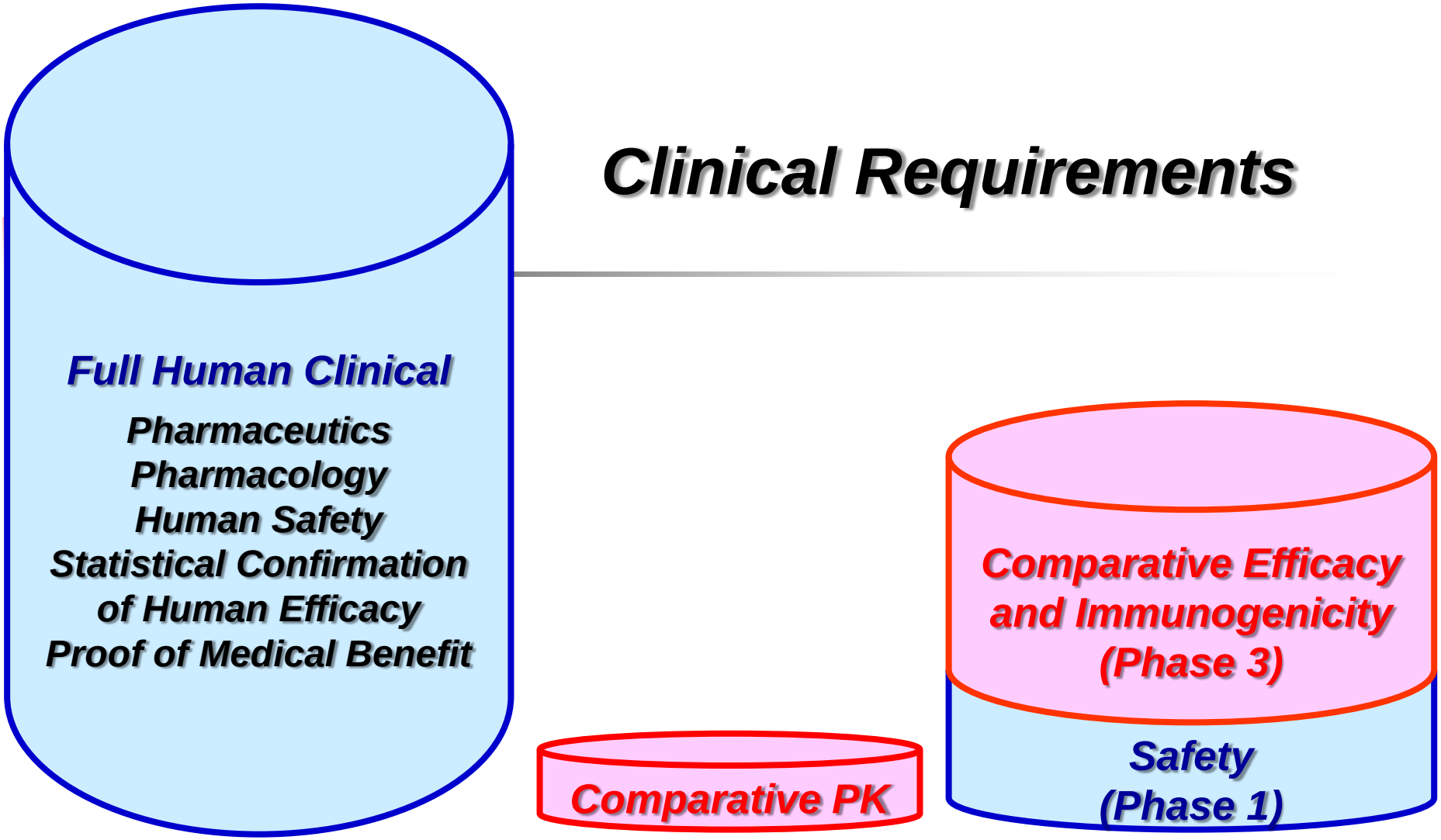
Nonclinical Requirements

Innovator
Chemical Drug
or Biologic

Chemical Generic

Biosimilar

Clinical Requirements

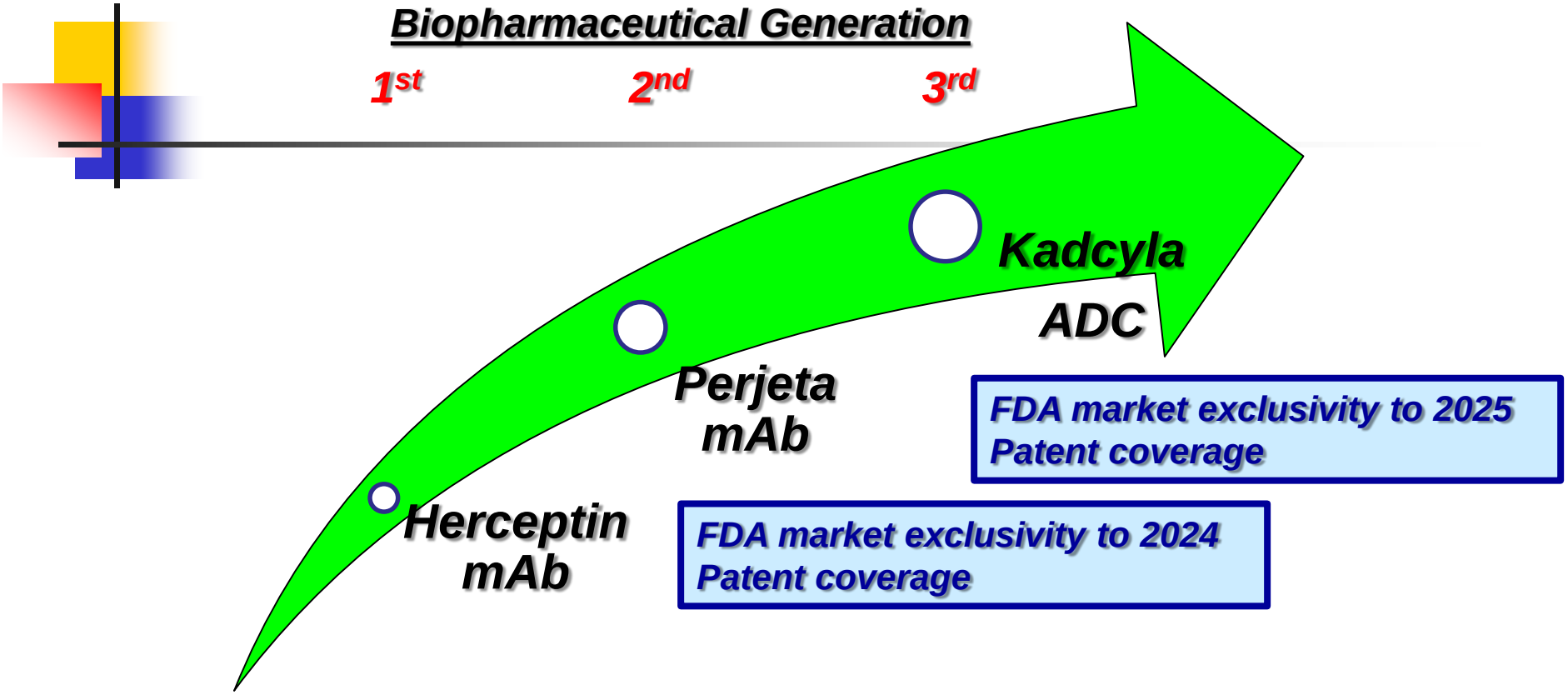


Innovator
Chemical Drug
or Biologic

Chemical Generic

Biosimilar

Roche: 'Biobetter' to advance breast cancer treatment



Approved Biosimilars

Biocon/Mylan	Ogivri
Celltrion/TEVA	Herzuma
Samsung	Ontruzant
Amgen	Kanjinti
Pfizer	Trazimera

International Nonproprietary Name (INN)

Innovator chemical drug → Chemical generic

FDA and EMA

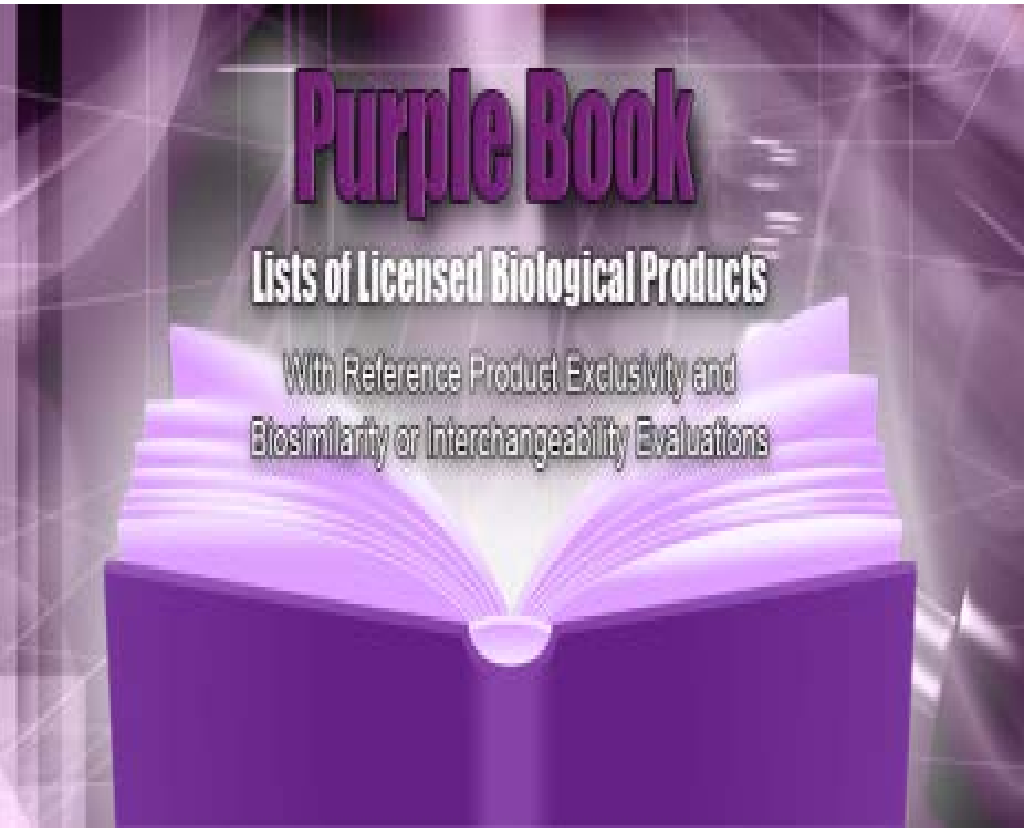
same INN

International Nonproprietary Name (INN)

Bioqualifiers used by FDA, not EMA

Innovator biologic → Biosimilar

different INN bioqualifier



AbbVie Humira
adalimumab

BI Cyltezo
adalimumab-adbm

Amgen Amjevita
adalimumab-atto

Sandoz Hyrimoz
adalimumab-adaz

Interchangeability

(two medical treatments that are therapeutically equivalent can be safely exchanged in clinical practice)

FDA and EMA

Innovator chemical drug → Chemical generic

interchangeable and automatic substitution at the pharmacy level without consulting a physician or the customer

Innovator biologic → Biosimilar

ENVIRONMENTAL SCAN

International Policies on the Appropriate Use of Biosimilar Drugs

CADTH October 2018

Policies Related to Interchangeability, Switching, and Substitution	Countries Where These Policies Exist
"Interchangeability" designation for a biosimilar approved by the regulatory agency	• US[a]
Market exclusivity (for a limited period of time) for the first interchangeable designated biosimilar	• US[a]
Automatic substitution allowed for biosimilars Note: Some condition may apply (e.g., automatic substitution may be prohibited by the physician) and policy may only apply to specific biosimilars only	• US ("interchangeable" designated biosimilars only)[a] • Germany ("bioidentical" biosimilars only) • France (for "treatment-naive" patients only) • Australia ("a-flag" designated biosimilars only)
Authorities recommend prescribing biosimilars for treatment-naive patients	• Germany • Norway • France • Netherlands • Australia
(Physician-led) switching is encouraged for patient already treated with a reference biologic	• Germany • France • Norway • Finland • Australia

[a]As of September 2018, none of the biosimilars approved by the FDA have received an interchangeable designation.[19-21]

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_____***

Philosophical Question

What about in vivo fetus genetic editing?

China (2018): Twin girls born with a normal gene (CCR5) knocked out by CRISPR to reduce the risk to a disease (HIV) that neither girl had!