CMC Regulatory Compliance Strategy for Recombinant Proteins and Monoclonal Antibodies

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PDA Parenteral Drug Association

CONNECTING PEOPLE SCIENCE AND REGULATION®

CMC Regulatory Compliance Strategy for Recombinant Proteins and Monoclonal Antibodies

Course Goal

Evaluate a risk-managed, cost-effective, regulatory-compliant CMC strategy across the lifecycle of the biopharmaceutical manufacturing process & product

Focus not on a list of what to do or not to do, but instead focus on a risk-based assessment of what is most important to do ('protect the patient'), and when to do it ('forward-thinking', 'doing it right the first time')

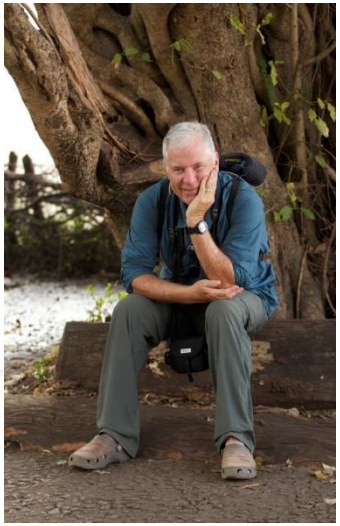
CMC Regulatory Compliance Strategy for Recombinant Proteins and Monoclonal Antibodies

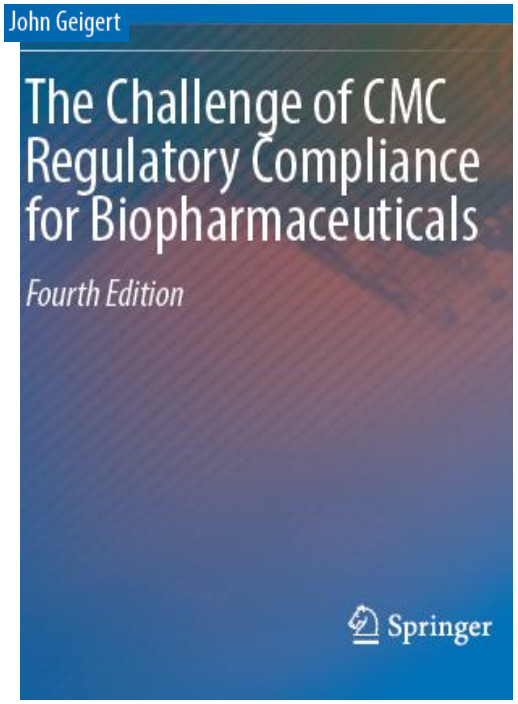
Course Summary

1. **CMC Regulatory Compliance Strategy is Challenging for Biopharmaceuticals**
   - Discussion of the increasing diversity of the protein-based biopharmaceuticals
   - Why these biopharmaceuticals are not regulated like chemical drugs
2. **Risk-Based Approach to Managing the CMC Regulatory Compliance Strategy**
   - Key elements of an effective risk-managed '<u>minimum</u> CMC regulatory compliance <u>continuum</u>' for biopharmaceuticals during clinical development
3. **<u>Applying</u> the Risk-Managed CMC Regulatory Compliance Strategy**
   - Applied CMC strategy applied across the manufacturing process from raw materials → starting materials → production → purification → drug substance (bulk) → formulation → drug product → administered drug product
4. **Challenges of Demonstrating Protein-Based Biopharmaceutical Comparability After Manufacturing Process Changes**
   - Three (3) key design concerns that must be addressed for all proposed changes

(Continuous presentation over the 3 days of instruction) *(Please ask your questions)*

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





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Springer.com
Amazon.com

- ***45 years experience in Chemistry, Manufacturing & Control (CMC) strategies for the clinical development and commercialization of recombinant proteins, monoclonal antibodies; and now gene therapies and cellular therapies***
- ***Senior CMC Expert and Vice President Quality in the industry (Cetus, Immunex, IDEC Pharm)***
- ***Past Chair PDA Biopharmaceutical Advisory Board***
- ***20 years as an independent CMC regulatory compliance consultant to the biopharmaceutical industry***

Who are you? Who do you work for? Interest/experience in CMC?

Manufacturing	***Process Development***	***Project Management***
Quality Control	***Analytical Development***	***Senior Management***
Quality Assurance	***Regulatory Affairs***	***…***

CMC Regulatory Compliance Strategy for Recombinant Proteins and Monoclonal Antibodies

Course Outline

1. **CMC Regulatory Compliance Strategy is Challenging for Biopharmaceuticals**
   - *Discussion of the increasing diversity of the protein-based biopharmaceuticals*
   - *Introduction to the regulatory authority systems (FDA, EMA) (IND → BLA; IMPD → MAA)*
   - *Why biopharmaceuticals are not regulated like chemical drugs*
   - *CMC regulatory compliance differences between protein-based biopharmaceuticals and chemical drugs*

DEFINE TERMS

'CMC Regulatory Compliance …'

***C**hemistry → the product*

- *Characterization*
- *Release criteria*
- *Stability profile*
- *In-use testing*

***M**anufacturing → the process*

- *Facility/Utilities*
- *Raw/Starting materials*
- *Process design*
- *cGMP operations*

***C**ontrol → the Quality System*

- *Production batch records*
- *Testing records*
- *Quality Unit oversight*
- *Auditing*

***REGULATORY COMPLIANCE** → that which is required or expected by a regulatory authority*

(e.g., SAFETY, identity, purity, quality, strength/potency)

'… Strategy for Biopharmaceuticals'

STRATEGY *→ the plan of action designed to lead to an overall* ***defined goal****.*

(e.g., initiating FIH clinical studies, obtaining market approval, etc.)

Risk-Based Approach *→ not to eliminate all risks, but to reduce the risk (i.e., residual uncertainty) to an acceptable level*

Biological Product, BIOPHARMACEUTICAL, … *→*

U.S. FOOD & DRUG ADMINISTRATION

Biological Product Definitions

What is a biological product?

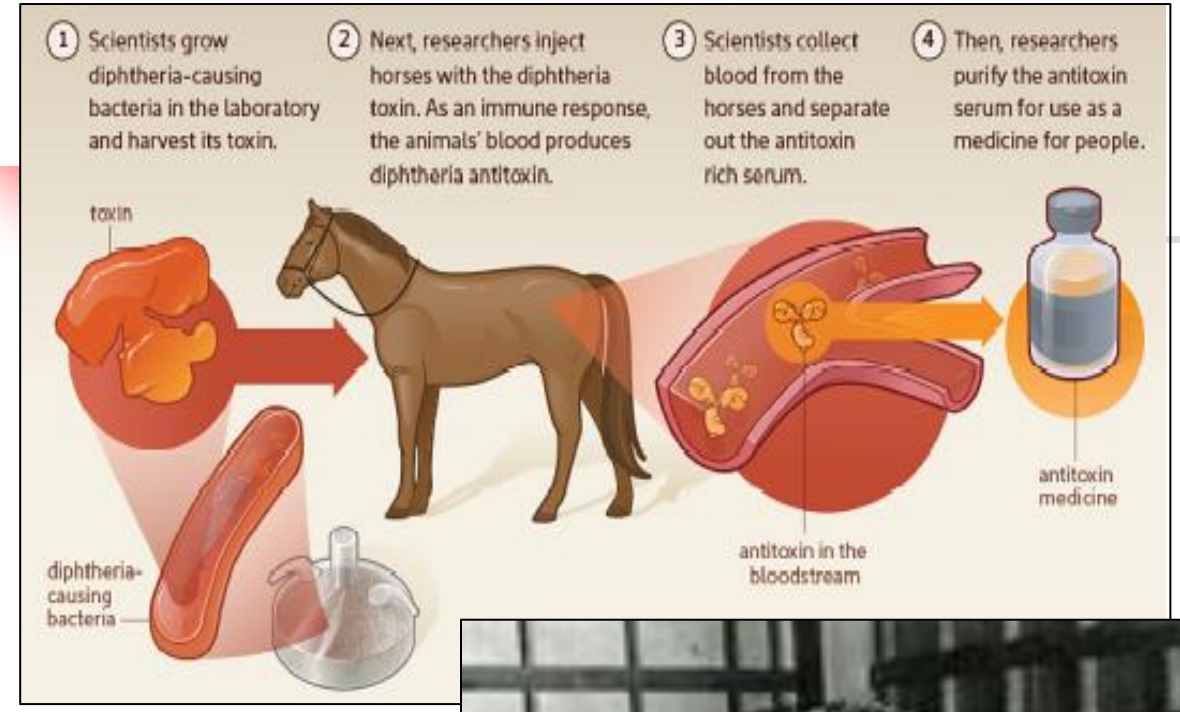
Biological products are regulated by the Food and Drug Administration (FDA) and are used to diagnose, prevent, treat, and cure diseases and medical conditions. Biological products are a diverse category of products and are generally large, complex molecules. These products may be produced through biotechnology in a living system, such as a microorganism, plant cell, or animal cell, and are often more difficult to characterize than small molecule drugs. There are many types of biological products approved for use in the United States, including therapeutic proteins (such as filgrastim), monoclonal antibodies (such as adalimumab), and vaccines (such as those for influenza and tetanus).

The nature of biological products, including the inherent variations that can result from the manufacturing process, can present challenges in characterizing and manufacturing these products that often do not exist in the development of small molecule drugs. Slight differences between manufactured lots of the same biological product (i.e., acceptable within-product variations) are normal

FDA's explanation of what is a 'biologic' is rather long and rambling, but includes the basic 3 components

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

Immune serums and natural biological proteins have been around for decades



Polyclonal antibodies in immune serums – since 1890s

Eli Lilly (1940s)

2 tons of pig pancreases → ~200 g pig insulin

Seismic shift in the manufacture of Biological Medicines occurred in the 1980's due to molecular biology discoveries

"BIOPHARMACEUTICALS"

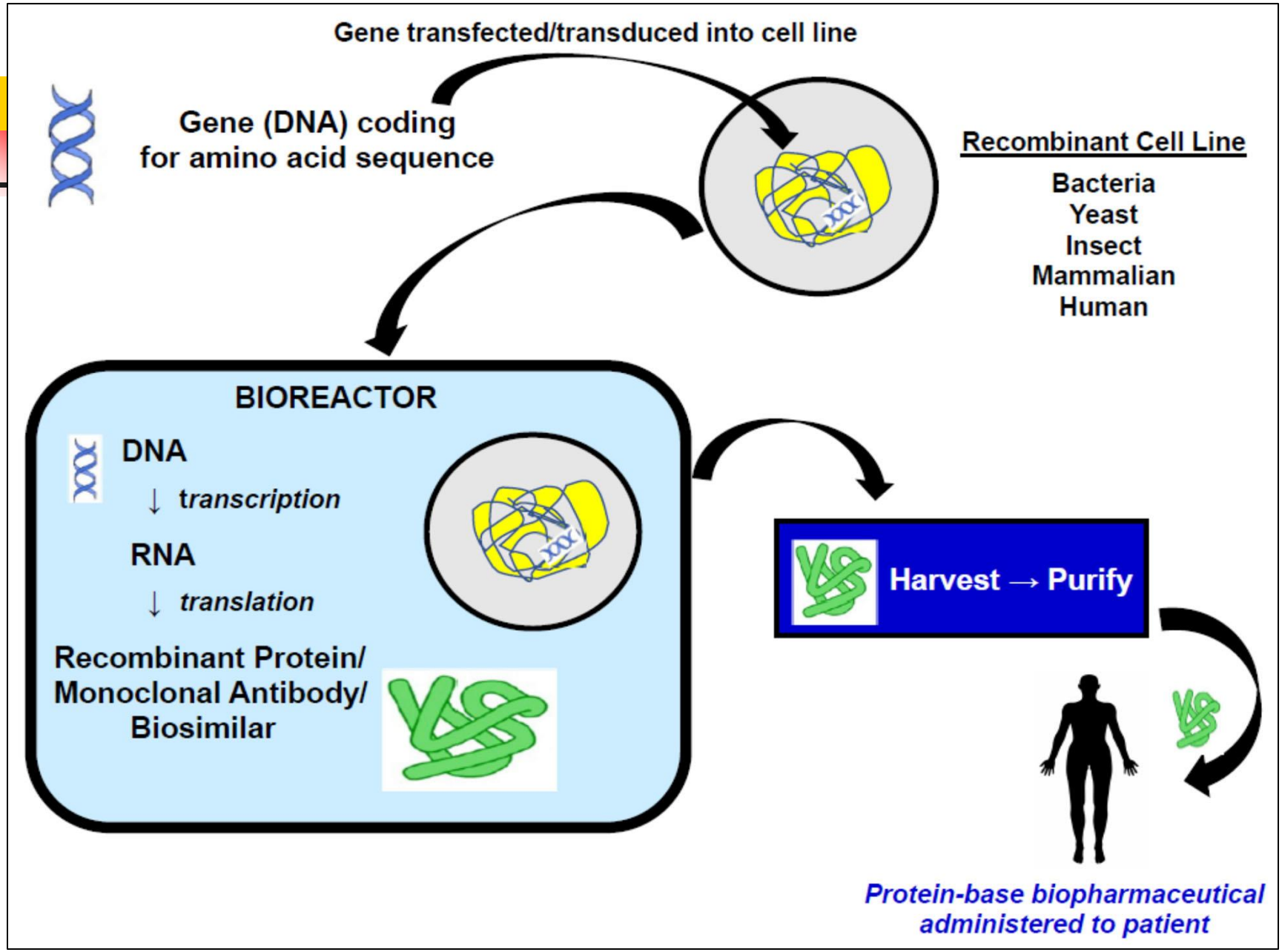
[a biological produced by biotechnology – the manipulation (as through genetic engineering) of living organisms]

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

FDA/EMA preferred terms → ***"recombinant DNA-derived"***
"genetically modified"

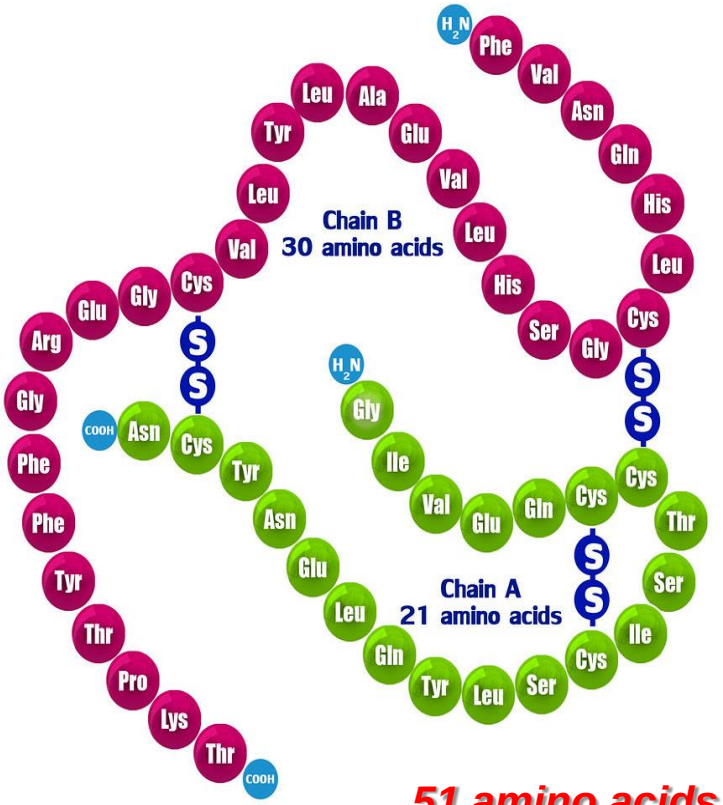
Biopharmaceutical medicine types have come in 4 ‘waves’!

WAVES 1, 2, 3 – Protein-based Biopharmaceuticals



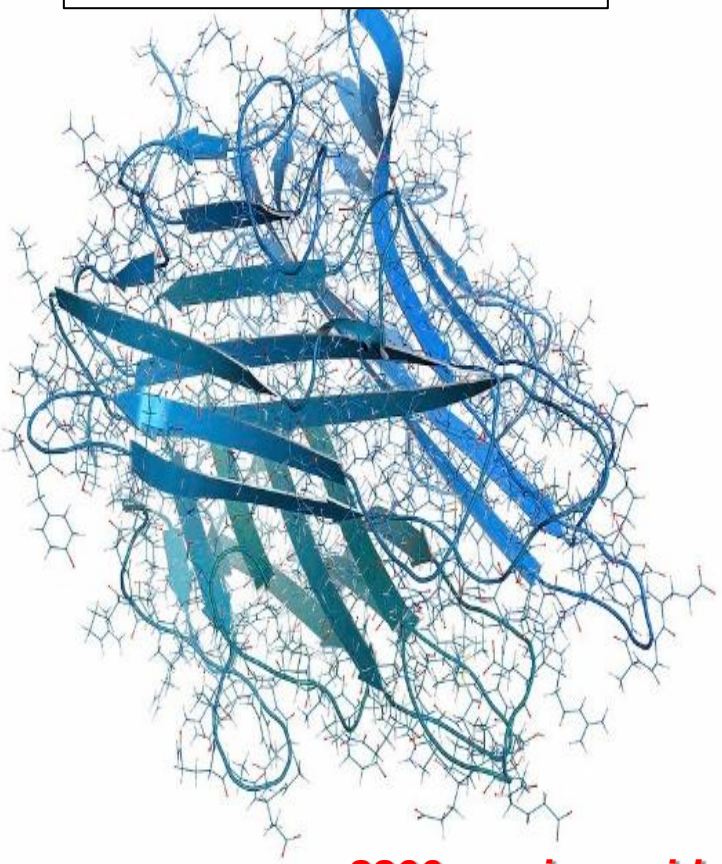
WAVE 1 Recombinant Proteins

Human Insulin



51 amino acids

Human Factor 8



2300+ amino acids

1982 1st recombinant protein

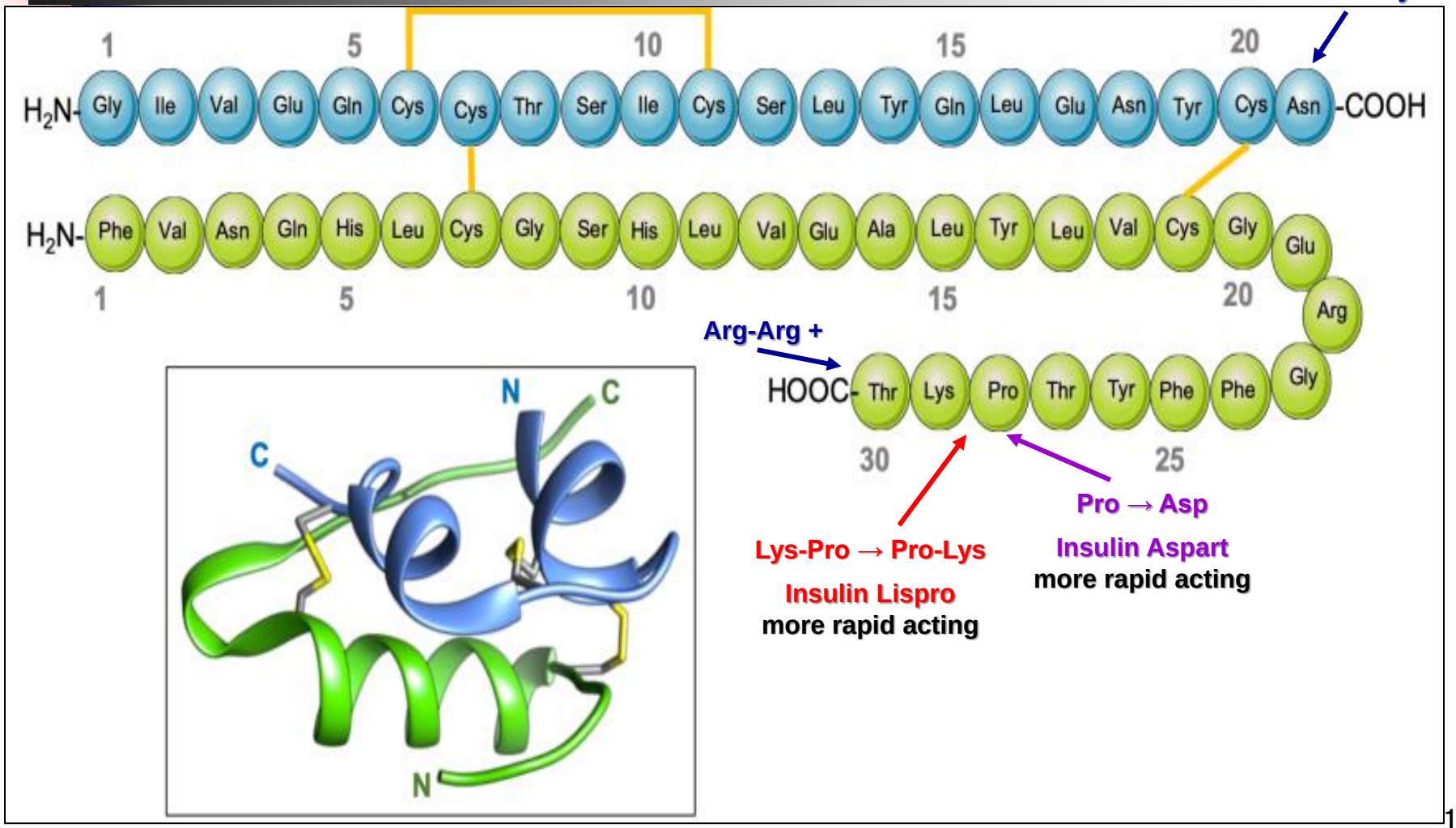
TODAY: > 100 recombinant proteins market-approved (FDA/EMA)

WAVE 1 ripples: molecular biologists enjoy DNA sequence changing!

Re-engineered Recombinant Proteins

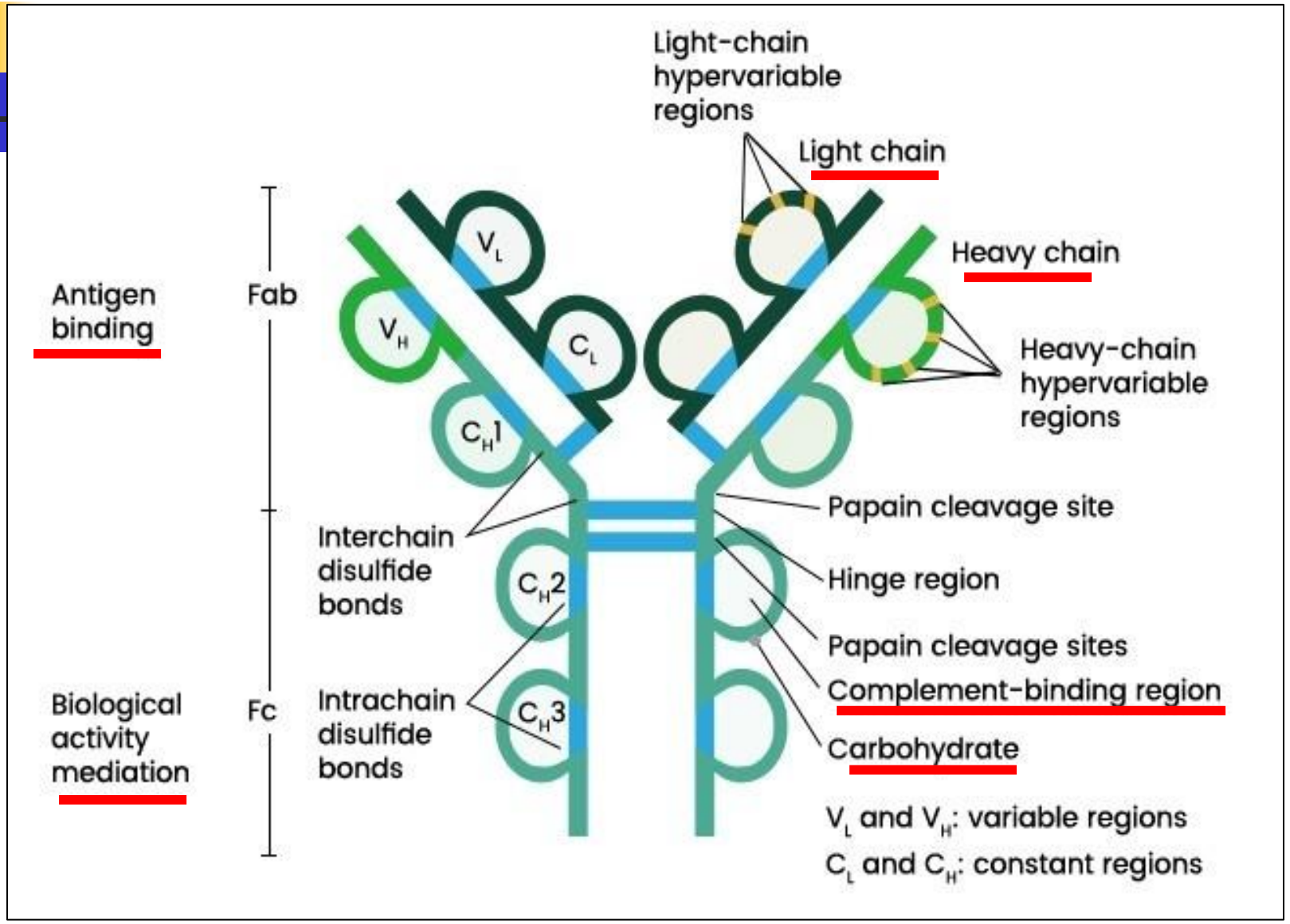
site-specific codon changes → specific amino acid changes in sequence

Recombinant Human Insulin

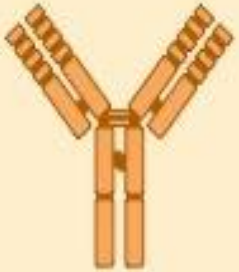
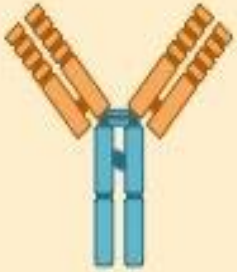
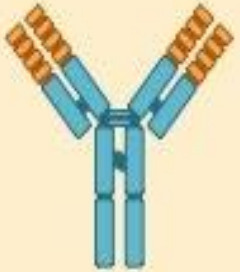
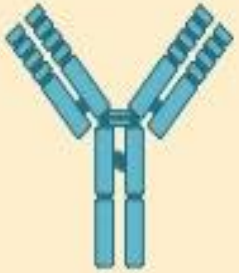


WAVE 2 Monoclonal Antibodies

recombinant immunoglobulin protein – single specific antigen binding



amino acid sequences

Type:	Murine (0% human)	Chimeric (65% human)	Humanised (>90% human)	Human (100% human)
				
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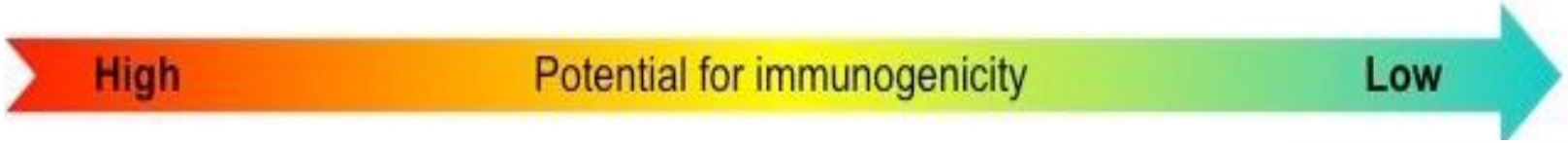


1986 1st mAb

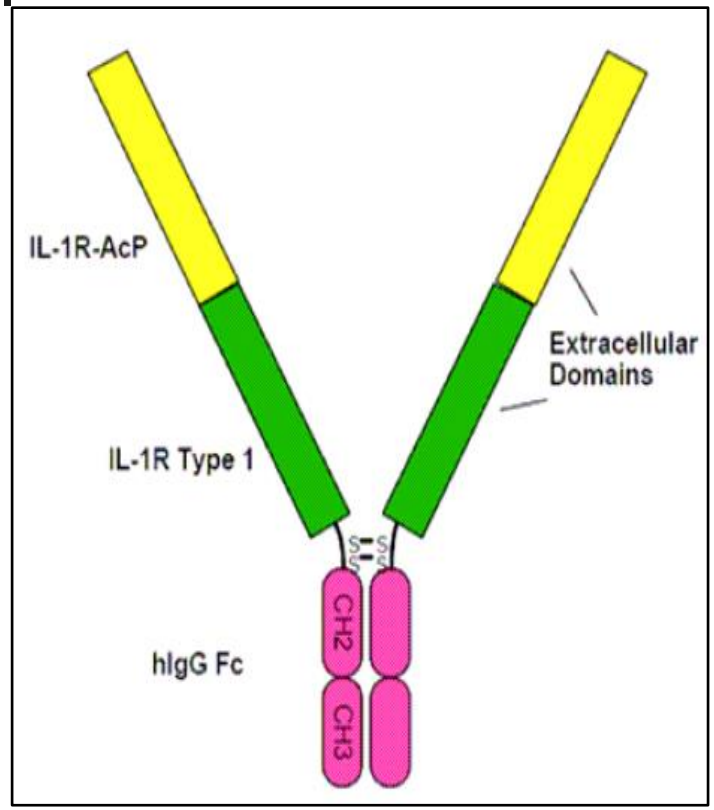
1997 1st commercially successful mAb

2022 Best selling drug in the world >$20B

TODAY: > 120 monoclonal antibodies market-approved (FDA/EMA)

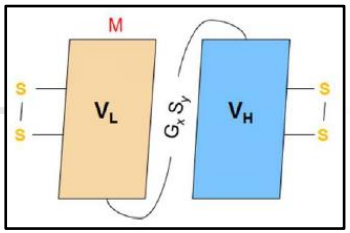
WAVE 2 ripples: molecular biologists enjoy DNA sequence chopping!

Fc Fragment



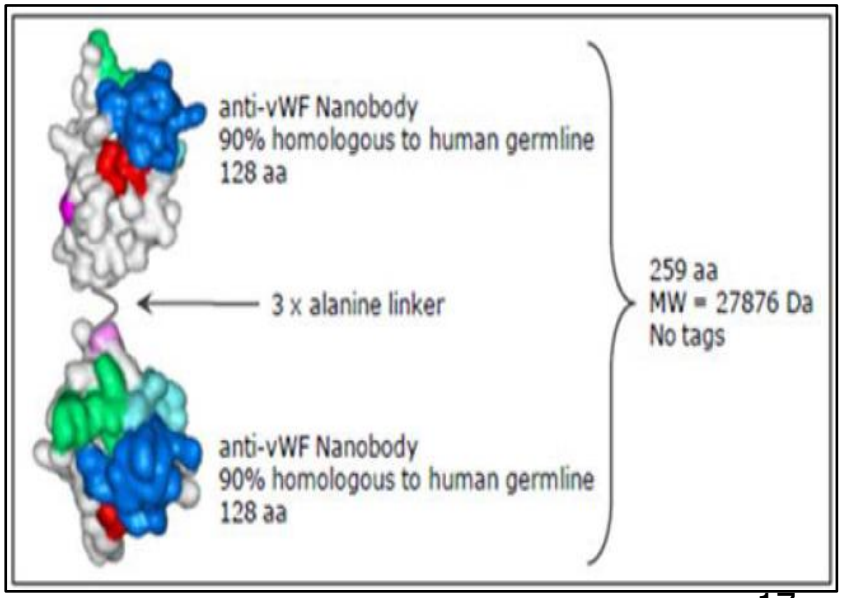
Fc-fusion protein
Arcalyst (rilonacept)

Fab Fragment



single chain Fragment variable (scFv)
Beovu (brolucizumab)

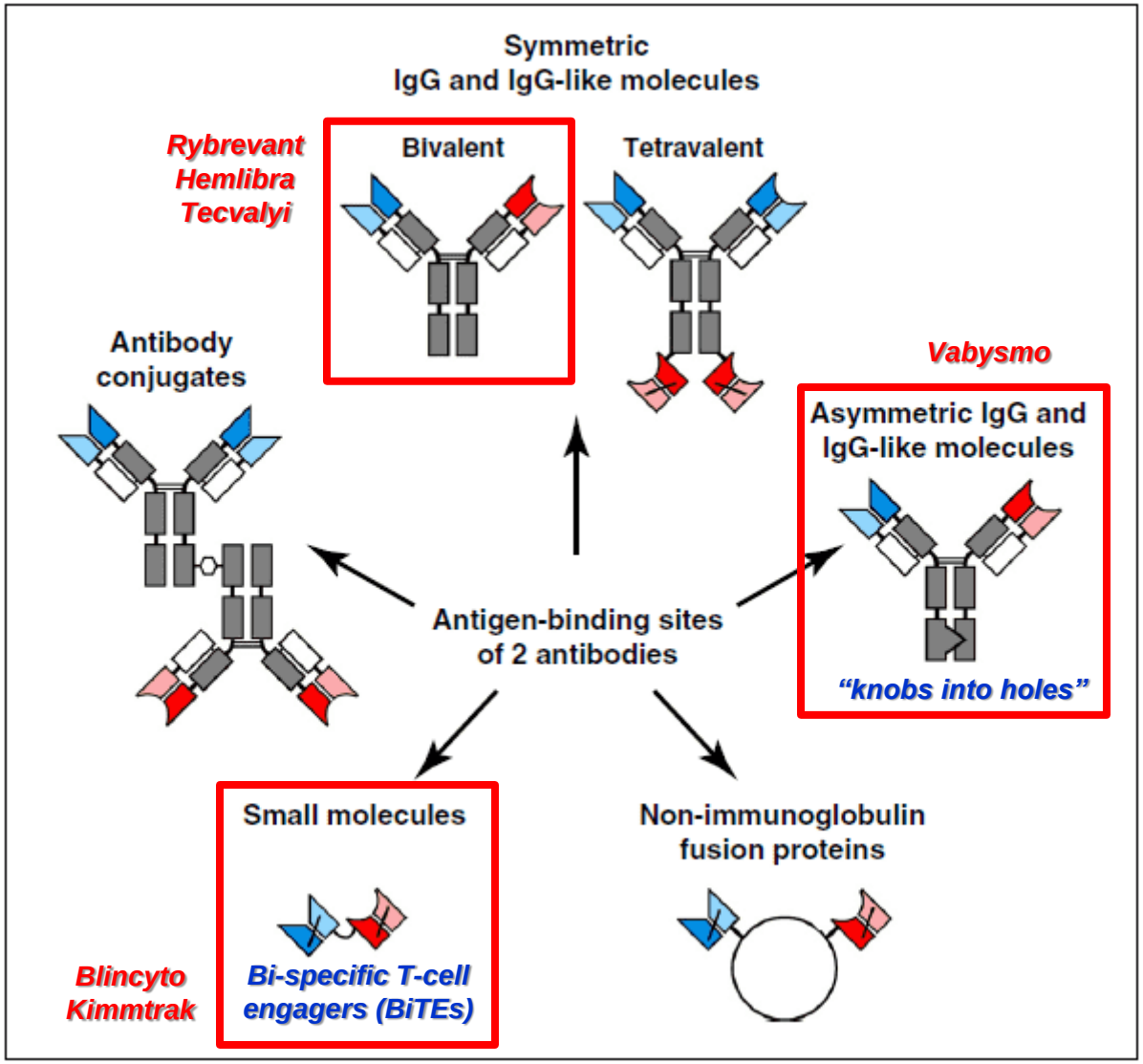
bivalent 'nanobody' (V_H-V_H)
Cablivi (caplacizumab)



WAVE 2 ripples

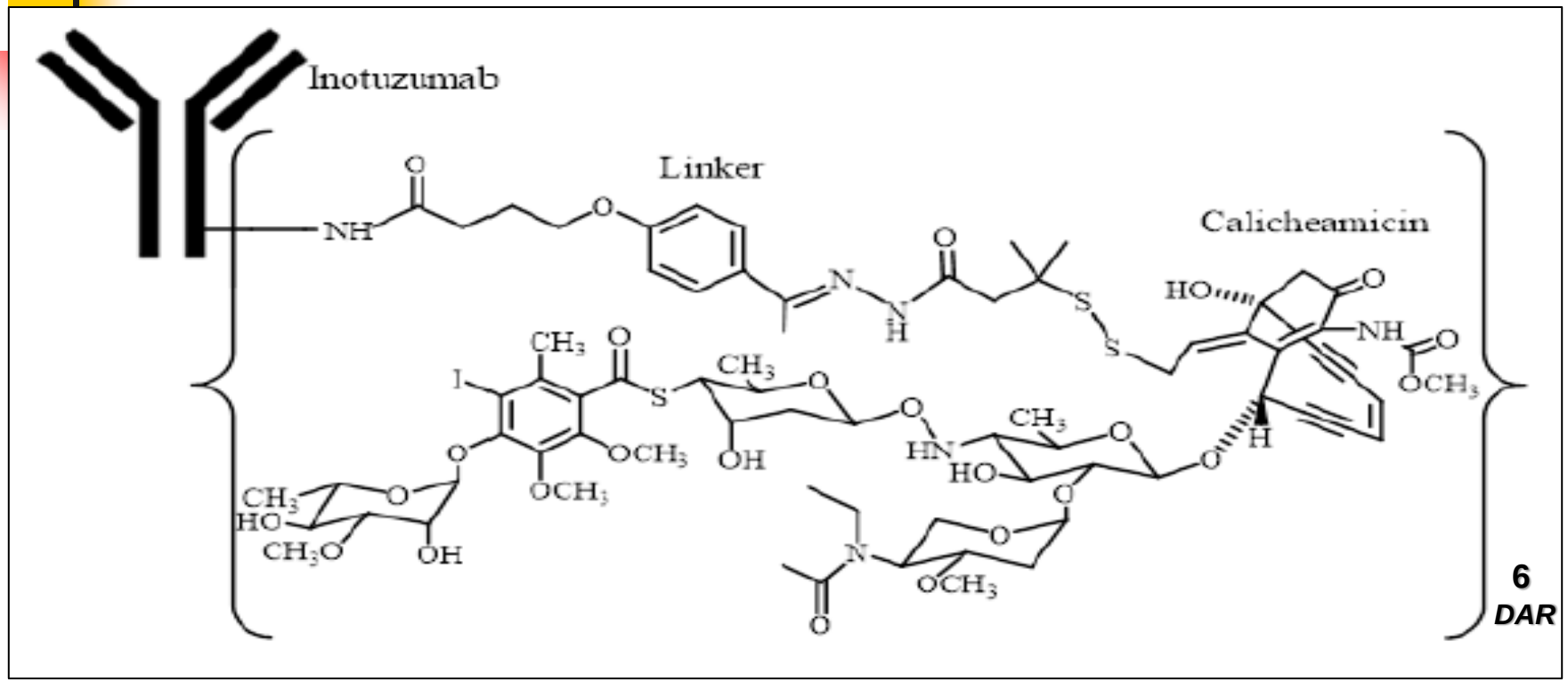
Bispecific Antibodies

2 different light chains + same/different/piece heavy chains



WAVE 2 ripples

Monoclonal Antibody coupled to a Chemical Drug



DAR – Drug Antibody Ratio

Antibody-Drug Conjugate (ADC)

ADCs take advantage of the targetability of a mAb to deliver a cytotoxic chemical drug directly to specific cells, minimizing general cell death ('kill cancer cells not healthy cells')

WAVE 3 Biosimilars

Currently* recombinant proteins and mAbs that have *lost patent coverage

A biosimilar is a biological product

FDA-approved biosimilars have been compared to an FDA-approved biologic, known as the reference product. Reference and biosimilar products are:

Large and generally complex molecules

Produced from living organisms

Carefully monitored to ensure consistent qualit

A biosimilar is highly similar to a reference product

For approval, the structure and function of an approved biosimilar were compared to a reference product, looking at key characteristics such as:

Purity

Molecular structure

Bioactivity

The data from these comparisons must show that the biosimilar is highly similar to the reference product.

A biosimilar has no clinically meaningful differences from a reference product

Studies were performed to show that biosimilars have no clinically meaningful differences in safety, purity, or potency (safety and effectiveness) compared to the reference product:

Pharmacokinetic and, if needed, pharmacodynamic studies

Immunogenicity assessment

Additional clinical studies as needed

Studies may be done independently or combined.

Biosimilars: market approved in EU since 2006; in USA since 2015

Innovator's Biopharmaceutical	Market-Approved Biosimilar	
	EU	USA
Adalimumab (Humira)	√	√
TNF-α/Fc Fusion Protein (Enbrel)	√	√*
Trastuzumab (Herceptin)	√	√
Bevacizumab (Avastin)	√	√
Rituximab (Rituxin/MabThera)	√	√
Infliximab (Remicade)	√	√
Ranibizumab (Leucentis)	√	√
Eculizumab (Soliris)	√	
Epoetin (Epogen/Procrit)	√	√
Filgrastim (Neupogen; G-CSF)	√	√
Pegfilgrastim (Neulasta; PEG-G-CSF)	√	√
Human Insulin (HI) & derivatives	√	√**
Human Growth Hormone (Humatrope; HGH)	√	**
Fertility Hormones	√	**
Heparin	√	chemical drug

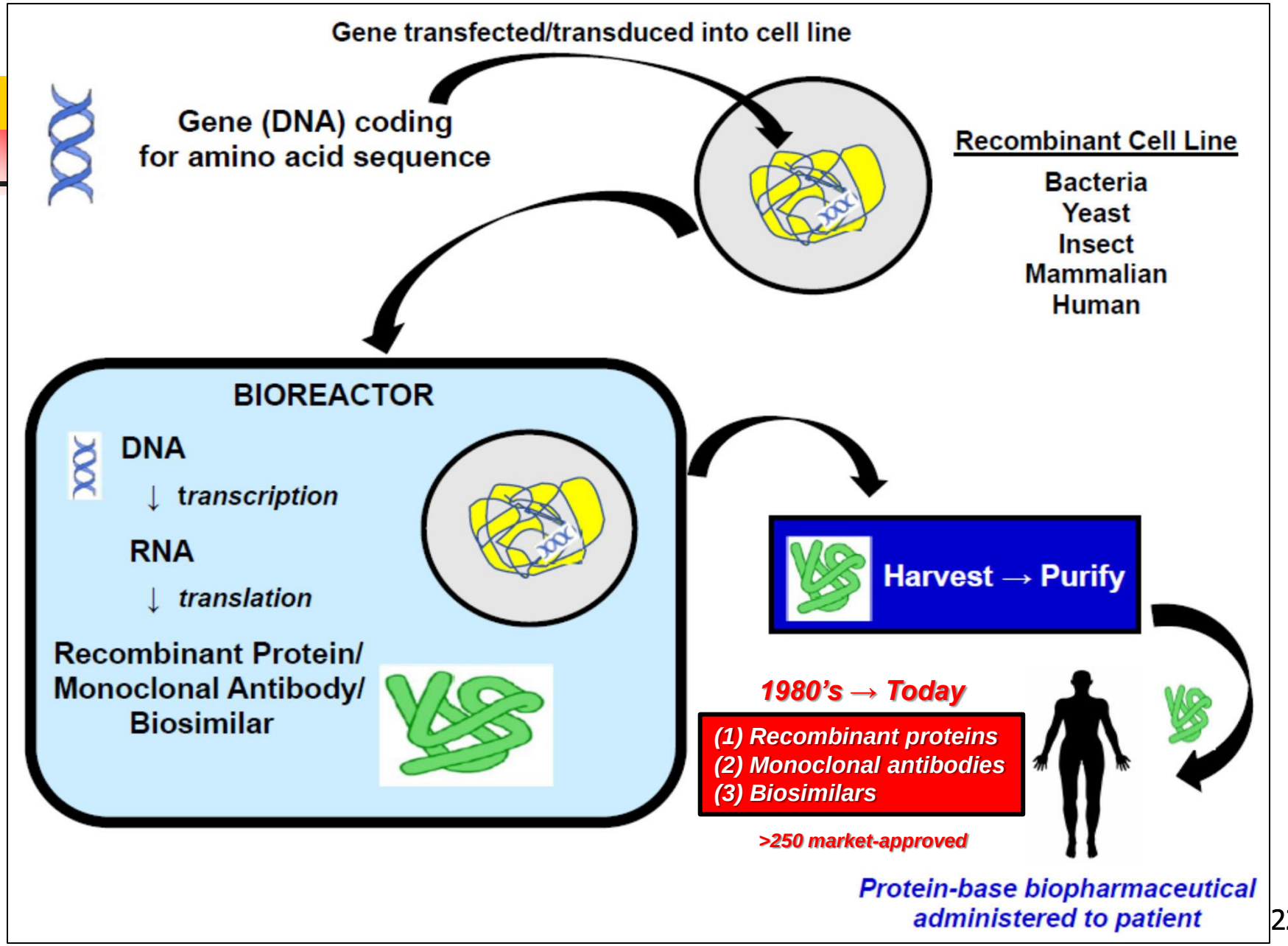
** FDA market-approved, but blocked by patents for now*

*** Up until March 2020, these were 'follow-on proteins', not biosimilars, within the FDA system*

80+ biosimilars market approved by FDA/EMA

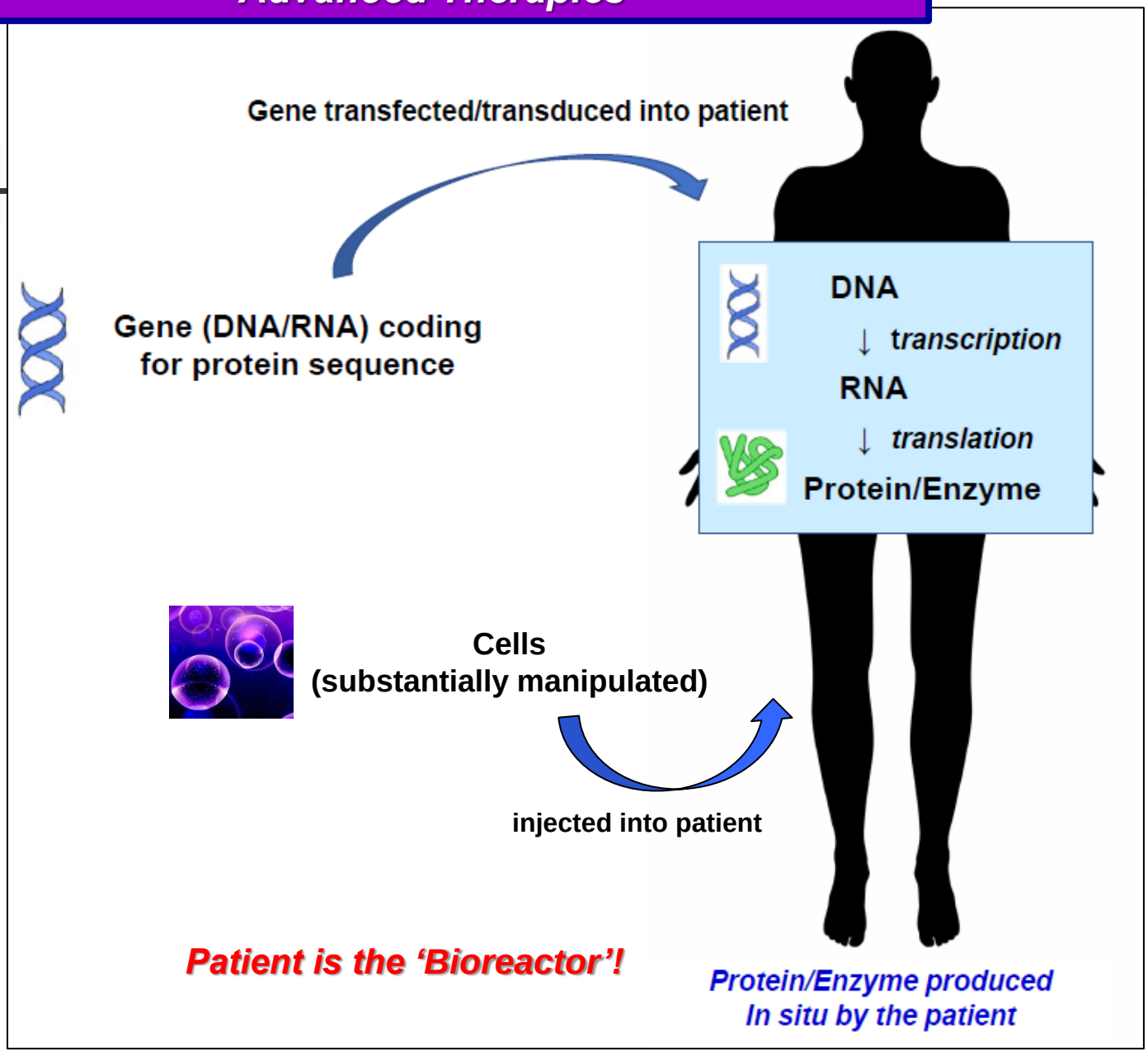
WAVES 1, 2, 3 – Protein-based Biopharmaceuticals

(the subject of today's course)

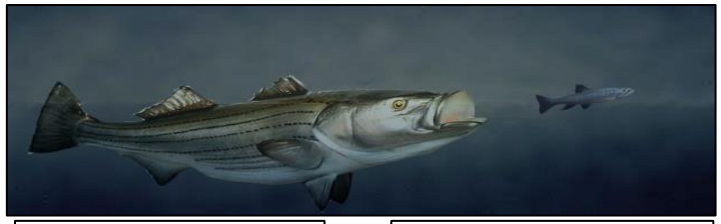


WAVE 4 – Gene Therapy (and Cellular Therapy) 'Advanced Therapies'

(the subject of the other course)



How successful will Wave 4 be? Follow the money ….



GILEAD

Kite
A GILEAD Company

NOVARTIS

avexis

Roche

Spark
THERAPEUTICS

Bristol-Myers Squibb

JUNO
THERAPEUTICS

janssen
PHARMACEUTICAL COMPANIES OF Johnson&Johnson

bluebirdbio

CSL Behring

FERRING
PHARMACEUTICALS

Orchard
therapeutics

BIOMARIN

Takeda

astellas

Biogen

AMGEN

BAYER

SAREPTA
THERAPEUTICS

Contract Development & Manufacturing Organization (CDMO)

Lonza

FUJIFILM
Diosynth
biotechnologies

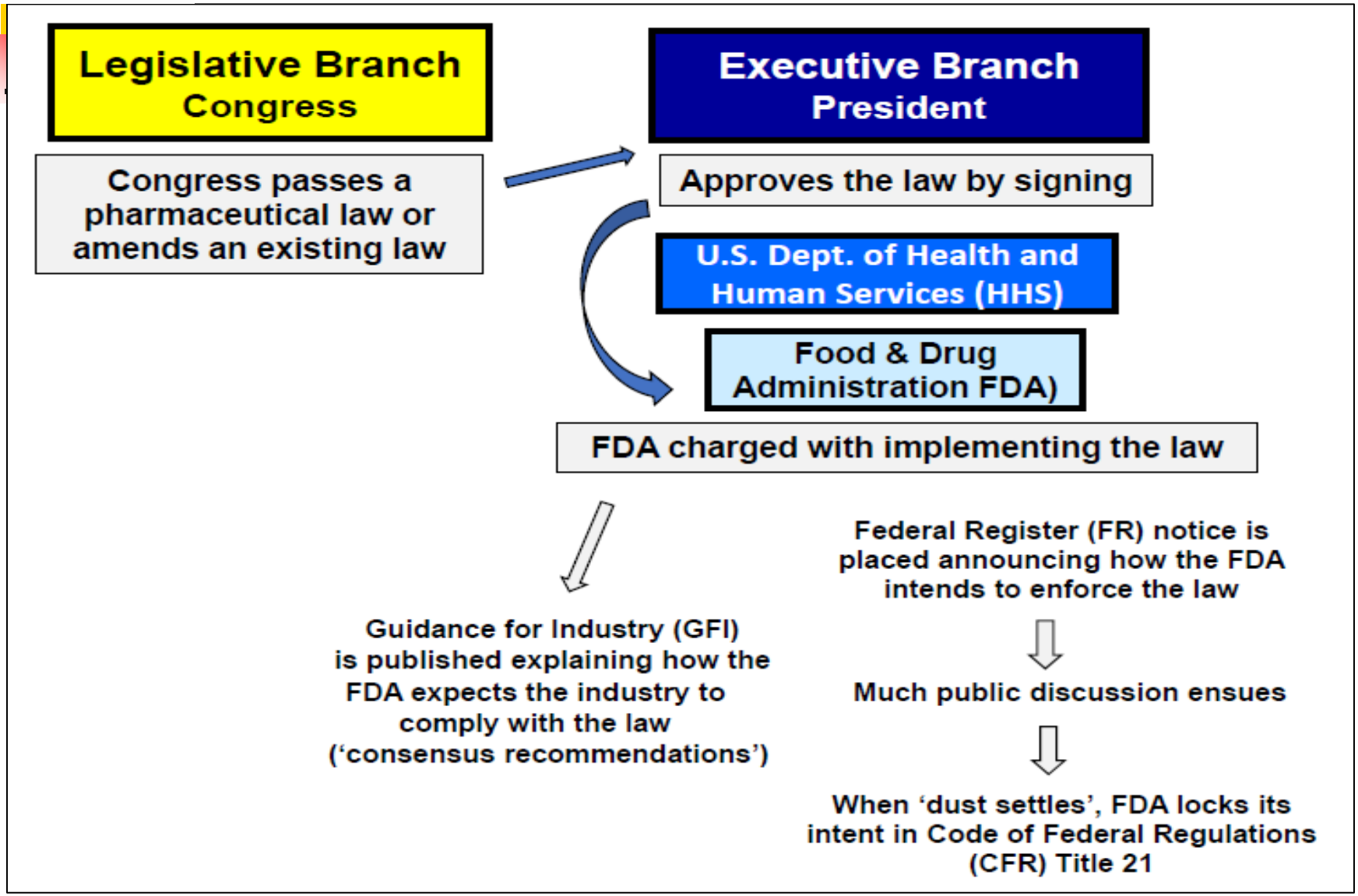
ThermoFisher
SCIENTIFIC

Catalent
BIOLOGICS

Introduction to Regulatory Authority Landscape for Biopharmaceuticals

(USA and EU to be discussed)

United States Pharmaceutical Law



1937 - antibacterial syrup for children was formulated with diethylene glycol (super sweet)

1941 – Insulin Amendment

'biological hormones and enzymes'

1938 – Food, Drug & Cosmetics Act
FD&C Act
NDA Pathway

New Drug Application (NDA)
21 CFR 314
(market approval)

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

Biologics License Application (BLA)
21 CFR 600-610
(market approval)

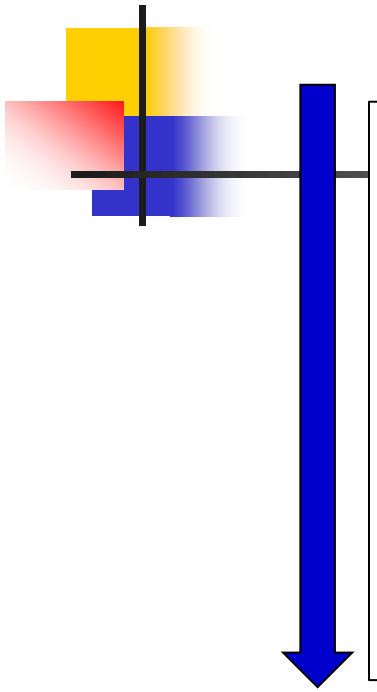
1944 – Public Health Services Act
PHS Act
BLA Pathway

Vaccines: pertussis, diphtheria
Immune serum polyclonal antibodies

'biologicals' – needed more testing and more controls than chemical drugs

PHS Act specifically defines which drugs are considered 'biological products'

has changed over time



- ***1944:*** ***'a virus, therapeutic serum, toxin, antitoxin or analogous product* or arsphenamine**'***
- ***1970 added:*** ***'vaccine, blood, blood component or derivative, allergenic products'***
- ***2010 added:*** ***'protein (except any chemically synthesized polypeptide)'***
- ***2020 changed:*** ***'protein ~~(except any chemically synthesized polypeptide)~~'***

21 CFR 600.3(h) Biological product means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

****Analogous = 'comparable in certain respects'***
(applies today to cell and gene therapy products)

*****arsphenamine, only chemical drug in PHS Act (in 1944 used to treat syphilis)***

U.S. Congress

Continually amending the two pharmaceutical laws

Major amendments allowing 'abbreviated' market approval pathways

FD&C Act 1984 Amendment

Innovator — **IND → New Drug Application (NDA) – 505(b)(1)**

Innovator — **IND → New Drug Application (NDA) – 505(b)(2)**

uses some data from existing NDA

Generic — **Abbreviated New Drug Application (ANDA) – 505j**

uses non-clinical & clinical data from existing NDA + bioequivalence study

PHS Act 2010 Amendment

Innovator — **IND → Biologics License Application (BLA) – 351(a)**

Biosimilar — **IND → Biologics License Application (BLA) – 351(j)**

uses non-clinical & clinical data from existing BLA + 3 comparative studies

Center for Drug Evaluation & Research (CDER)

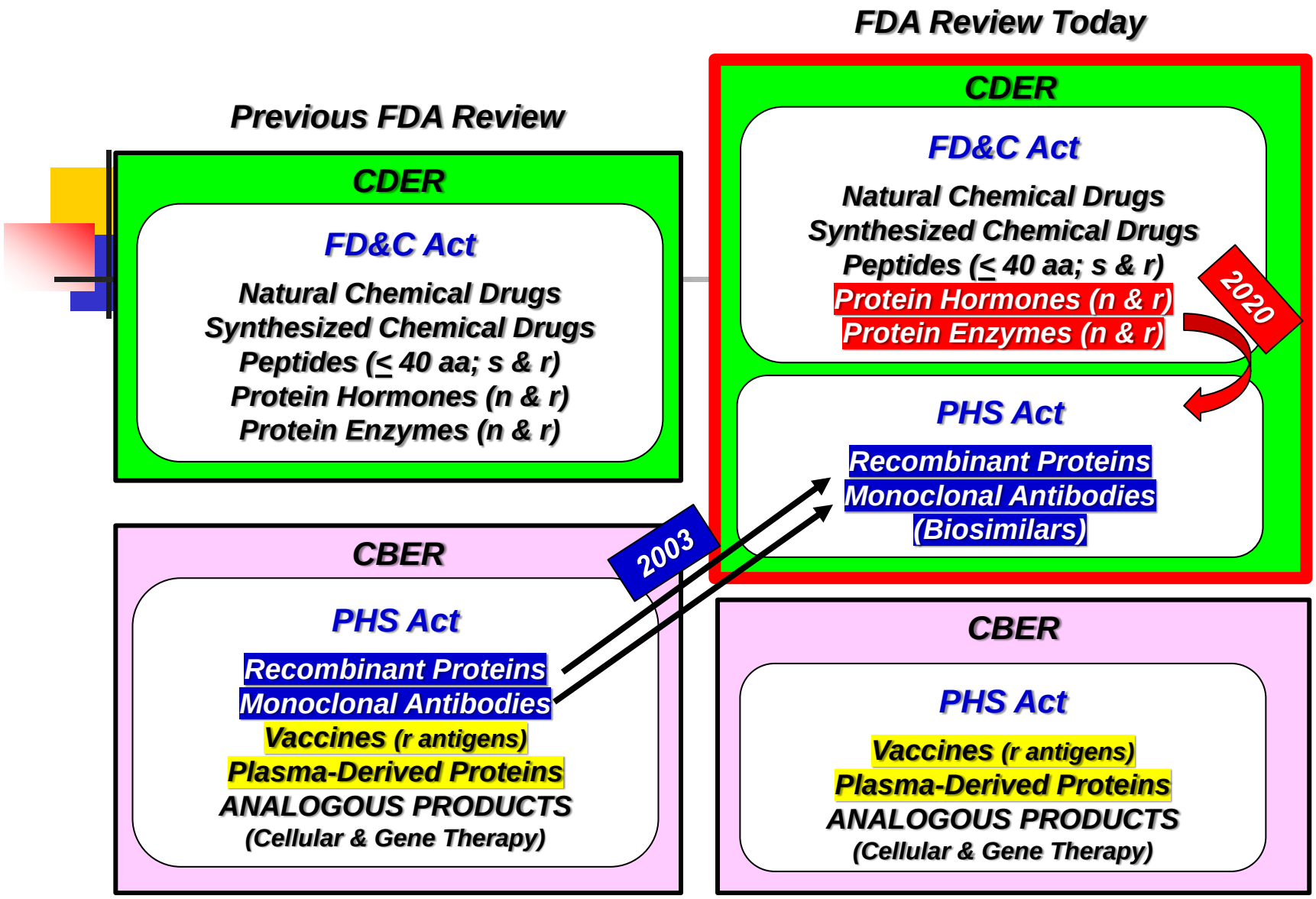
Center for Biologics Evaluation & Research (CBER)

Center for Devices and Radiological Health (CDRH)

'combination products'

Which FDA Center reviews and approves the protein-based biologics?

A protein is any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size. When two or more amino acid chains in an amino acid polymer are associated with each other in a manner that occurs in nature, the size of the amino acid polymer for purposes of this paragraph (h)(6) will be based on the total number of amino acids in those chains, and will not be limited to the number of amino acids in a contiguous sequence.

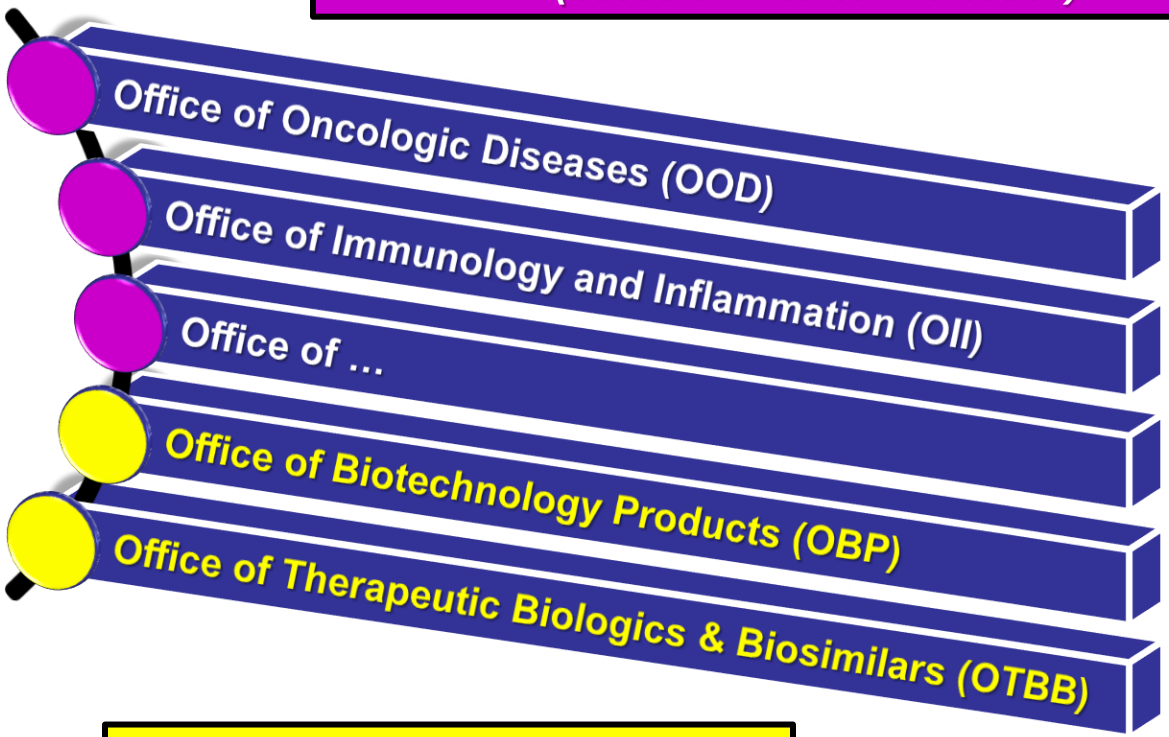


n - natural r - recombinant s - chem synthesized aa - amino acids

Proteins (> 40 amino acids) regulated as biologic
Peptides (≤ 40 amino acids) regulated as chemical drug

Center for Drug Evaluation & Research (CDER)

Submissions (IND and BLA) of rProteins, mAbs and biosimilars filed to Divisions inside respective Offices (based on medical indication)



Supports the medical Offices when they review biopharmaceuticals

European Parliament (EP) *(1953)*

Final approval of laws

European Commission (EC) *(1967)*

Proposes new/amended pharmaceutical laws
Implements laws approved by EP
Final approval of EMA recommendations

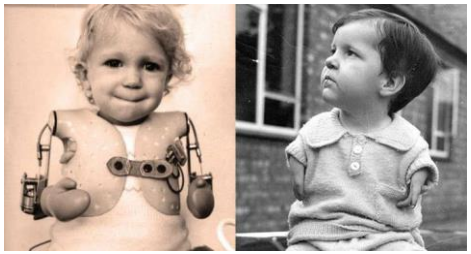
National Competent Authority (NCA)

Review/evaluation of medicines during human clinical development

European Medicines Agency (EMA) *(1993)*

Review/evaluation of medicines for market approval

Guidelines are published explaining how the EMA expects the industry to comply with the law



Thalidomide was a drug that was developed as a sedative in the 1950's, but was soon used for treating morning sickness in pregnant women

Clinical Trial Authorisation (CTA)
[IMPD for CMC]
(human clinical studies)

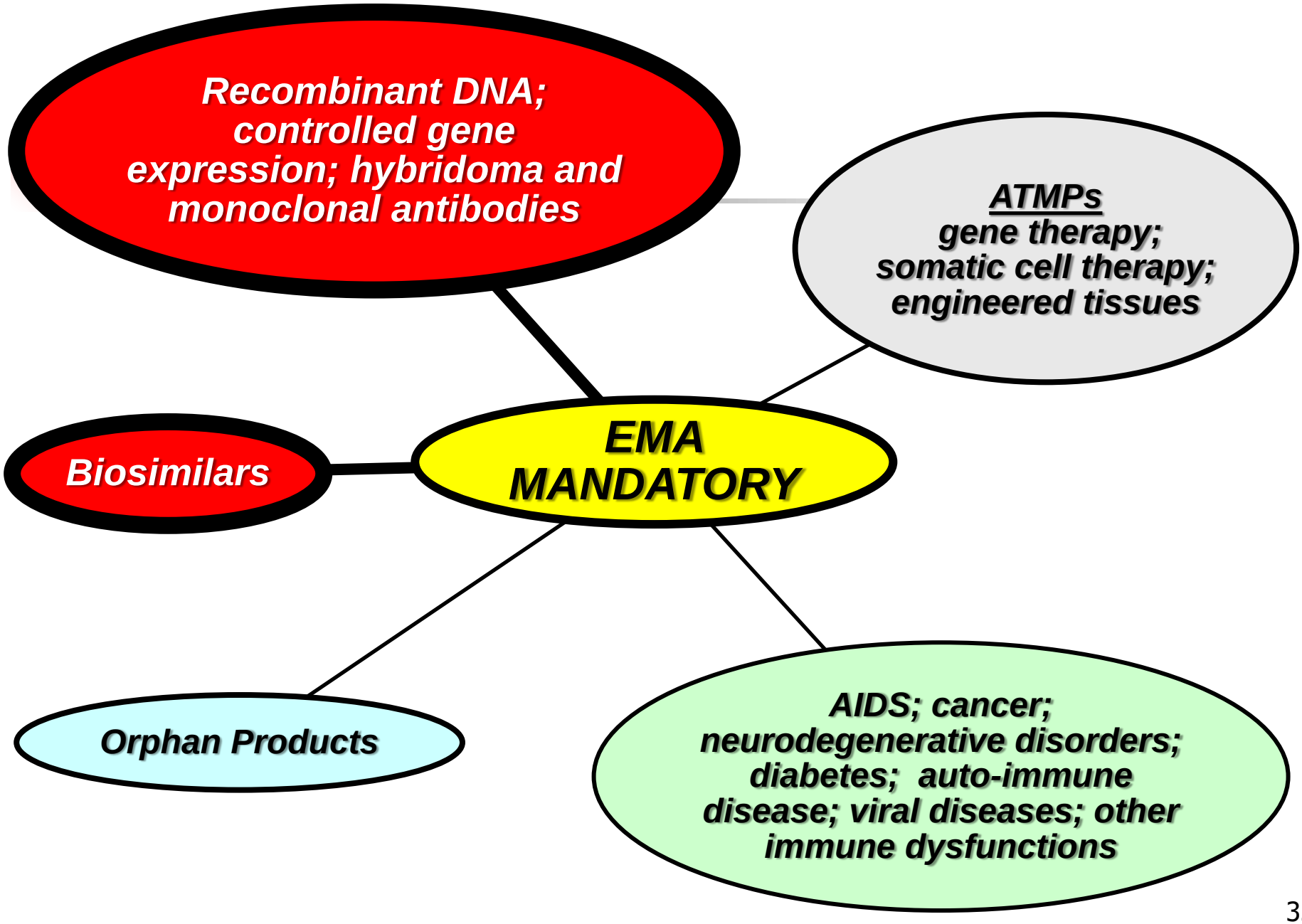
Marketing Authorisation Application (MAA)
[Module 3 for CMC]
(market approval)

NCA review
required for all pharmaceuticals

EMA centralized review
MANDATORY for most chemical drugs
(AIDS, cancer, diabetes, orphan drugs, etc.)

Clinical Trial Regulation (536/2014)
effective January 2023
'submitted, reviewed, authorized' – single portal entry

EMA centralized review
MANDATORY for all biopharmaceuticals


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

From a CMC Regulatory Compliance Perspective Are Protein-Based Biopharmaceuticals Regulated Like Chemical Drugs?

Attendee CMC Experience

ASO – antisense oligonucleoside (a short mRNA strand)

Chemical Drugs / ASOs _____

Recombinant Proteins _____

Monoclonal Antibodies (mAb) _____

Bispecific Antibodies (BsAb) _____

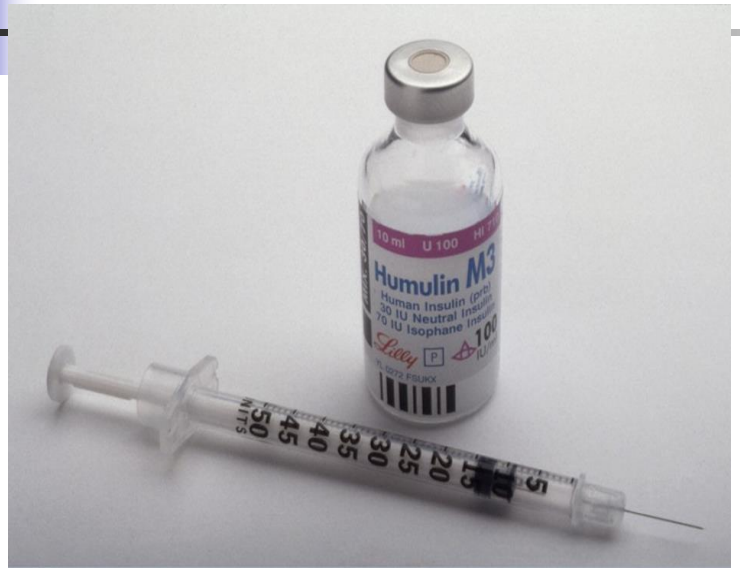
Fc-Fusion Proteins _____

Fab Fragments _____

Biosimilars _____

From a CMC Regulatory Compliance Perspective Are Protein-Based Biopharmaceuticals Regulated Like Chemical Drugs?

No!



4 Major Differences

1) *Difference due to type of starting material*
2) *Difference due to inconsistency of manufactured product*
3) *Difference due to complexity of molecular structure*
4) *No 'bio-generics'*

1) Difference due to type of starting material

Chemical Drug	Protein-Based Biopharmaceutical
• Chemical synthesis using non-living reagents • Harsh environments for synthesis (e.g., high temp, high pressure, organic solvents, etc.)	• Biosynthesized using living microorganism cells • Protein induction under mild conditions (e.g., mild temp, aqueous medium)

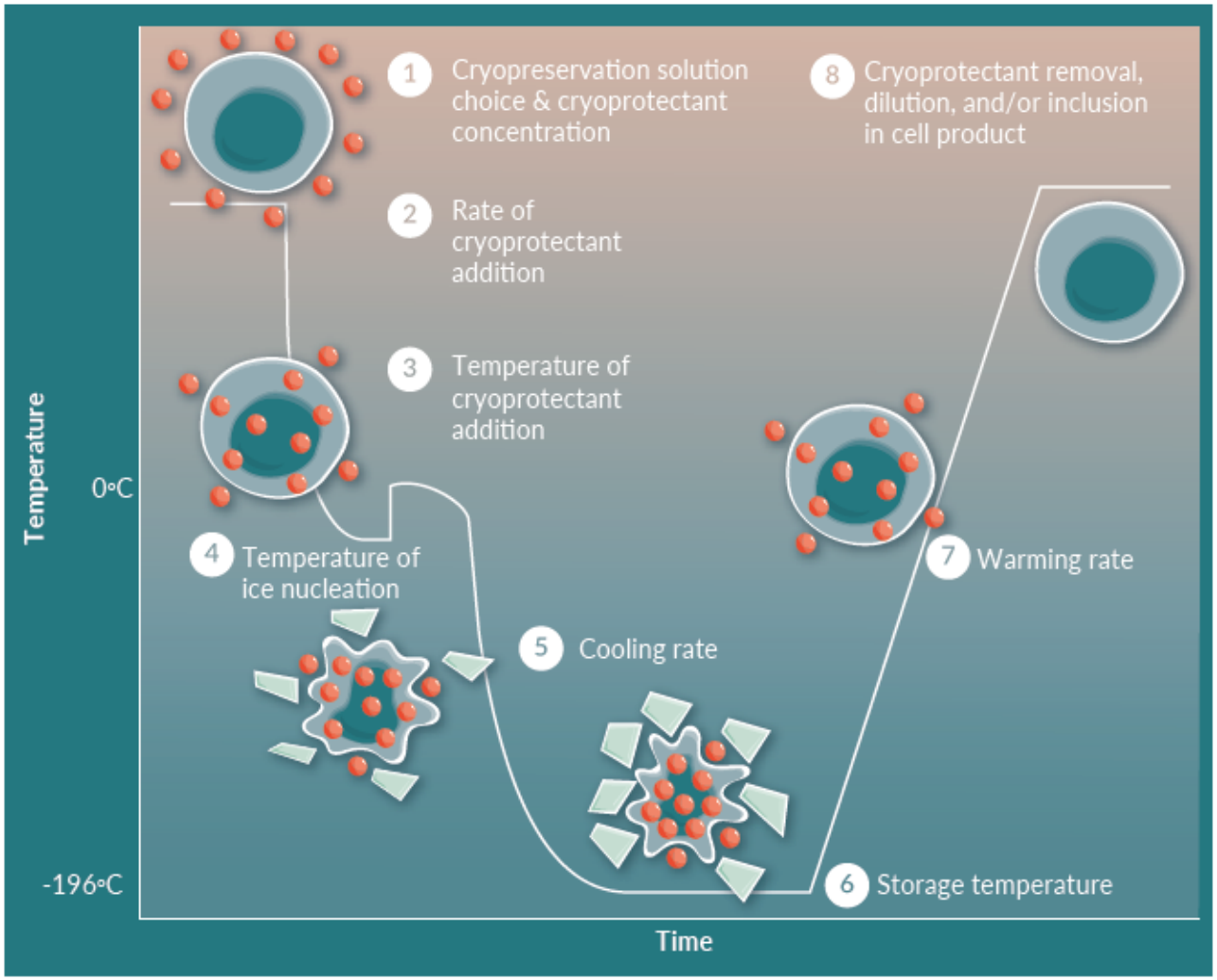
2 major challenges when using living cells →

Challenge when using living cells

#1: Must be kept 'Alive'! Around the clock – 24/7

dead organisms do <u>not</u> produce!

Critical steps in the cryopreservation process.



'life clock' can't be stopped, but it can be slowed!

living organisms 'hibernate' under liquid N_2 temp (-196°C)

<u>but</u> apoptosis can occur even at that low temp

controlled slow freeze
(to prevent ice formation from damaging the cell)

fast thaw

Challenge when using living cells

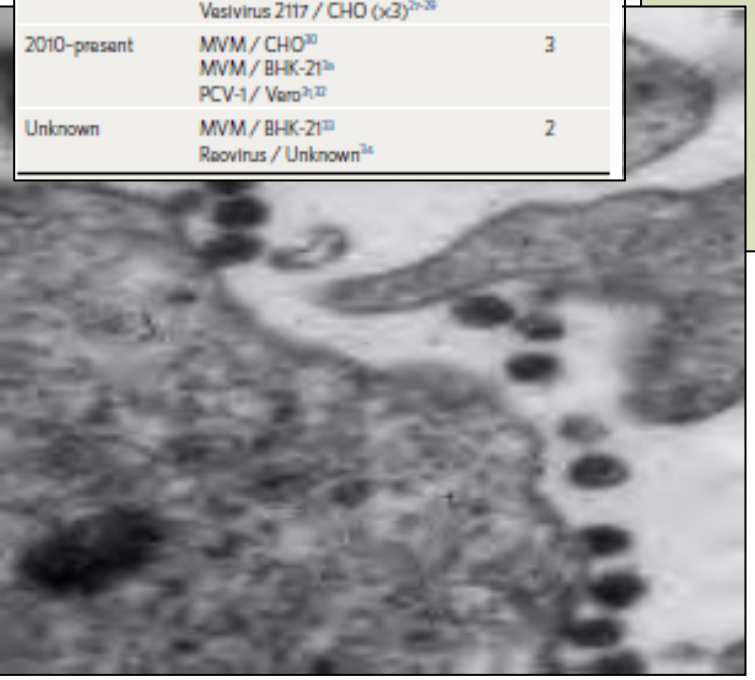
#2: Must be kept 'Healthy'!

a nasty world – an abundance of 'adventitious agents'!

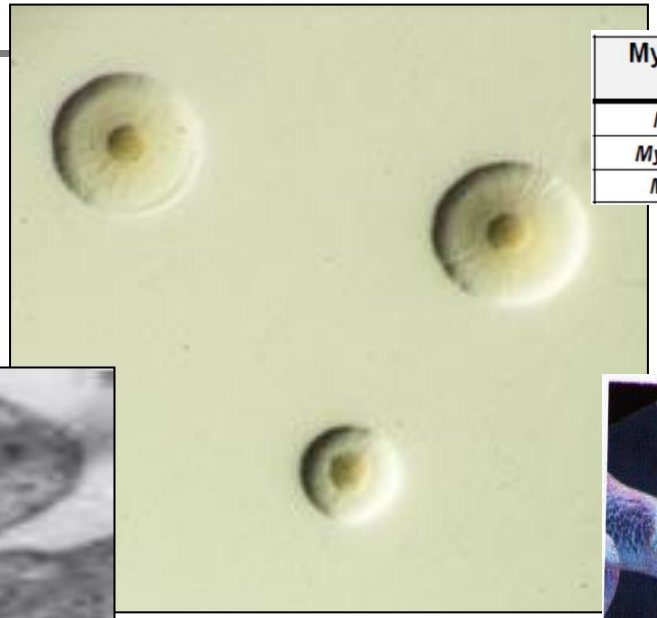
NATURE BIOTECHNOLOGY | VOL 38 | MAY 2020 | 563–572 |

Table 1 | Virus contaminations of mammalian cell culture to produce proteins and vaccines, segregated by year, both publicly reported and contained in the CAACB study

Year of contamination	Contaminations (virus / host cell)	Total
1985–1989	Blue tongue / CHO EHDV / CHO[18,19]	2
1990–1994	Herpesvirus / primary monkey Herpesvirus / Vero MVM / CHO (×2)[20–22] Parainfluenza 3 / MRCs Reo3 / MRCs Simian adenovirus / primary monkey	7
1995–1999	CVV / CHO Reovirus / human primary kidney[23] Vesivirus 2117 / CHO[24]	3
2000–2004	CVV / unknown (×2)[25] Human adenovirus / HEK293[26]	3
2005–2010	CVV / CHO MVM / CHO (×2) Vesivirus 2117 / CHO (×3)[27–29]	6
2010–present	MVM / CHO[30] MVM / BHK-21[31] PCV-1 / Vero[31,32]	3
Unknown	MVM / BHK-21[33] Reovirus / Unknown[34]	2



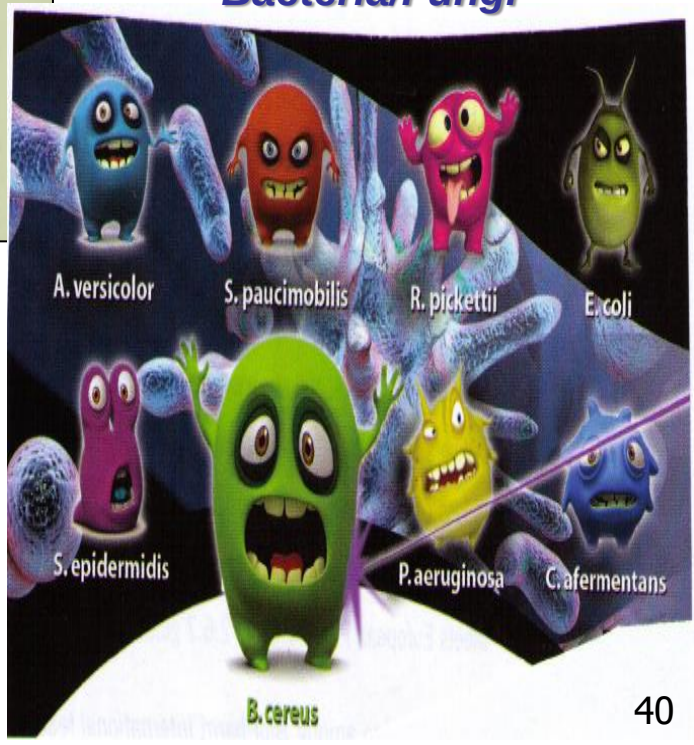
Viruses



Mycoplasmas

Mycoplasma Species Reported to Contaminate Mammalian Cell Culture Manufacturing	
Mycoplasma hyorhinis	*Mycoplasma orale*
Mycoplasma salivarium	*Mycoplasma fermentans*
Mycoplasma arginini	*Acholeplasma laidlawii*

Bacteria/Fungi

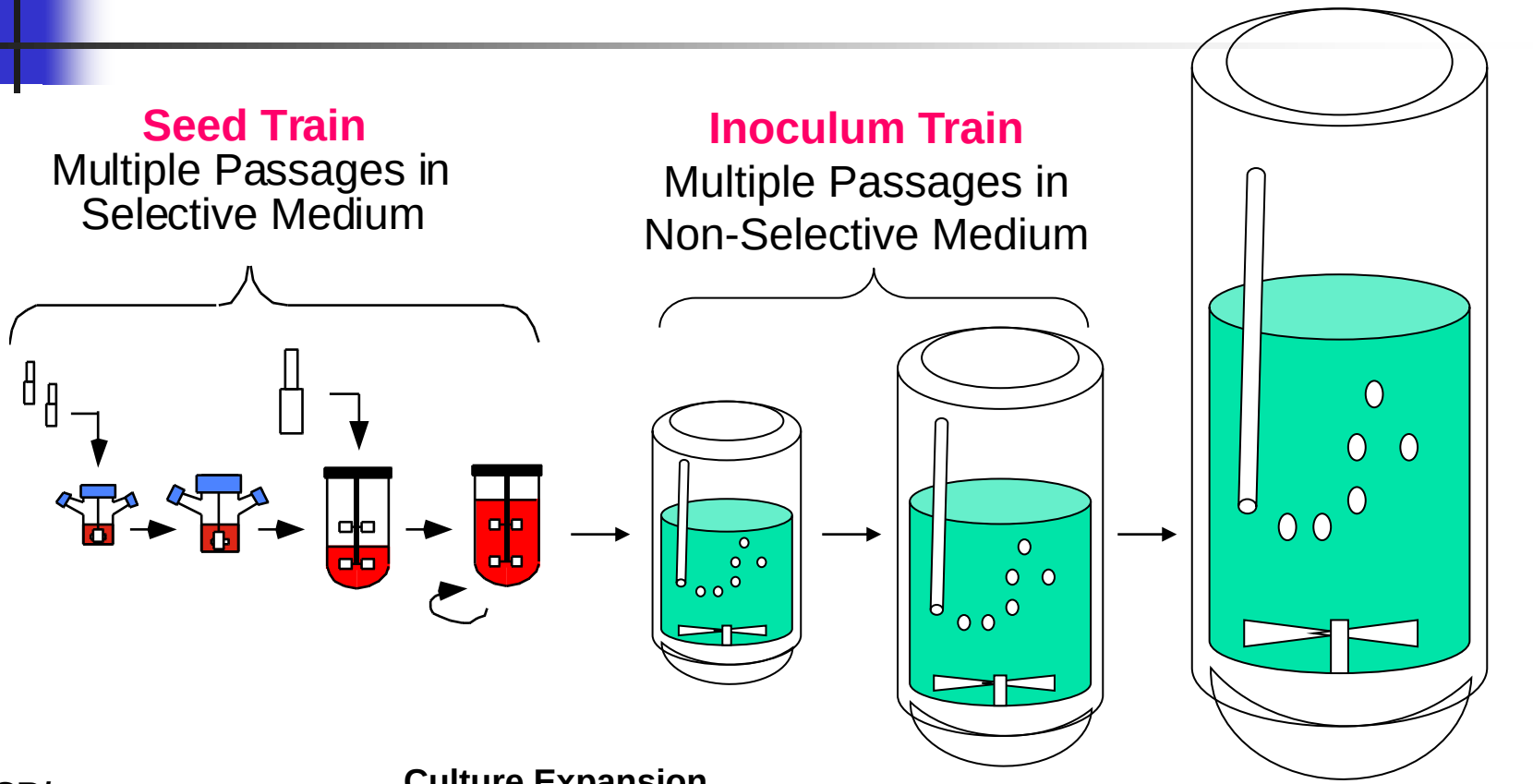


Once an adventitious agent contaminates a living cell, proliferation occurs and <u>all following upstream steps are impacted</u>!

Production

Seed Train
Multiple Passages in Selective Medium

Inoculum Train
Multiple Passages in Non-Selective Medium



MCB/ WCB

Culture Expansion

Product Expression

(must be kept 'healthy' for several months)

2) Difference due to inconsistency of manufactured product

Chemical Drug	Protein-Based Biopharmaceutical
• The synthetic manufacturing process for a chemical product yields a high degree of product consistency	• The biosynthetic manufacturing process for a protein product yields varying degrees of product inconsistency

Recombinant Proteins/Monoclonal Antibodies

the quality, purity and/or potency of the protein-based product may weakly ↔ strongly be defined by the manufacturing process

Although, by definition, mAbs are characterised by a single amino acid sequence, they are subject to post-translational modifications as well as physicochemical transformations that arise during their production and storage. In practice, the drug substance and the drug product usually also include a low level of sequence variants that arise from the inherent errors normally occurring during transcription and translation. Heterogeneity is specific to the manufacturing process and its potential impact on the activity, efficacy, safety, and pharmacokinetic properties of a mAb product should be understood to be able to ensure batch-to-batch consistency. In addition, heterogeneity may affect both the long-term stability and the immunogenicity of a therapeutic mAb, though in general, modifications that are found in natural human antibodies are less likely to be immunogenic. The types of modification commonly associated with therapeutic mAbs include: N- and C-terminal modifications, glycosylation, glycation, disulphide bond formation and various other amino acid related modifications.

WHO Guideline for the safe production and quality control of monoclonal antibodies for use in humans

World Health Organization

WHO/MAB/DRAFT/12 October 2021

Variation of biological processes → – Amgen 5 min video

Amgen

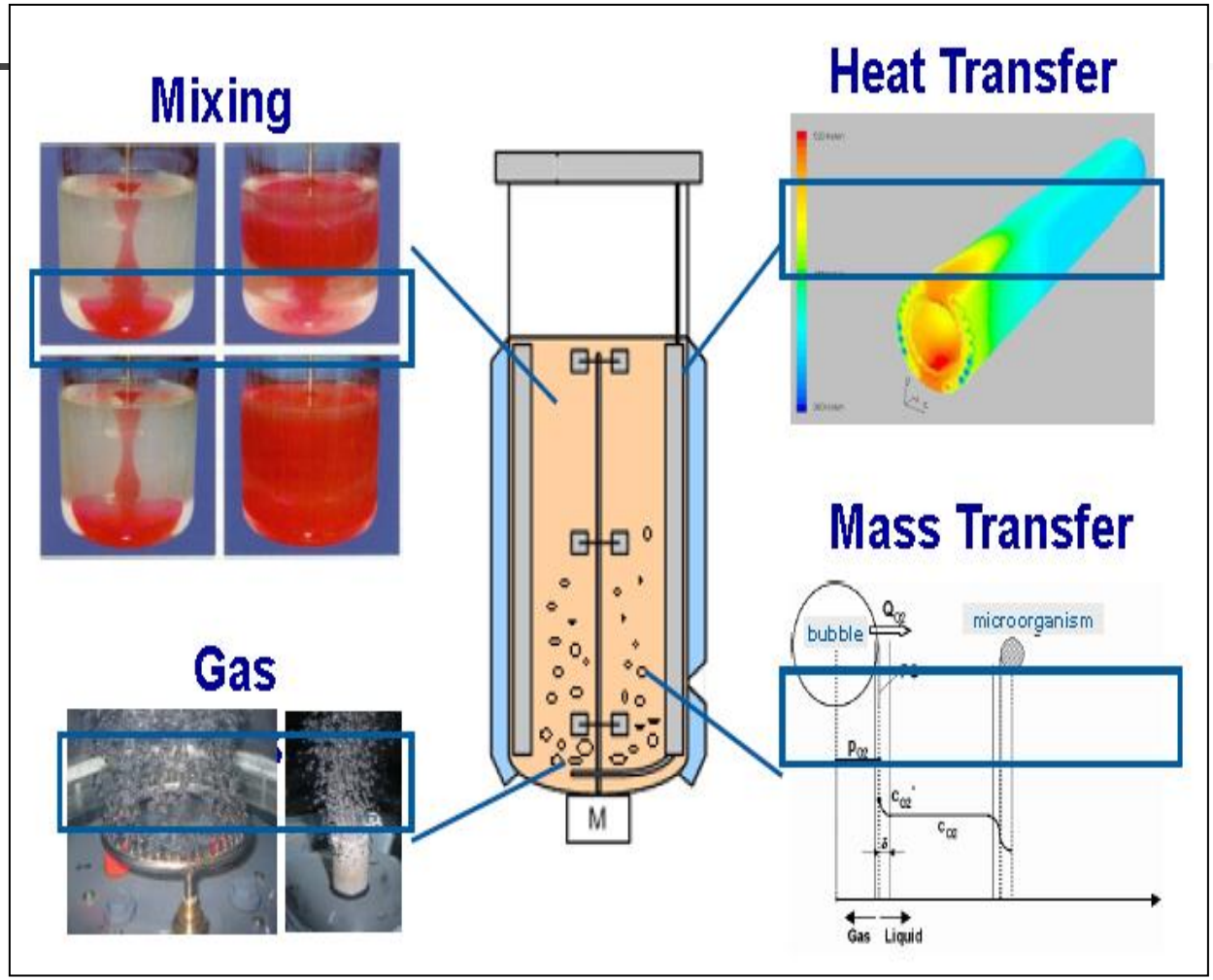
Control of Living Cells – Consistency of Product Depends On It!

up to 12 critical process parameters may need to be controlled

cells are fragile

CO_2 out

O_2 in



multiplying cells generate heat

nutrients toward

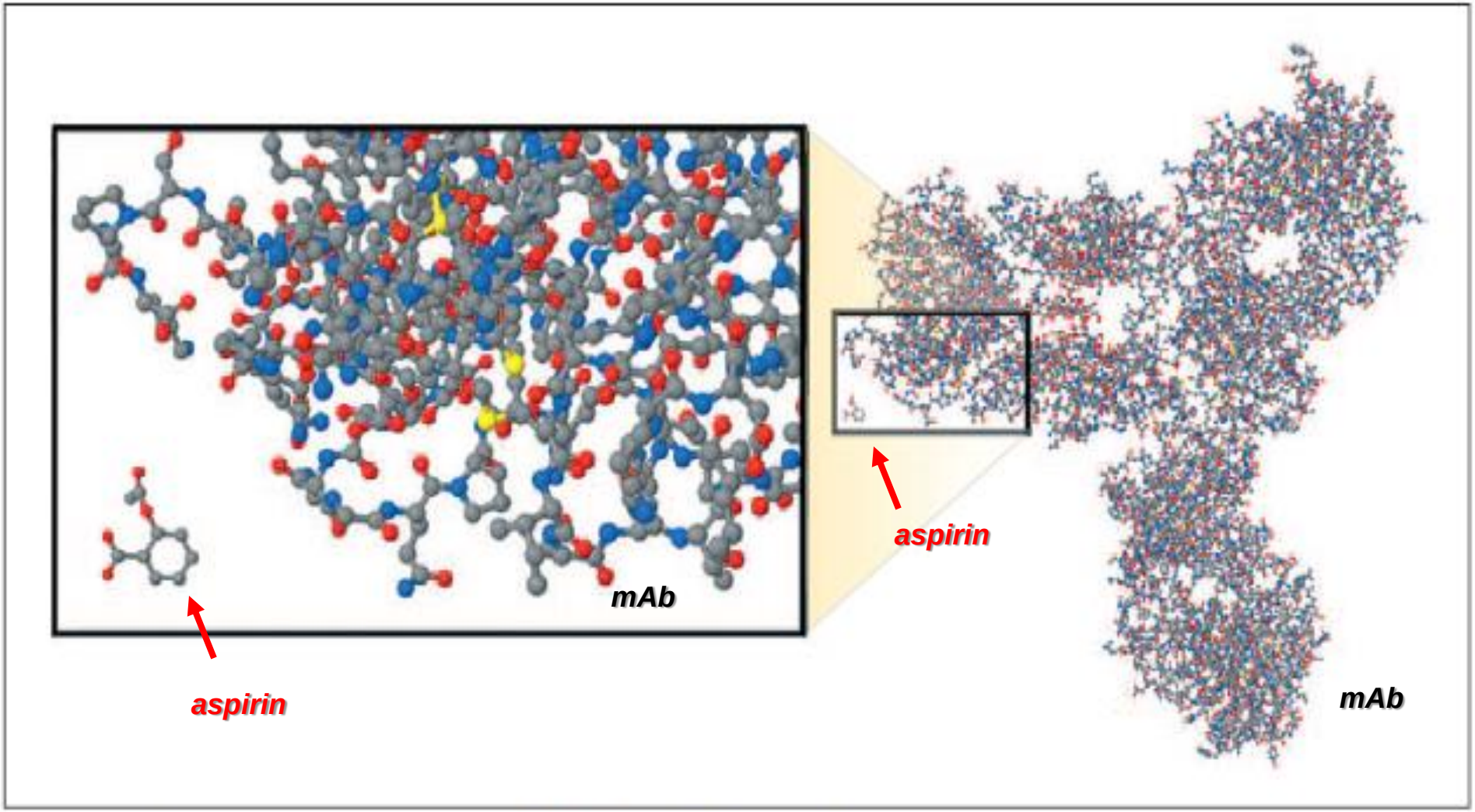
waste products away

3) Difference due to complexity of molecular structure

Chemical Drug	Protein-Based Biopharmaceutical
• Molecular structure of a chemical drug can be simple or slightly complex	• Molecular structure of a protein is complex, with numerous molecular structural variants

Typical perception of size of a chemical drug vs a biopharmaceutical

common slide used in FDA presentation



Comparison between a Biologic Monoclonal Antibody and an Aspirin Molecule.

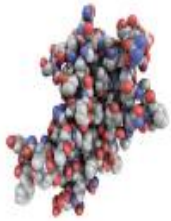
But chemical drugs can also be large – just not as large nor as complex as proteins!

chemically synthesized ASO

siRNA (small, interfering RNA) for gene silencing
double-stranded RNA: 44 nucleosides

Givlaari
MW 17,246 Da

~150 kDa; ~10 nm

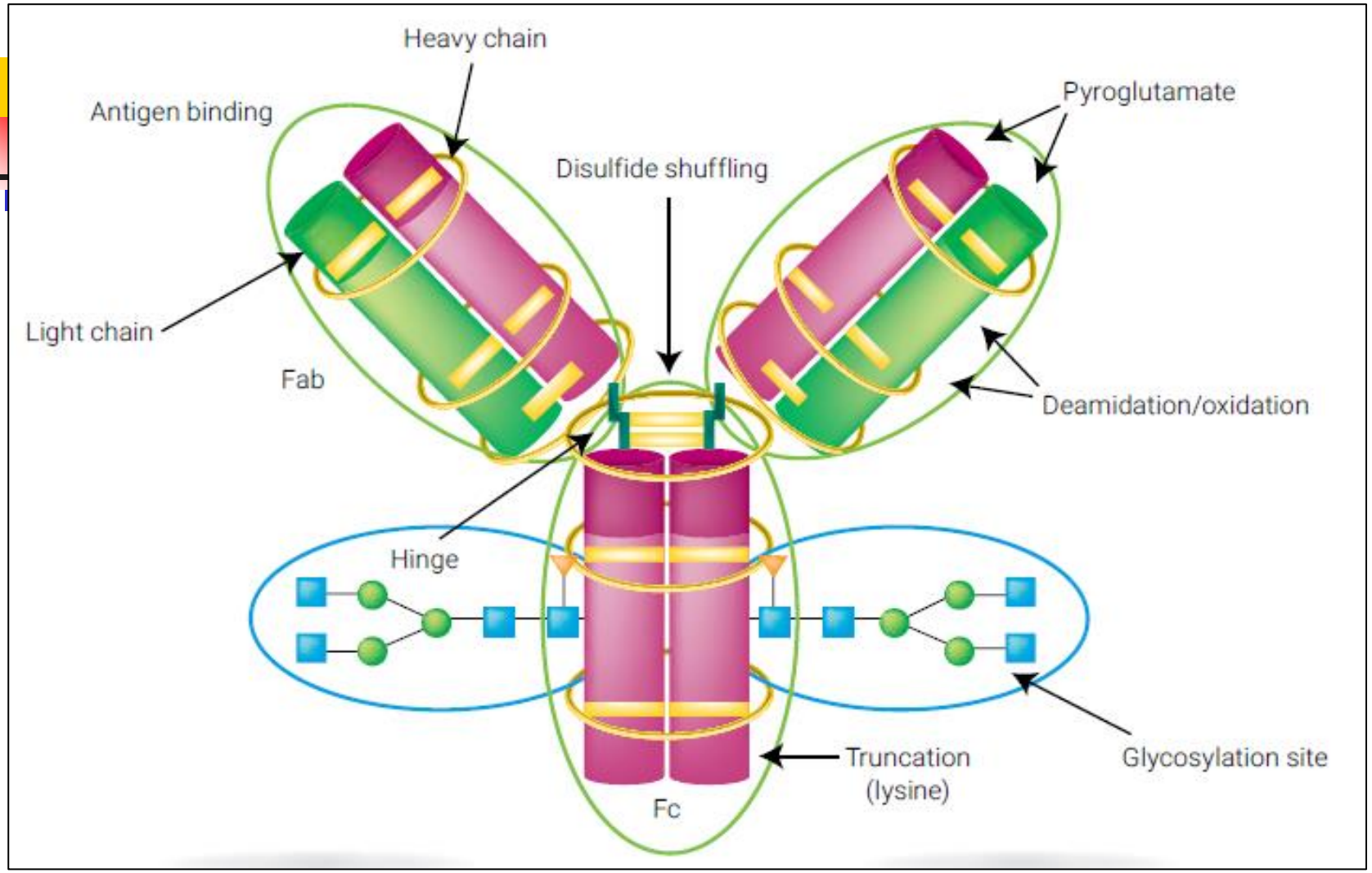


Insulin
5,808 daltons

Growth hormone
22,000 daltons

Monoclonal antibody
150,000 daltons

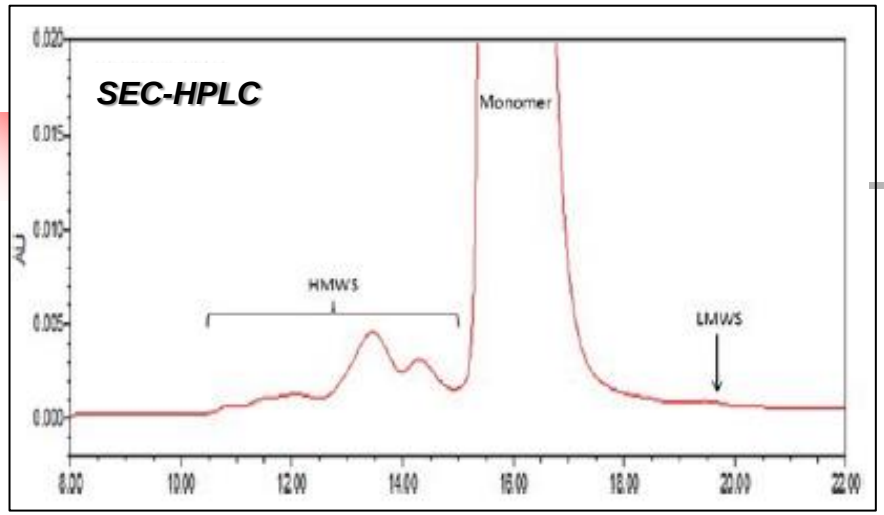
Abundance of protein molecular variants leads to complexity!

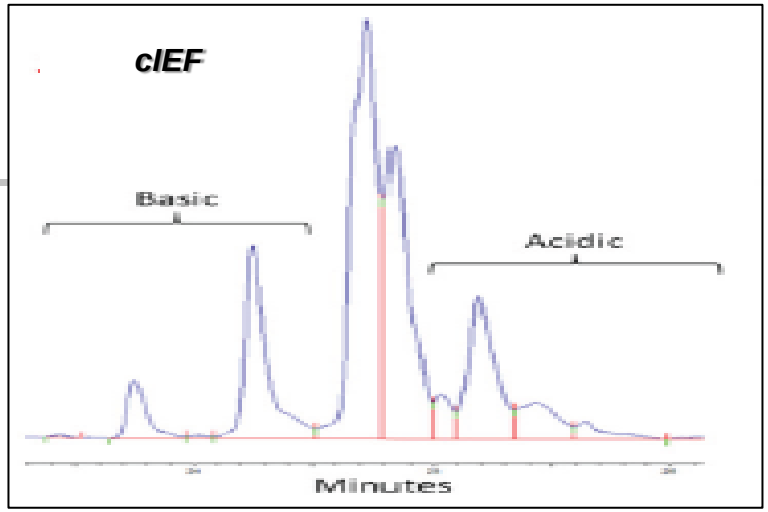


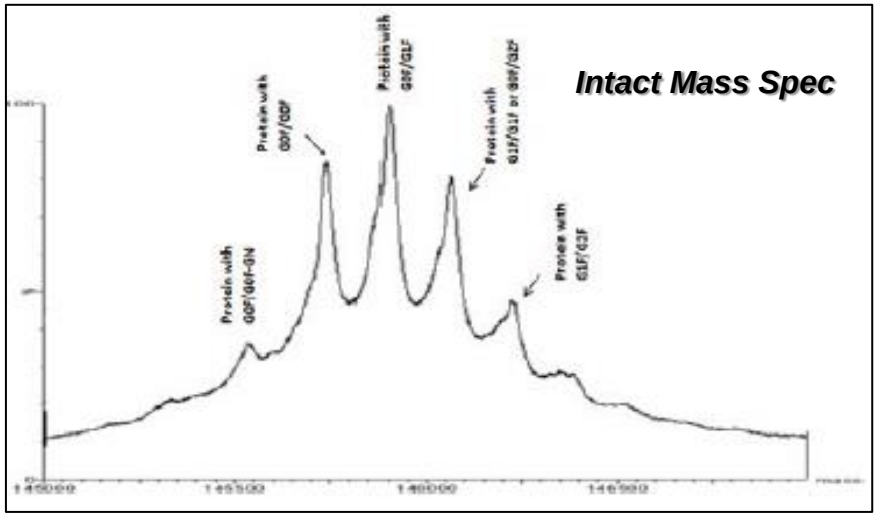
Kozlowski and Swann, Current and Future Issues in the Manufacturing and Development of Monoclonal Antibodies; Advanced Drug Delivery Reviews, 58 (5-6), 7 Aug 2006, pp 707-722

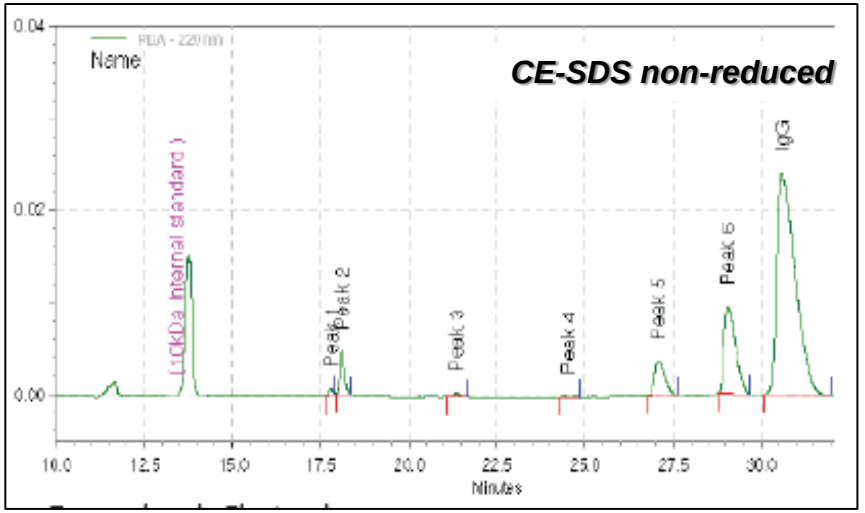
Total theoretical molecular variants → 100 million!

But, how many molecular variants can we actually see today in a mAb?









How many variants in a 'blob'?

Major safety challenge for biopharmaceuticals due to this complexity

not toxicity (like chemical drugs) but how the body's immune system reacts!

Assuring the quality of biological medicinal products is challenging, as they often consist of a number of product variants and process related impurities whose safety and efficacy profiles are difficult to predict. However, unlike chemical entities, toxic impurities are generally not an issue, and the safety issues of biological / biotechnological products are more often related to the mechanism of action of the biological product or to immunogenicity.

EUROPEAN MEDICINES AGENCY

Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials

27 January 2022
EMA/CHMP/BWP/534898/2008 Rev. 2

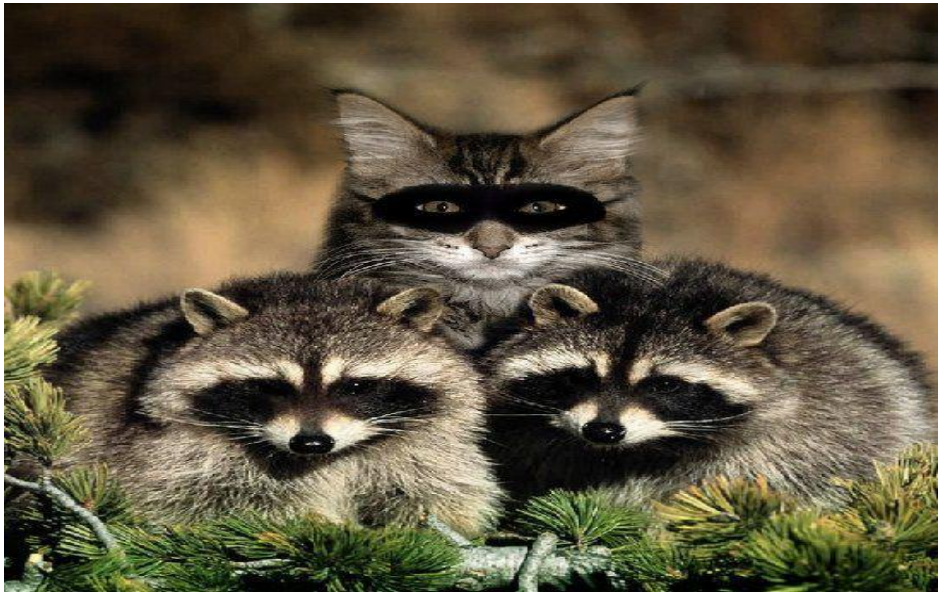
Chemical drugs are too small to be immunogenic – not recognized by the immune system as 'invaders'

4) No Bio-Generics

Generic Chemical Drug: must be identical, equivalent to innovator chemical drug

Biosimilar: must be 'highly similar' to innovator biopharmaceutical

What is "Highly Similar"?



<u>Not</u> equivalent

<u>Not</u> identical

FDA Website for Biosimilars

www.FDA.gov/drugs/therapeutic-biologics-applications-bla/biosimilars

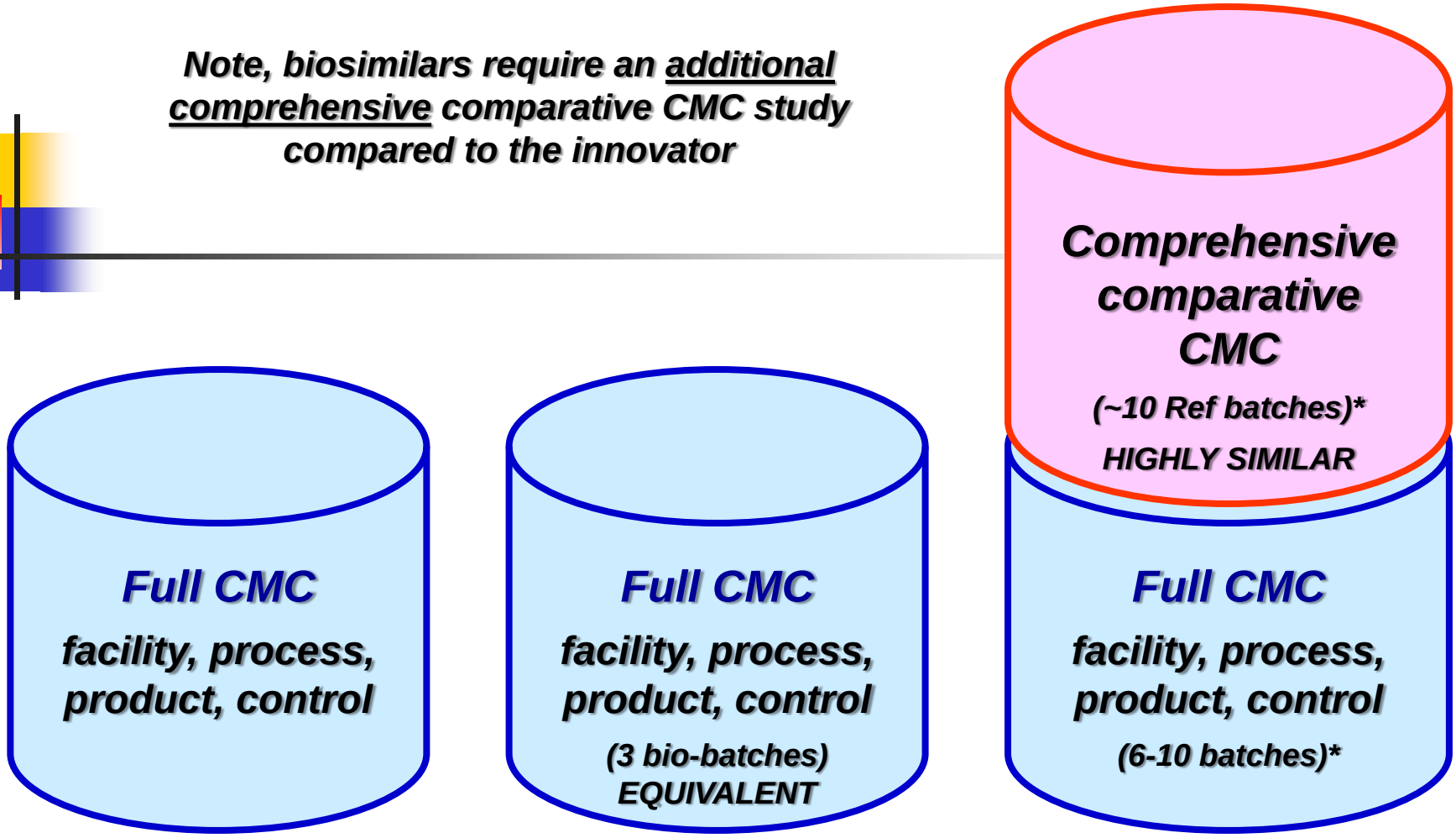
Are biosimilars the same as generic drugs?

Biosimilars and generic drugs are versions of brand name drugs and may offer more affordable treatment options to patients. Biosimilars and generics are each approved through different abbreviated pathways that avoid duplicating costly clinical trials. But biosimilars are not generics, and there are important differences between biosimilars and generic drugs.

For example, the active ingredients of generic drugs are the same as those of brand name drugs. In addition, the manufacturer of a generic drug must demonstrate that the generic is bioequivalent to the brand name drug.

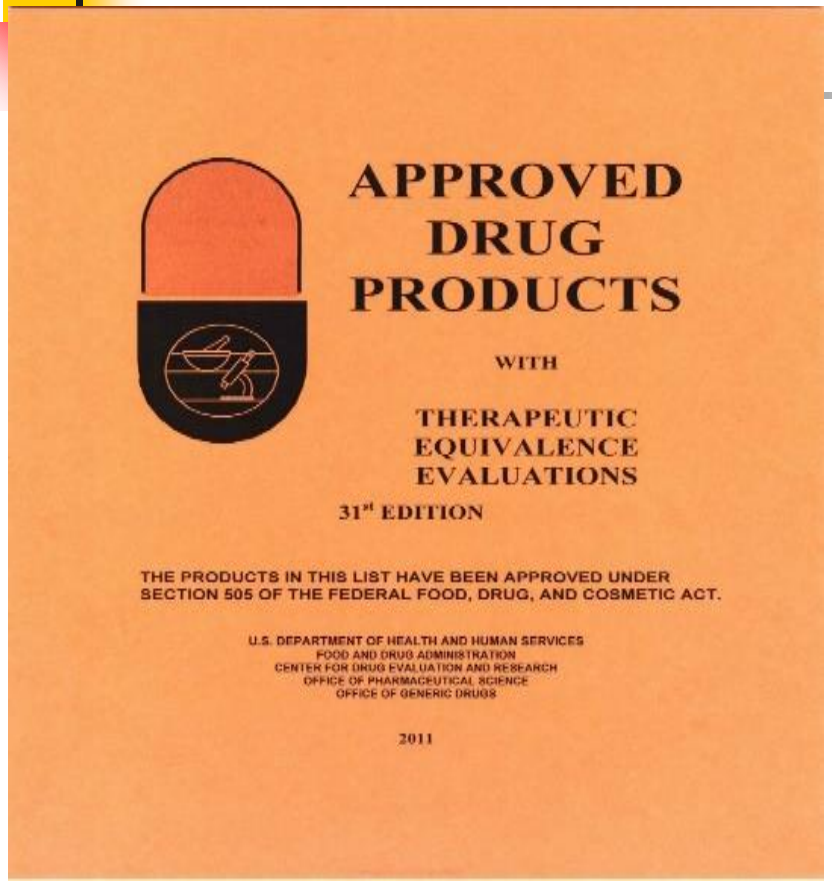
By contrast, biosimilar manufacturers must demonstrate that the biosimilar is highly similar to the reference product, except for minor differences in clinically inactive components. Biosimilar manufacturers must also demonstrate that there are no clinically meaningful differences between the biosimilar and the reference product in terms of safety and effectiveness.

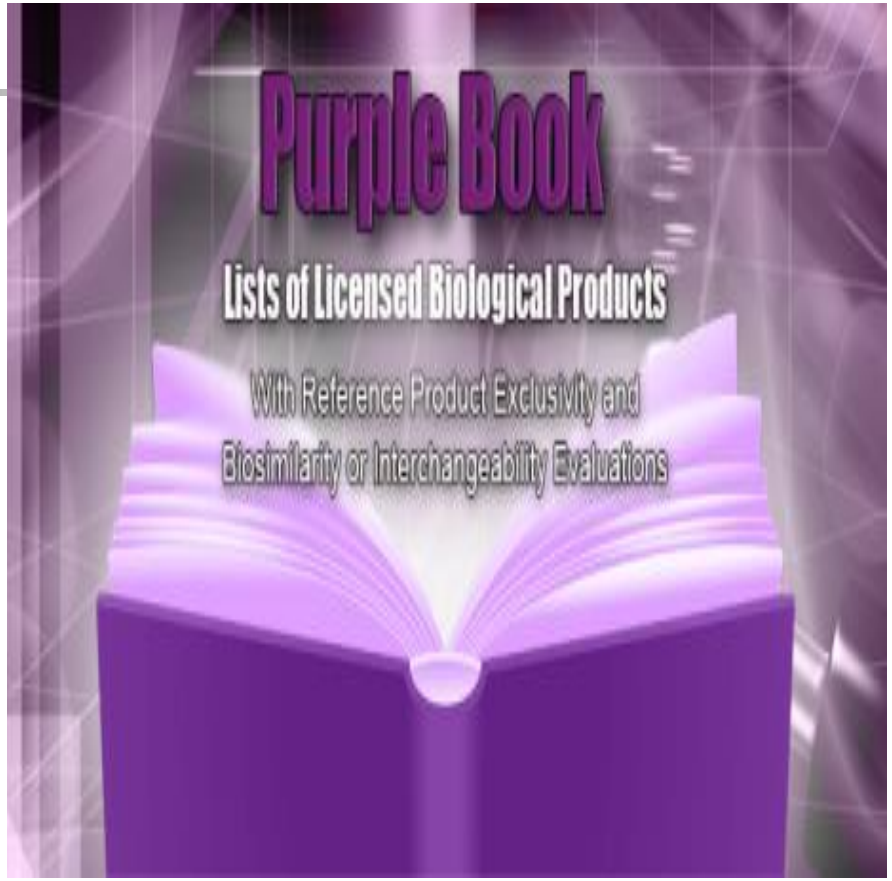
Note, biosimilars require an <u>additional comprehensive</u> comparative CMC study compared to the innovator



**FDA GfI Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations (2019)*

	Investment	Elapsed Time	Clinical
Chemical Generic	~ $3 million	~ 2 years	~30 volunteers (bioequivalent pK study)
Biosimilar	~ $150 million	~ 5 years	~800 patients (comparative clinical study)





FDA list of market-approved chemical drugs and <u>chemical generics</u>

FDA list of market-approved biologics and <u>biosimilars</u>

(note, colors are more for explanation; lists are on the computer)

3 major CMC regulatory compliance differences between biopharmaceuticals and chemical drugs, only upon market approval by the FDA

FDA differences are due to PHS Act vs FD&C Act

these differences are not in EMA market approval!

1) FDA Commercial Batch-to-Batch Biologic Product Release – 21 CFR Part 610.2

2) Identity Testing of Commercial Finished Drug Product After Labeling – 21 CFR Part 610.14

3) Extra 4-Letter 'Bioqualifier' Suffix Added by FDA to INN Assigned to Commercial Products

1) FDA Commercial Batch-to-Batch Biologic Product Release – 21 CFR Part 610.2

§ 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,

NOTE: FD&C Act does not require this for NDAs!
(QA solely determines batch release to commercial inventory)

FDA pre-release of Commercial Recombinant Proteins

automatic waiver granted by FDA since 1995!

Besremi (ropeginterferon alfa-2b-njft) 11/12/2021

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Besremi 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.

ASPARLAS (calaspargase pegol-mknl) 12/20/2018

FDA LOT RELEASE

You are not currently required to submit samples of future lots of ASPARLAS to the Center for Drug Evaluation and Research (CDER) for release by 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.

as stated in CDER market approval letters

FDA pre-release of Commercial Monoclonal Antibodies

automatic waiver granted by FDA since 1995!

ADBRY (tralokinumab-ldrm) 12/27/2021

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Adbry 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.

Blenrep – Belantamab Mafodotin-blmf (ADC) (August 05, 2020)

You are not currently required to submit samples of future lots of Blenrep to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2.

Reblozyl – Luspatercept-aamt (Fusion Protein) (November 2019)

You are not currently required to submit samples of future lots of REBLOZYL to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2.

Hulio – Adalimumab-fkjp (Biosimilar) (July 06, 2020)

You are not currently required to submit samples of future lots of Hulio to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2.

as stated in CDER market approval letters

FDA pre-release of Commercial Human Plasma-Derived Proteins depends!

Natural Proteins - YES

RYPLAZIM® (plasminogen, human-tvmh) June 4, 2021

FDA LOT RELEASE

Please submit 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).

Recombinant Proteins - NO

ESPEROCT [antihemophilic factor (recombinant), glycopegylated-exei] February 19, 2019

FDA LOT RELEASE

You are not currently required to submit samples or protocols of future lots of Antihemophilic Factor (Recombinant), GlycoPEGylated-exei 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.

as stated in CBER market approval letters

FDA pre-release of Commercial Recombinant Antigen (Protein) Vaccines required!

PREHEVBRIO [Hepatitis B Vaccine (Recombinant)] November 30, 2021

FDA LOT RELEASE

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).

AREXVY (Respiratory Syncytial Virus Vaccine, Adjuvanted) is a sterile suspension for intramuscular injection. The vaccine is supplied as a vial of lyophilized recombinant respiratory syncytial virus glycoprotein F stabilized in pre-fusion conformation (RSVPreF3) as the antigen

May 3, 2023

FDA LOT RELEASE

Please submit final container samples of the product in final containers together with protocols showing results of all applicable tests. Please submit 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).

as stated in CBER market approval letters

2) Identity Testing of Commercial Finished Drug Product After Labeling – 21 CFR Part 610.14

***Extra* Commercial Testing PHS Act Requirement**	***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 ID test after final labeling*)	***STILL IN EFFECT (2023)***

** note, this is not the required identity test for batch release of all pharmaceuticals*

NOTE: FD&C Act does not require this for NDAs!

21 CFR 610.14 Mandatory for Market Approval!

Idacio (Adalimumab-aacf) Monoclonal Antibody – Stated in Market Approval Letter (December 2022)

We remind you of your postmarketing commitments: To implement identity test(s) for final MSB11022 drug product assembled in prefilled syringe with the autoinjector devices after labeling and secondary packaging per 21 CFR 610.14. The final identity test and supporting information will be submitted to the BLA per 21 CFR 601.12.

Final report submission: June 2023

FDA Drug Databases: Drugs@FDA – FDA Approved Drug Products: Idacio (Adalimumab-aacf) – Approval History, Letters, Reviews and Related Documents – Market Approval Letter (December 13,2022); www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/761255Orig1s000ltr.pdf

Zolgensma (Onasemnogene Abeparvovec-xioi) Recombinant AAV Viral Vector – During FDA Late-Cycle BLA Meeting (March 18, 2019)

On February 6, 2019, you informed FDA inspectors that a single DP lot may be for … different markets. FDA inspectors informed you that each lot … of DP intended for the US market must be tested for identity after completion of labeling operations, to comply with 21 CFR 610.14. Please confirm that you will perform identity testing in this manner. Please submit to the BLA an updated labeling MBR. Discussion: FDA noted that identity testing should be performed on all lots and … after labeling.

The applicant stated that they will provide the requested information.

FDA Vaccines, Blood Products & Biologics – Cellular & Gene Therapy Products: Zolgensma (Onasemnogene Abeparvovec-xioi) – Approval History, Letters, Reviews, and Related Documents – Late-Cycle Meeting Memorandum (March 28, 2019); www.fda.gov/vaccines-blood-biologics/zolgensma

Filing the BLA without this required test can cause delay in market approval!

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)

3) Extra 4-Letter 'Bioqualifier' Suffix Added by FDA to INN Assigned to Commercial Products

"The Agency considers appropriate pharmacovigilance fundamentally important for biological products. Although safety of biological products is rigorously assessed before approval, safety issues that are specific to a manufacturer may arise after approval with any marketed product."

Biopharmaceutical Type	Commercial Biopharmaceutical Product		
	Brand Name	International Nonproprietary Name (INN)	Added Bioqualifier
Recombinant Protein	Palynziq	pegvaliase	-pqpz
Monoclonal Antibody	Enspryng	satralizumab	-mwge
Antibody-Drug Conjugate	Zynlonta	loncastuximab tesirine	-lpyl
Biosimilar mAb	Yusimry	adalimumab	-aqvh
	Hulio		-fkjp
	Hadlima		-bwwd
In Vivo AAV Viral Vector	Zolgensma	onasemnogene abeparvovec	-xioi
Genetically Modified Patient Cells	Breyanzi	lisocabtagene maraleucel	

FDA Guidance for Industry (GfI): Nonproprietary Naming of Biological Products (January 2017)

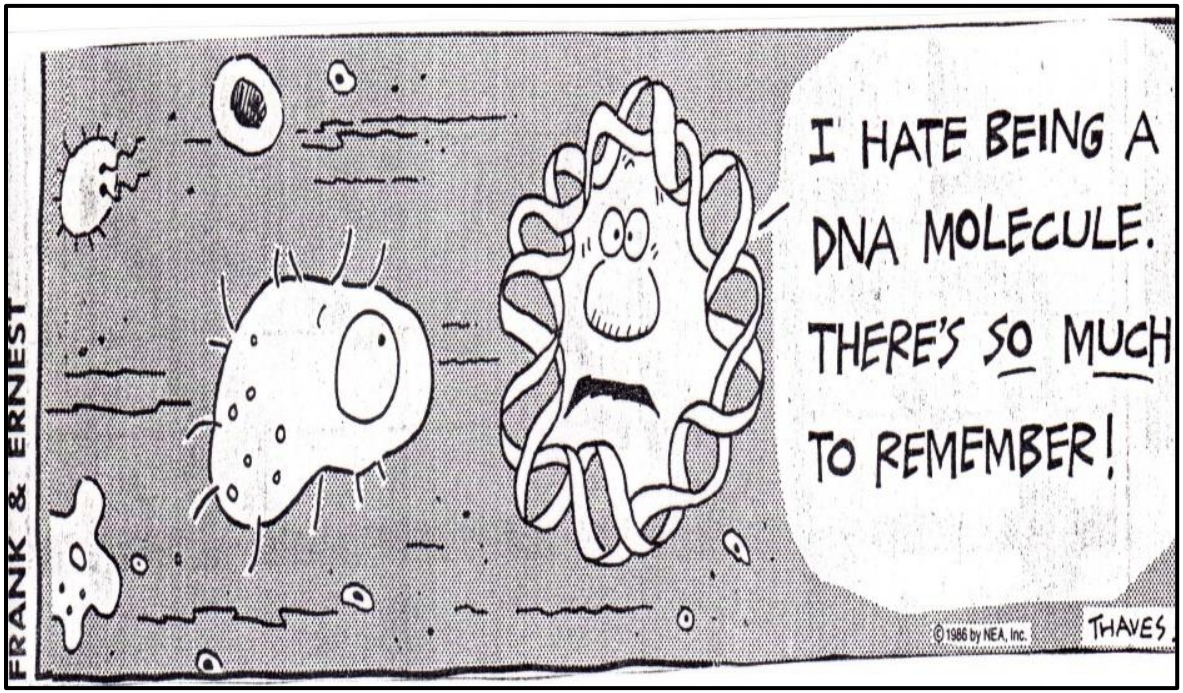
EMA does not use bioqualifiers

Summary: CMC Regulatory Compliance is Challenging for Recombinant Proteins and Monoclonal Antibodies

- ✓ ***Ever increasing diversity of the protein-based biopharmaceuticals***
- ✓ ***Regulatory authority systems are in place***

  FDA: IND → BLA EMA: IMPD → MAA

- ✓ ***Biopharmaceuticals are <u>NOT</u> regulated like chemical drugs***



Questions??

Course Outline

2. Risk-Based Approach to Managing the CMC Regulatory Compliance Strategy

- ***RBA: The 'minimum CMC regulatory compliance continuum'***
  - ***Applied to CMC Regulatory (what/when CMC content is required to be submitted to FDA/EMA)***
  - ***Applied to cGMPs (flexibility in level of risk-based manufacturing process control)***
  - ***Applied to Quality System (flexibility in amount of involvement)***
- ***QbD/QRM – the language of communicating the RBA CMC strategy to the regulatory authorities***

Patient Safety Risk – The Major Concern of the Regulatory Authorities

The safety and well-being of trial subjects (be they patients or healthy volunteers) should always be the priority and special consideration should be given to characterising risk and putting in place appropriate strategies to minimise risk. The guideline aims to address as far as possible the important issues that may need consideration during the process of designing a set of studies in a clinical development programme. As IMPs are widely different in their pharmacological features and intended use different parts of the guideline may be important for some and inapplicable to others.

Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products

20 July 2017
EMEA/CHMP/SWP/28367/07 Rev. 1

application (§ 312.23(a)(7)) (Refs. 1 through 6). FDA reviews the submitted IND to determine whether the phase 1 investigational drug to be used in the clinical trial is sufficiently safe to permit the trial to proceed. This determination is based, in part on whether the investigational product has the identity, strength, quality, and purity, and purported effect described in the IND application. In certain circumstances, FDA also may choose to conduct an inspection (e.g., if there is insufficient information to assess the risks to subjects or if the subjects would be exposed to unreasonable and significant risk). Finally, FDA could decide to place a proposed or ongoing phase 1 clinical trial on clinical hold or terminate the IND. FDA can also take any of these actions if there is evidence of inadequate QC procedures that would compromise the safety of an investigational product.

Guidance for Industry
CGMP for Phase 1 Investigational Drugs

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Office of Regulatory Affairs (ORA)

July 2008

Biopharmaceutical CMC Control

Necessity of a Risk-Base Approach (RBA)

The complexity involved with control of the biopharmaceutical manufacturing process coupled with control of the produced biopharmaceutical, introduces an abundance of CMC regulatory compliance risks, which need to be effectively managed.

- ***RISK: the combination of the probability that an event might occur and the degree of harm should that event occur***
- ***Every activity, every decision, every change, carries risk; but not all risks carry the same level of concern***
- ***A risk-based approach is necessary to sort through all of the identified risks, and then prioritize the risks so that the focus of limited resources can be applied to addressing and controlling the more critical identified risks***
- ***A risk-based approach does not mean doing less; but doing the right activities, to the extent necessary, at the right time!***

'good regulatory sense and good business sense'

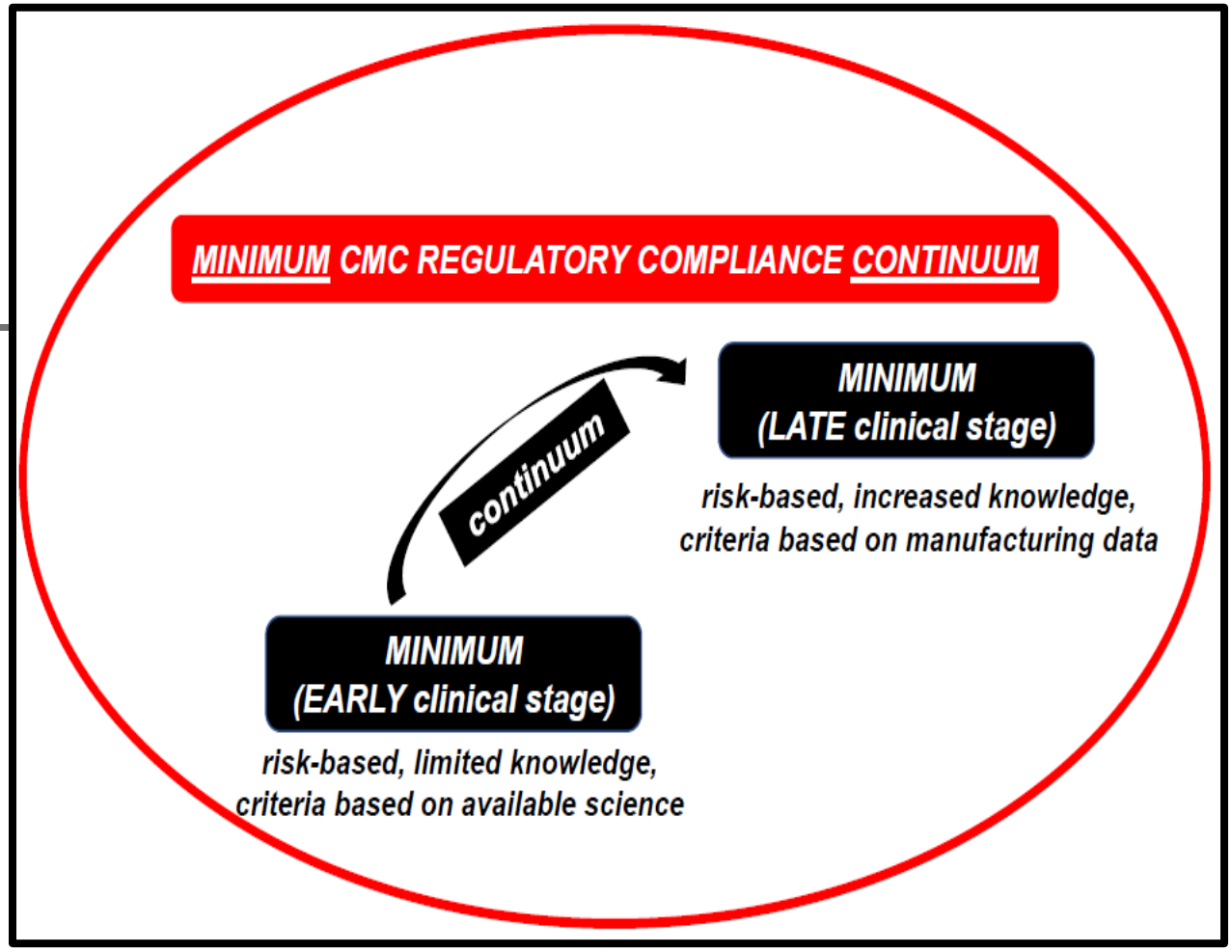
RBA

'Minimum' - 'the least quantity assignable.'

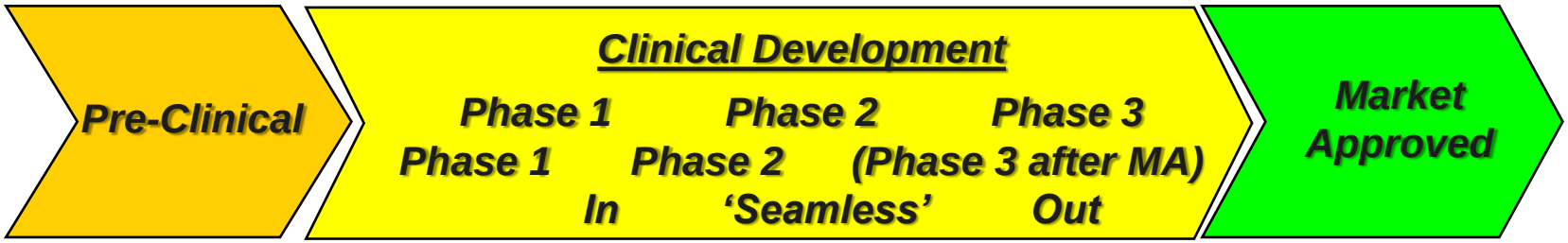
CMC regulatory compliance: a threshold of compliance that must be achieved – cannot go below – at given stages of clinical development.

'Continuum' - 'a coherent whole characterized as a progression of values varying by degrees.'

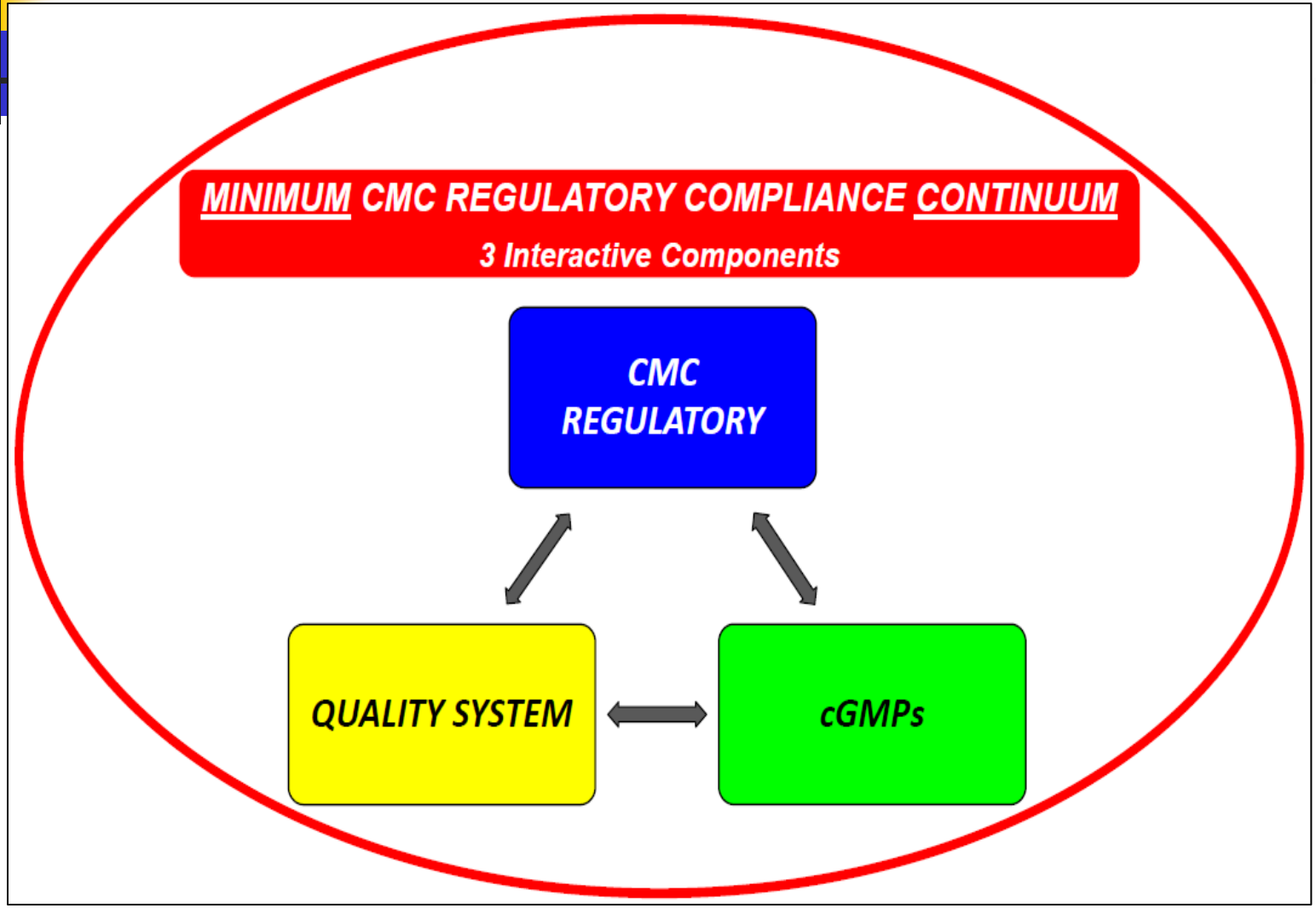
CMC regulatory compliance: the threshold of compliance that must keep rising as clinical development advances



also known as 'phase-appropriate' – but … Changing Nature of Clinical Studies



Three interactive CMC regulatory compliance components lead to an effective minimum CMC regulatory compliance continuum strategy



CMC Regulatory

CMC content to submit to regulatory authorities to independently access patient safety risk

Drug Substance (DS, API)	Drug Product (DP)
Manufacturer & Sites of Manufacture	Manufacturer & Sites of Manufacture
Manufacturing Process Description	Manufacturing Process Description
Manufacturing Process Controls	Manufacturing Process Controls
Source Material(s)	Excipients
Characterization of Product	Formulation
Release Testing of DS	Release Testing of DP
Stability Testing of DS	Stability Testing of DP
Adventitious Agent Control (TSE, Virus, Mycoplasma, Microbial)	

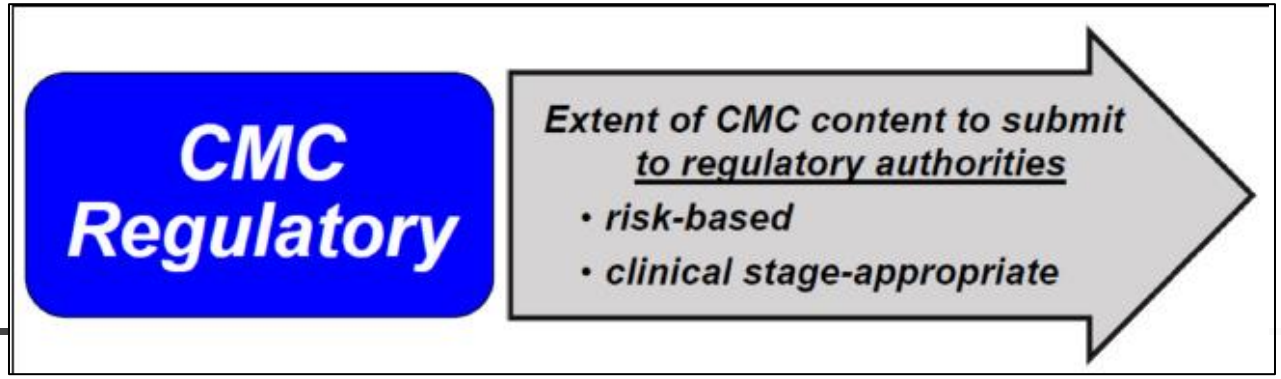
THE COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE: QUALITY

QUALITY OVERALL SUMMARY OF MODULE 2
MODULE 3 : QUALITY

ICH M4Q(R1)

PROTEIN-BASED BIOPHARMACEUTICALS
ICH website (www.ICH.org)
Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin Q5A(R2)
Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products Q5B
Quality of Biotechnological Products: Stability Testing of Biotechnological/ Biological Products Q5C
Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products Q5D
Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process Q5E
Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products ICH Q6B

… but how much and when?



(7) *Chemistry, manufacturing, and control information.* (i) As appropriate for the particular investigations covered by the IND, a section describing the composition, manufacture, and control of the drug substance and the drug product. Although in each phase of the investigation sufficient information is required to be submitted to assure the proper identification, quality, purity, and strength of the investigational drug, the amount of information needed to make that assurance will vary with the phase of the investigation, the proposed duration of the investigation, the dosage form, and the amount of information otherwise available. FDA

FDA CFR Code of Federal Regulations Title 21 – Part 312.23, IND Content and Format

In determining the content of the IMPD, a risk-based approach can be applied[2]. The content of the dossier can be adapted having regard to the identified risks. In particular, the applicant can perform at the beginning of product development an initial risk analysis based on existing knowledge on the type of product and its intended use. Aspects to be taken into consideration include the origin of the cells, the type of vector and/or the method used for the genetic modification, the manufacturing process, the non-cellular components and the specific therapeutic use as applicable.

The risk analysis should be updated by the applicant throughout the product life cycle as new data become available. Key points relevant to the understanding of the product development approach chosen, should be summarized in the IMPD.

EMA Guideline on Quality, Non-Clinical and Clinical Requirements for Investigational Advanced Therapy Medicinal Products in Clinical Trials (January 2019)

CMC Regulatory

‘minimum CMC regulatory compliance continuum’

Acknowledged by regulatory authorities during clinical development!

EUROPEAN MEDICINES AGENCY

Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials

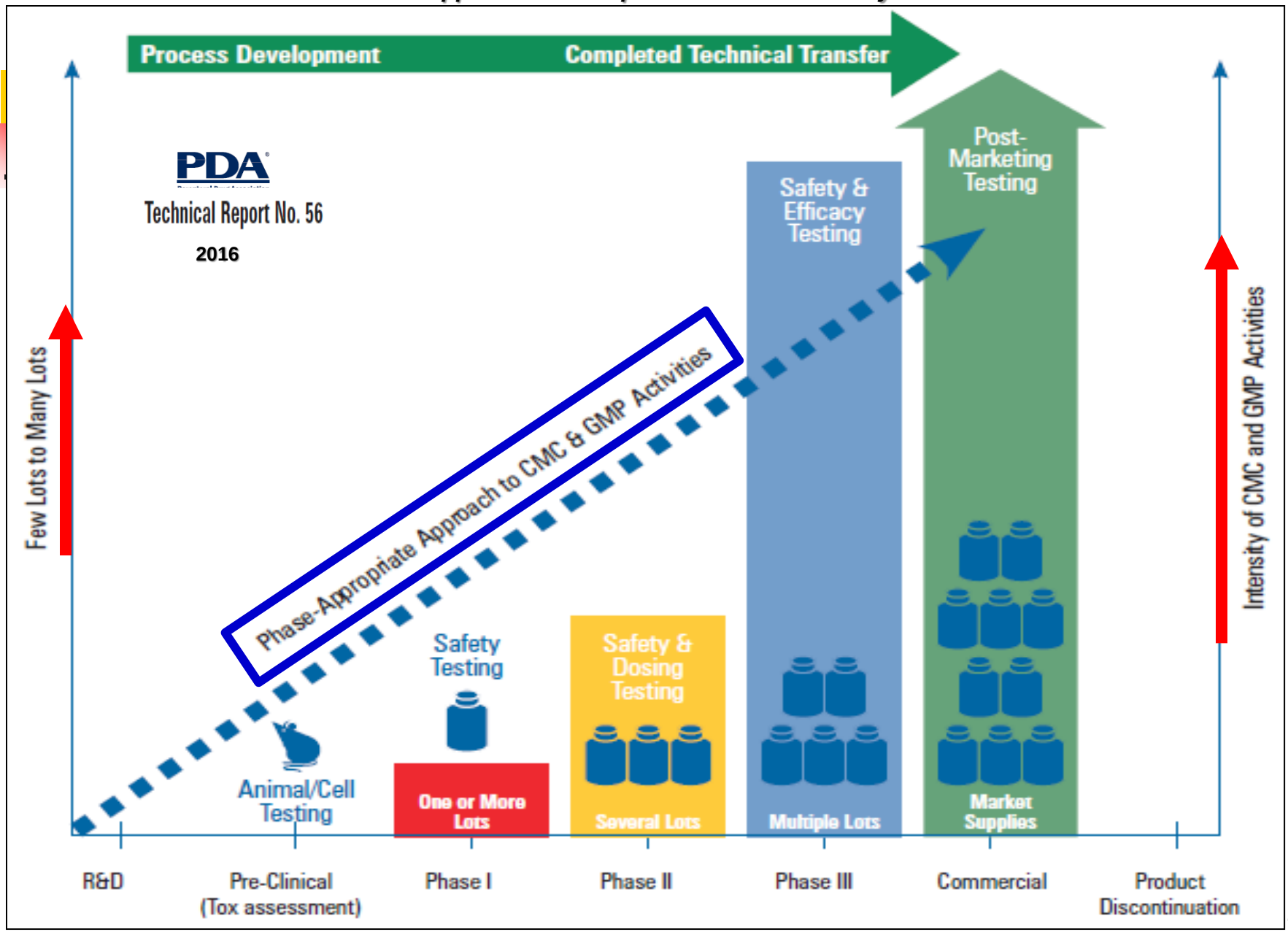
27 January 2022
EMA/CHMP/BWP/534898/2008 Rev. 2

IMPD CMC Section		EMA CMC Content Guideline for Protein-Based IMPDs
S.2.2 P.3.3	Description of Manufacturing Process and Process Controls	Since early development control limits are normally based on a limited number of development batches, they are inherently preliminary. During development, as additional process knowledge is gained, further details of IPCs should be provided and acceptance criteria reviewed.
S.2.6	Manufacturing Process Development	Manufacturing processes and their control strategies are continuously being improved and optimised, especially during the development phase and early phases of clinical trials.
S.3	Characterisation	Usually, prior to initiation of phase I studies, the biological activity should be determined using an appropriate, reliable and qualified method. Lack of such an assay should be justified. It is recognised that the extent of characterisation data will increase during development.
S.4.1 P.5.1	Specifications	As the acceptance criteria are normally based on a limited number of development batches and batches used in non-clinical and clinical studies, they are by their nature inherently preliminary and may need to be reviewed and adjusted during further development. Additional information for phase III clinical trials As knowledge and experience increases, the addition or removal of parameters and modification of analytical methods may be necessary. Specifications and acceptance criteria set for previous trials should be reviewed and, where appropriate, adjusted to the current stage of development.
S.4.3 P.5.3	Validation of Analytical Procedures	For phase I and II clinical trials, the suitability of the analytical methods used should be confirmed. For phase III clinical trials: Validation of the analytical methods provided

CMC Regulatory

'minimum CMC regulatory compliance continuum'

applied in the biopharmaceutical industry



cGMPs

Enforced regulatory requirements to ensure proper design, monitoring, and operation of the manufacturing facility, control over the manufacturing process, and appropriate handling and release of the product

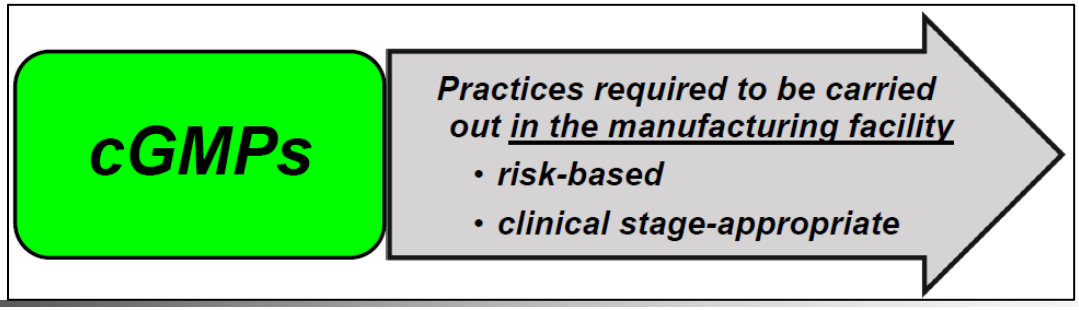
- ***Minimum requirements for patient safety***
- ***In effect from FIH (e.g., Phase 1) clinical studies onward***
- ***Not 'rocket-science' – common sense!***
- ***Basic GMPs***

Premises should be suitable for the operations to be carried out

- ✓ ***designed to minimize the opportunity for extraneous contamination, cross-contamination, the risk of errors***
- ✓ ***kept clean (disinfection to be applied as appropriate)***
- ✓ ***carefully maintained***
- ✓ ***…***

Process equipment should be suitable for its intended purpose

- ✓ ***Product contact surfaces should not have unwanted reactive properties***
- ✓ ***Location and installation should be adequate to minimize risks of errors or contamination***
- ✓ ***adequately maintained and cleaned to avoid the risk of contamination***
- ✓ ***…***



The CGMP requirements were established to be flexible in order to allow each manufacturer to decide individually how to best implement the necessary controls by using scientifically sound design, processing methods, and testing procedures. The flexibility in these regulations allows companies to use modern technologies and innovative approaches to achieve higher quality through continual improvement. Accordingly, the "C" in CGMP stands for "current," requiring companies to use technologies and systems that are up-to-date in order to comply with the regulations. Systems and equipment that may have been "top-of-the-line" to prevent contamination, mix-ups, and errors 10 or 20 years ago may be less than adequate by today's standards.

FDA website **Facts About the Current Good Manufacturing Practices**

The controls used in the manufacture of APIs for use in clinical trials should be consistent with the stage of development of the drug product incorporating the API. Process and test procedures should be flexible to provide for changes as knowledge of the process increases and clinical testing of a drug product progresses from pre-clinical stages through clinical stages. Once drug development reaches the stage where the API is produced for use in drug products intended for clinical trials, manufacturers should ensure that APIs are manufactured in suitable facilities using appropriate production and control procedures to ensure the quality of the API.

ICH Q7 GOOD MANUFACTURING PRACTICE GUIDE FOR ACTIVE PHARMACEUTICAL INGREDIENTS 19. APIs FOR USE IN CLINICAL TRIALS

FDA: General guidance on flexible risk-based cGMPs during early clinical stage development

Consistent with the FD&C Act (§ 501(a) (2) (B)), CGMP must be in effect for the manufacture of each batch of investigational drug used during phase 1 clinical trials. Manufacturers should establish manufacturing controls based on identified hazards for the manufacturing setting that follow good scientific and QC principles. The following manufacturing controls are applicable to the manufacture of phase 1 investigational drugs and in some specific manufacturing situations. These recommendations provide flexibility to the manufacturers in implementing CGMP controls appropriate to their specific situation and application.

Adherence to CGMP during manufacture of phase 1 investigational drugs occurs mostly through:

- **Well-defined, written procedures**
- **Adequately controlled equipment and manufacturing environment**
- **Accurately and consistently recorded data from manufacturing (and testing)**

A number of technologies and resources are available that can facilitate conformance with CGMP and streamline product development. Some examples include: Use of disposable equipment and process aids to reduce cleaning burden and chances of contamination; Use of commercial, prepackaged materials (e.g., Water For Injection (WFI), pre-sterilized containers and closures) to eliminate the need for additional equipment or for demonstrating CGMP control of existing equipment; Use of closed process equipment (i.e., the phase 1 investigational drug is not exposed to the environment during processing) to alleviate the need for stricter room classification for air quality; Use of contract or shared CGMP manufacturing facilities and testing laboratories (including specialized services).

FDA **Guidance for Industry CGMP for Phase 1 Investigational Drugs** **July 2008**

QUALITY SYSTEM

The management systems that ensure appropriate documentation and quality control of the manufacturing process and the product release, including detecting and investigating process and product deviations

- ***'Checks and Balances' – to ensure that CMC Regulatory commitments are carried out and that cGMPs are followed***

During product development, the quality and safety of phase 1 investigational drugs are maintained, in part, by having appropriate QC procedures in effect. Using established or standardized QC procedures and following appropriate CGMP will also facilitate the manufacture of equivalent or comparable IND product for future clinical trials as needed.

FDA — **Guidance for Industry** — **CGMP for Phase 1 Investigational Drugs** — **July 2008**

Three key aspects of the Quality Unit (QA/QC)

1) Quality Unit independence from Manufacturing

Although quality is the responsibility of all personnel involved in manufacturing, we recommend that you assign an individual(s) to perform QC functions independent of manufacturing responsibilities, especially for the cumulative review and release of phase 1 investigational drug batches.

---

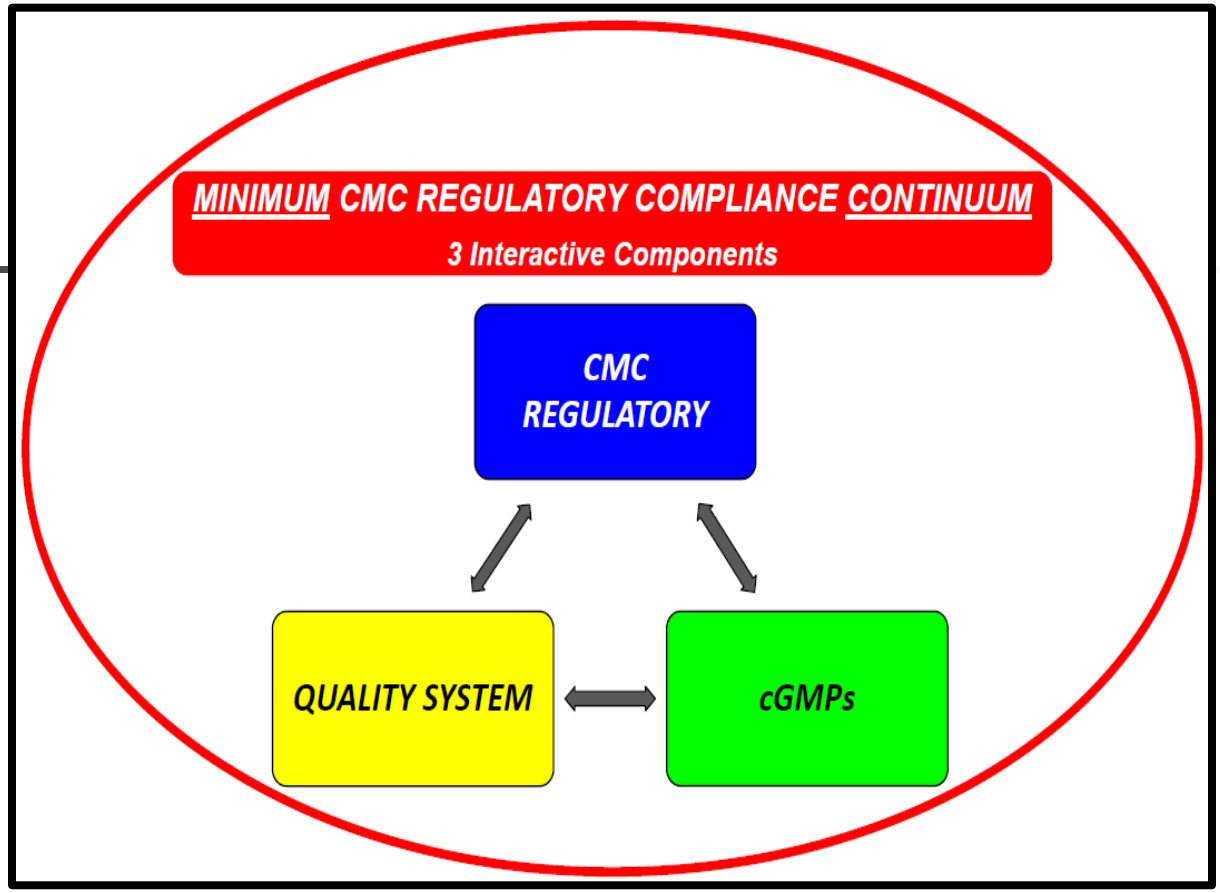
[8] For some manufacturers, the Quality Control Function as described in this guidance may be assigned between a quality control and quality assurance group and may be integrated into a more comprehensive quality system.

FDA — **Guidance for Industry** — **CGMP for Phase 1 Investigational Drugs** — **July 2008**

2) Quality Unit has a critical role to ensure effective training is carried out (in 4 areas)

1) All personnel should receive training on the principles of GMP that affect them and receive initial and periodic training relevant to their tasks.
2) There should be appropriate (and periodic) training in the requirements specific to the manufacturing, testing, and traceability of the product.
3) Personnel working in clean areas should be given specific training on aseptic manufacturing, including the basic aspects of microbiology. Prior to participating in routine aseptic manufacturing operations, personnel should participate in a successful process simulation test.
4) In addition, there should be appropriate training to prevent the transfer of communicable diseases from biological raw and starting materials to the operators and vice versa.

3) Quality Unit needs 'backbone' – standup respectfully to senior management – the QU is the last safety defense for the patient!



Case Examples

How it should work – Roche video →

Perfect storm – Emergent BioSolutions

The Perfect Storm

- *Inadequate cGMP*
- *Lack of appropriately trained operators*
- *Dominant senior management/ weak QU*

Emergent enters into multi-product manufacturing
J&J – human AV
AZ – chimp AV

March 2021 J&J informs FDA that AZ's chimp virus was found in their human virus vaccine

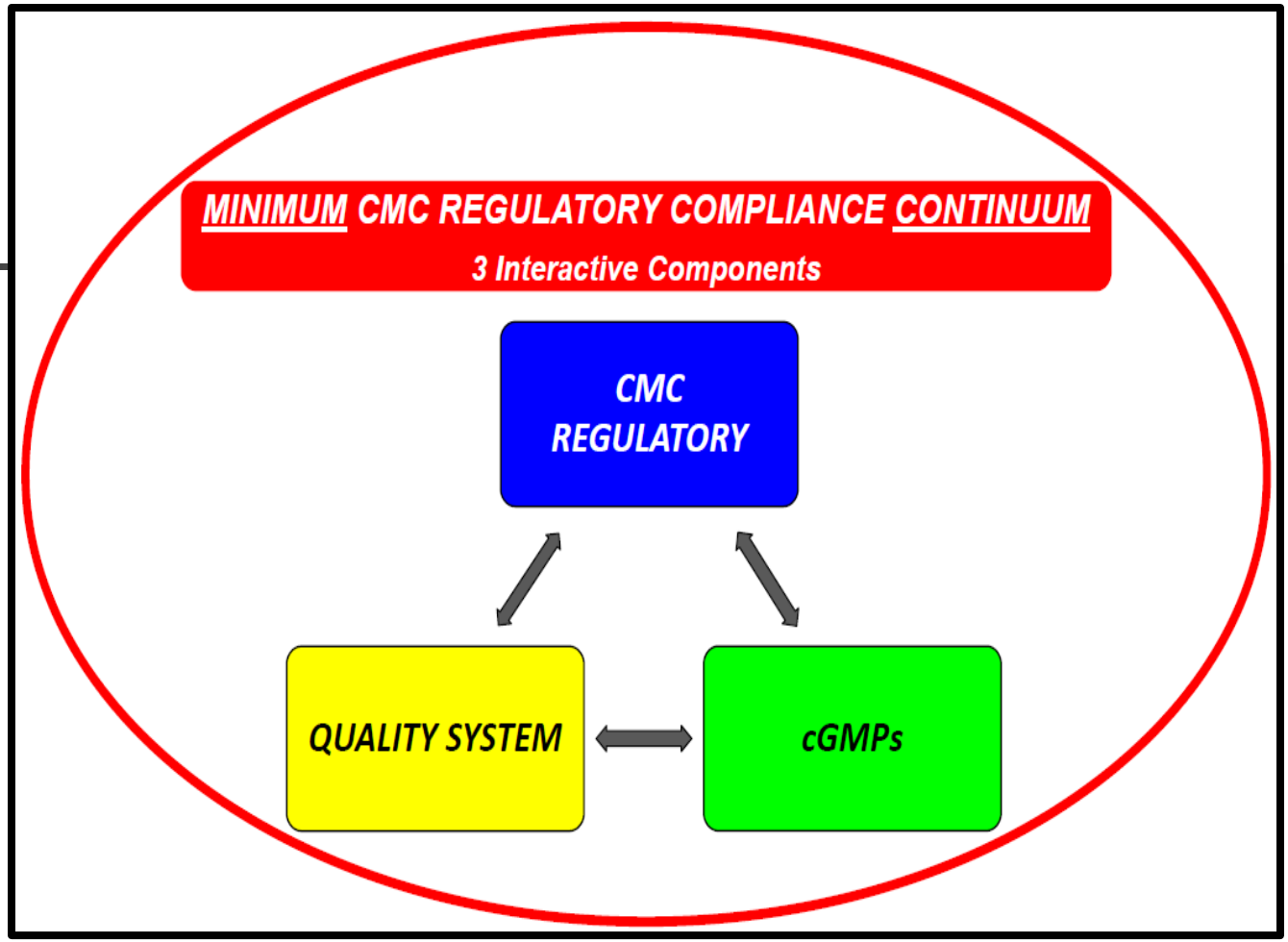
400 million doses of J&J vaccine destroyed

Emergent executives promoted the company's manufacturing capabilities despite being warned of severe deficiencies. Documents obtained by the Committees reveal that before Emergent finalized manufacturing agreements with Johnson & Johnson and AstraZeneca, Emergent's then-Executive Vice President of Manufacturing and Technical Operations privately acknowledged that he had warned Emergent senior executives "for a few years" about the company's deficient quality systems, including that "room to improve is a huge understatement." Despite these internal warnings, Emergent entered into contracts with Johnson & Johnson and AstraZeneca to manufacture coronavirus vaccines for $482 million and $174 million, respectively. After manufacturing started, internal Emergent communications reveal that the Senior Director of Quality at the Bayview manufacturing facility stated, "Our risk is high!" and, "we lack commercial GMP [good manufacturing practices] compliance maturity."

FDA, Johnson & Johnson, and AstraZeneca identified multiple deficiencies at Bayview, which Emergent failed to remediate despite urgent warnings. Documents reveal that the Trump Administration was aware, prior to awarding the contract in May 2020, of serious deficiencies at Emergent's Bayview facility that could impact manufacturing. In July 2020, AstraZeneca personnel raised concerns to Emergent about the need to remediate these deficiencies before starting manufacturing, noting that they were "concerned that the FDA observation was that Emergent isn't prepared for commercial manufacturing as things stand currently, and yet we will start commercial manufacture [sic] there very soon." Internal Johnson & Johnson communications from October 2020 show that Emergent had struggled to maintain quality standards and that it was "unclear" if the site was ready for commercial manufacturing and to "effectively manage all the remediation efforts." An outside consultant to Emergent provided a stark warning in November 2020 with regards to manufacturing: "I am stating very loudly that this work is NON-CGMP compliant. And a direct regulatory risk."

Inexperienced staff and high staff turnover contributed to vaccine contamination. The investigation revealed that Emergent acknowledged in July and August 2020 that their staff were insufficiently trained, noting that "most temporary employees [have] little or no pharmaceutical experience." In November and December 2020, following persistent issues with contamination, AstraZeneca sent teams to Bayview because Emergent "lacked the appropriate level of knowledge or expertise." Ultimately, AstraZeneca concluded that "poor cleaning was part of the root cause."

U.S. House Committee on Oversight and Reform: Committees' Report on Emergent BioSolutions Uncovers Extensive Vaccine Manufacturing Failures, Deliberate Efforts to Hide Deficiencies (May 2022);

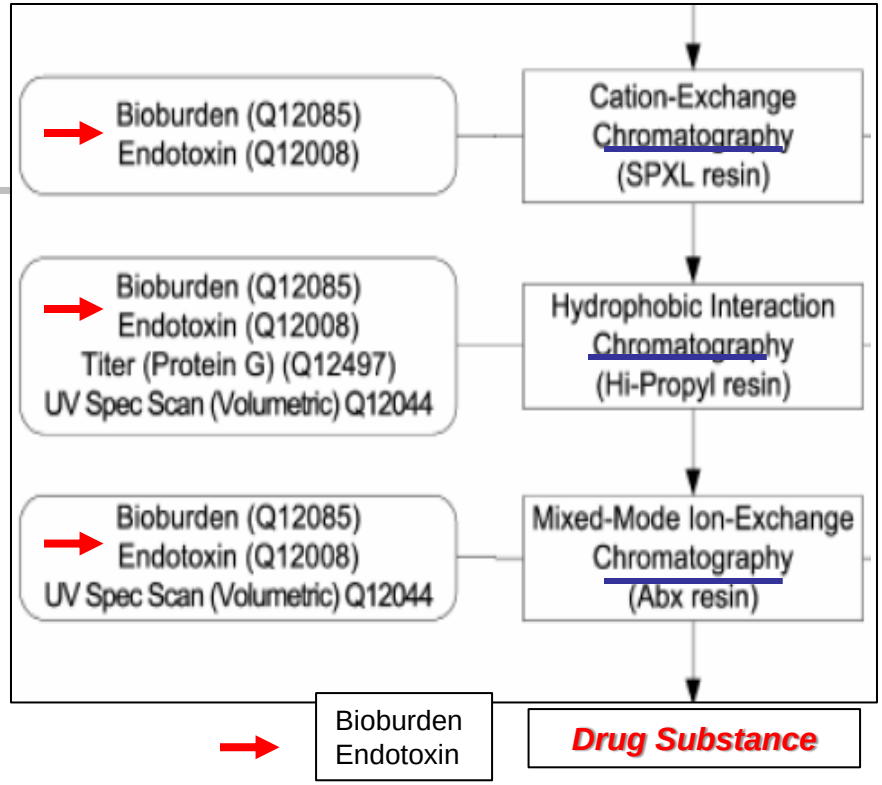


Caution with Risk-Based Approaches (RBAs): ***Relevant Experience Needed!***

Illustration of Establishing Acceptable Risk Level

Question Posed to CMC Team

Why does QC need to test for bioburden/endotoxin at each purification step? Is that cost effective? Why not just test only at the Drug Substance stage?

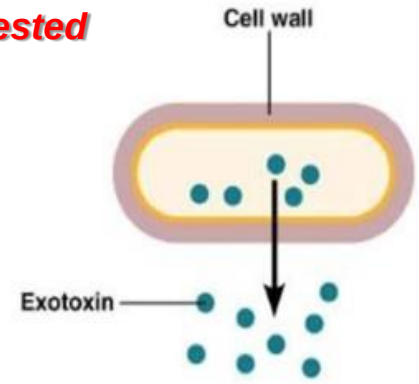


Risk Assessment (QA/ QC/ Mfg/ Dev/ Reg Affairs):

- ***highest severity if we only test at the DS?***
- ***statistical probability that a problem/ patient harm could occur?***
- ***perceived probability that a problem/ patient harm could occur?***

What possible problem/ patient harm could occur?

not tested



Exotoxins are produced and released by gram-positive bacteria as part of their growth and metabolism.

Staphylococcus aureus can release toxins that cause cytokine toxic shock syndrome

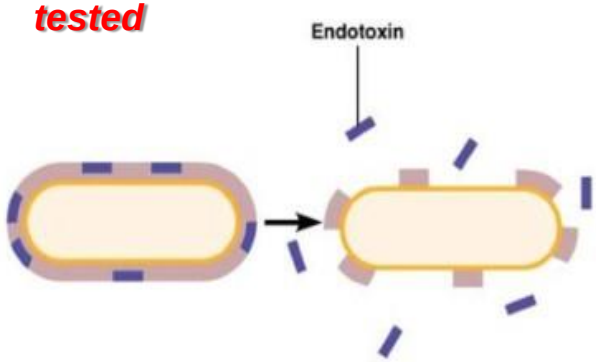
QC only tests for that which is expected to be present!

Bioburden/endotoxin testing serves as a monitor for what we don't or can't test for!

Might we miss a high level of excreted exotoxins at an in-process purification step if not bioburden/endotoxin tested?

(patient safety)

tested



Endotoxins are a portion of the outer cell wall of gram-negative bacteria. As bacteria die, the cell wall breaks apart and endotoxins are released.

Might we miss a high level of excreted peptidases at an in-process purification step if not bioburden/endotoxin tested?

(shelf life instability)

Regulatory authorities usually have a scientific reason/experience behind what they expect a manufacturer to do!

ICH harmonisation for better health

International Council for Harmonisation

USA/EU/Japan + 15 other members + 20 observers

Two Strategic Risk-Based Quality Approach Guidelines

ICH Q8(R2) Quality by Design (QbD) 2006

"to design a manufacturing process to consistently deliver the intended performance of the product"

Quality by Design (QbD):

A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

From a strategic viewpoint, how important is your Process Development and Analytical Development groups in the development of the biological manufacturing process?

Cell line development in preparation of a MCB
Cell culture optimization for enhancing productivity
Process purification design in controlling the impurity profile
Characterization of the product to understand its functionality
Selection/development of relevant and appropriate test methods

Do they understand that what they do impacts clinical development or market approval?

Two Strategic Risk-Based Quality Approach Guidelines

ICH Q9(R1) Quality Risk Management (QRM) 2023

Quality Risk Management:

A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle.

From a strategic viewpoint, how important is it to identify and then seek to mitigate risks that could impact the development of the biological manufacturing process?

QRM project management tools	QRM statistical analysis tools
Risk Ranking and Filtering (RRF) Failure Mode Effects Analysis (FMEA) Preliminary Hazard Analysis (PHA)	Control Charts (Shewhart) Process Capability Analysis (Cpk) Design of Experiments (DOE) →

OFAT – 'one factor at a time'

works for simple processes – chemical drug synthesis

2 Levels

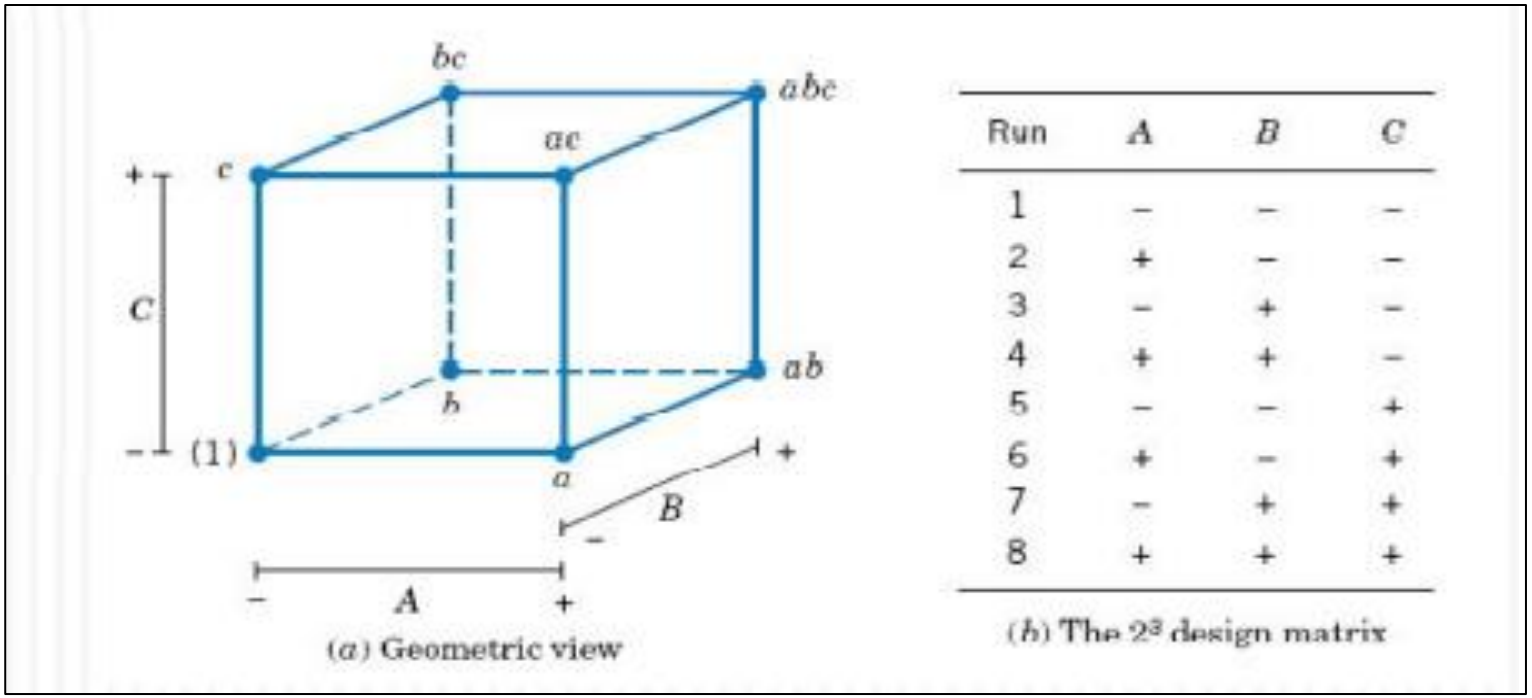
low
high

3 Process Parameters

temperature
pressure
duration

Chemical Synthesis Vessel L^{PP}

Levels (L)	Process Parameters (PP)	OFAT runs (total number
2	3	8



(a) Geometric view

Run	A	B	C
1	−	−	−
2	+	−	−
3	−	+	−
4	+	+	−
5	−	−	+
6	+	−	+
7	−	+	+
8	+	+	+

(b) The 2^3 design matrix

DOE – 'Design of Experiments'

critically needed for complex processes – biopharmaceutical production

2 Levels

low
high

9 Process Parameters

starting seed density
air/gas sparging rate
feed composition
feed concentration
duration after induction
feed rate
agitation rate
temperature
pH

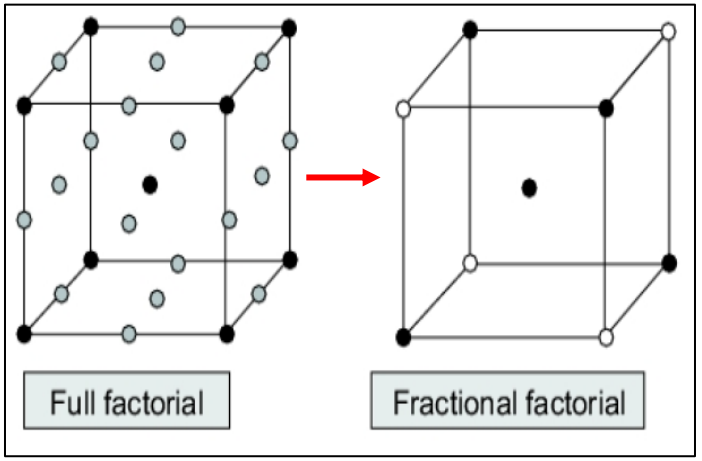
PDA TR 60-3 Process Validation (2021)

Biopharmaceutical Bioreactor

L^{PP}

Levels (L)	Process Parameters (PP)	OFAT runs (total number
2	9	512

No lack of DOE instructional videos on YouTube



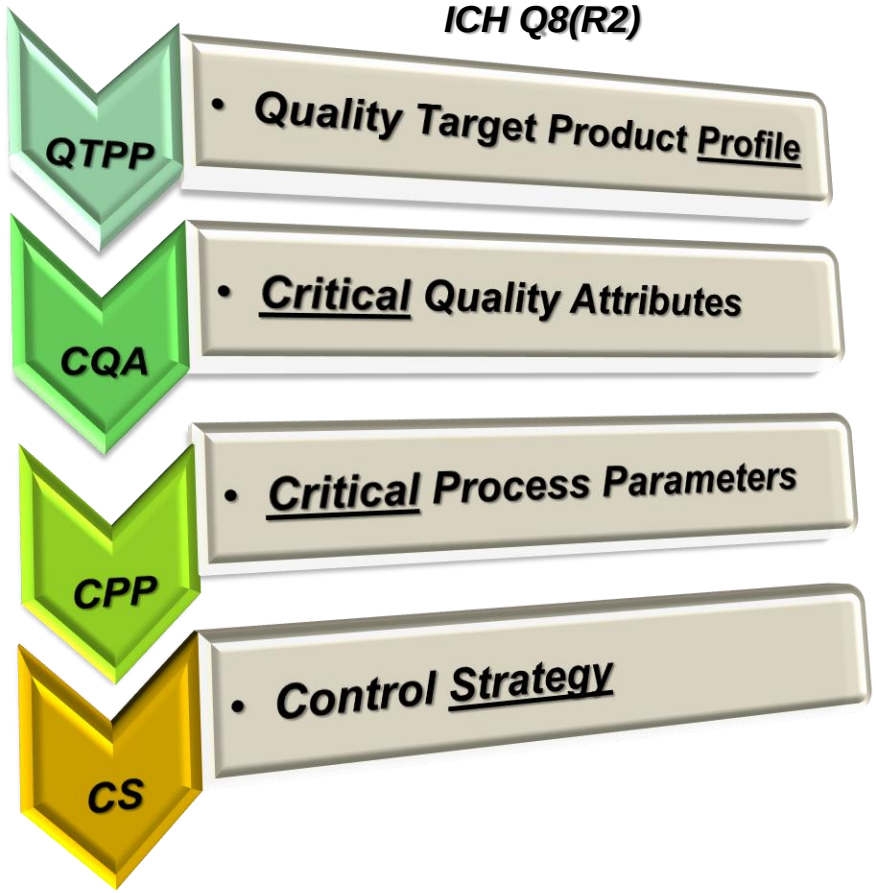
Will you get full understanding of the manufacturing process with DOE?

Can you get adequate understanding of the manufacturing process with DOE?

Regulatory Authority recommended Risk-Based Approach (RBA) to establish an adequate and appropriate control strategy for manufacture of the CGT product

Quality by Design (QbD)

ICH Q8(R2)



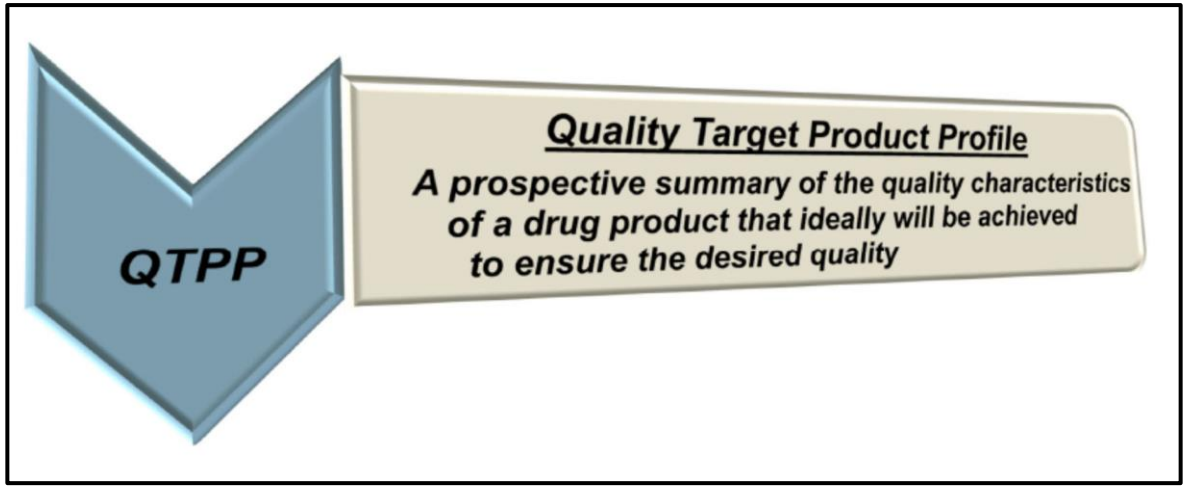
Quality Risk Management (QRM)

ICH Q9(R1)

The 'language' of the regulatory authorities

Target Product Profile (TPP) – the company's **strategic vision** of its **future commercial drug product**

(why the product is so great; why you should invest in the company)



ICH Q8(R2)

The QTPP – a project management tool – to guide the direction of development
(shared by all CMC disciplines: Development, Manufacturing, QC, QA, Reg Affairs)

The QTPP – a living document, subject to change as the TPP shifts

What guidance does this QTPP communicate to the CMC team?

MONOCLONAL ANTIBODY	
Target Product Profile (TPP)	
Indication	N-mab is a humanized IgG1 antibody intended as a treatment for indolent non-Hodgkin's Lymphoma (NHL) in an adult population
Mechanism of Action (MOA)	The mechanism of action for N-mab is through binding to a tumor cell surface antigen, Lymph-1, and stimulating B cell killing.
Route of Administration	Initial: IV administration Future: SC injection
Quality Targe Product Profile (QTPP)	
Dosage Form	Sterile liquid formulation Initial: single-use glass vial Future: single-use glass syringe
Dosage Strength	1 mL Initial: 75 mg/mL Future: 150 mg/mL
Shelf-Life	2-3 year stability refrigerated 2-4 week stability at room temperature
CQAs to Control	Glycosylation (N-glycans) Deamidation (Asn325) Aggregation Residual HCP impurity

CASE EXAMPLE

A Quality Target Product Profile (QTPP) as described by the ICH Guideline Q8 (R2) was defined to ensure that the safety and efficacy of Jemperli could be maintained as described in the Target Product Profile (TPP). The QTPP for the finished product was refined over time and was used to guide the product development effort to satisfy clinical and commercial requirements.

a living document

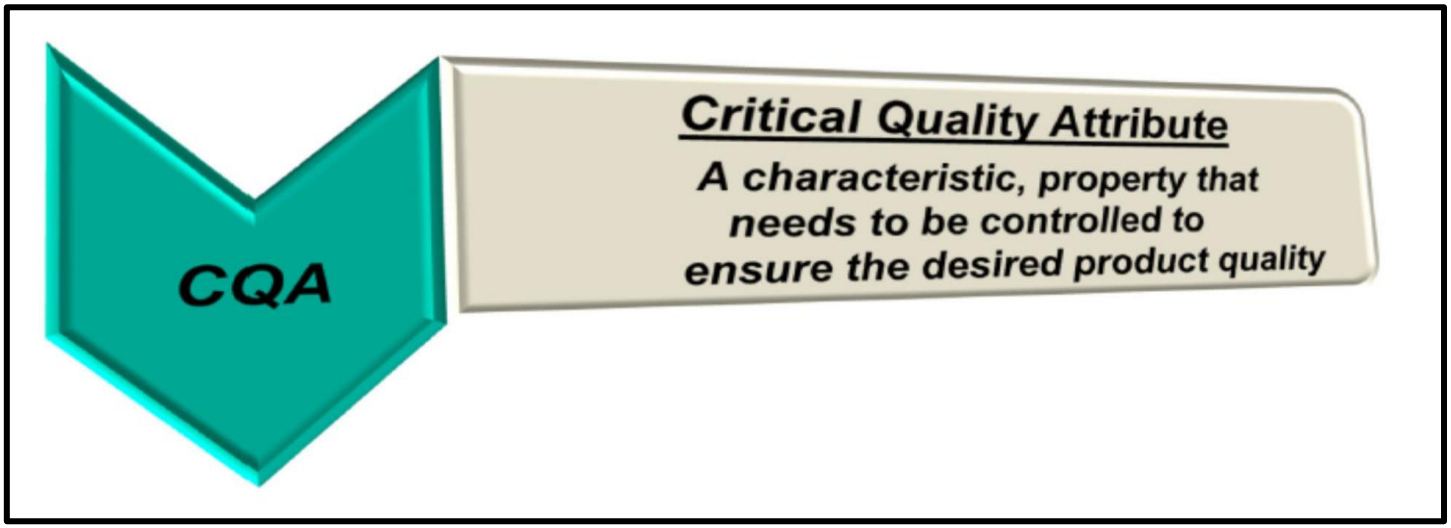
Jemperli dostarlimab GlaxoSmithKline EPAR 25 February 2021 EMA/176464/2021

***Quality Attribute (QA)* – a physical, chemical, biological or microbiological *property or characteristic* of the product**

impact on patient safety

(changeable, not static, as scientific understanding about the product increases)

ICH Q8(R2)

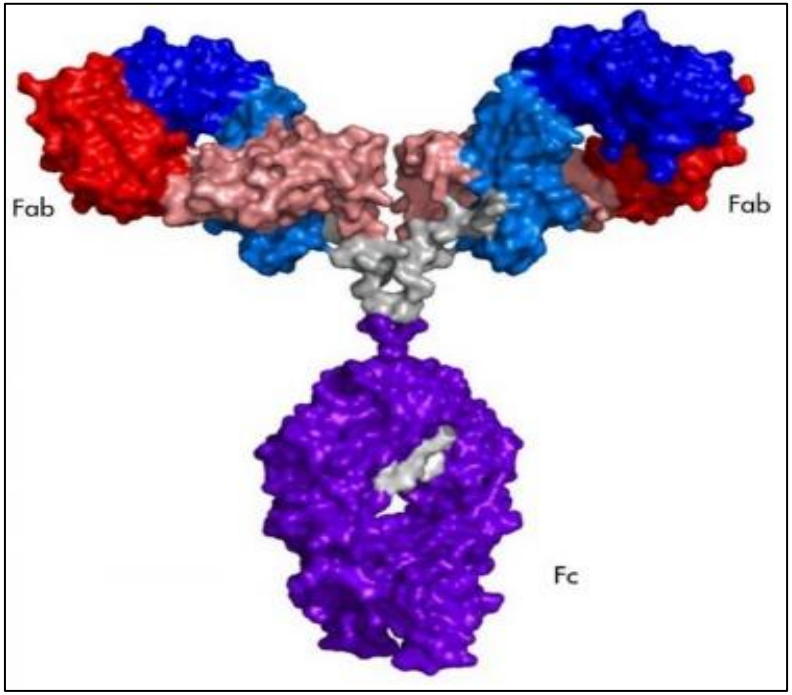


CQA – forces the focus onto those properties or characteristics of the product that are most important – especially those that are related to patient safety!

3 Step Process: Determining which QA's are CQA's

Step 1 of 3: Identify ALL Quality Attributes (QAs)

monoclonal antibody



How many Quality Attributes (QA's) can you identify?

properties/characteristics

breakout

read & fill-in table

TEAM DISCUSS

Quality Attributes (QA's) of a mAb	
MOLECULAR PROPERTIES	**FUNCTIONAL ACTIVITY (COMPENDIAL CQAs)**
Isoelectric Point Molecular Weight Molecular Size Molecular Charge Profile	Biological Activity(ies) Immunochemical Binding(s)
PRIMARY AMINO ACID SEQUENCE & AMINO ACID VARIANTS	**PRODUCT QUALITY (COMPENDIAL CQAs)**
Amino Acid Sequence C-Terminal Sequence(s) N-Terminal Sequence(s) Internal Sequence Variants Disulfide Bridges	Visual Appearance (Color, Clarity) Protein Content Osmolality pH Dose Form (Liquid – Extractable Volume Lyophilized – Residual Moisture)
HIGHER ORDER STRUCTURES (HOS)	**SAFETY (COMPENDIAL CQAs)**
Secondary Structure Tertiary Structure Quaternary Structure Thermodynamic Properties Aggregation	Absence of Adventitious Agents (Virus, Mycoplasma) Bacteria, Fungi Control (DS – Bioburden; DP – Sterility) Endotoxin Particulate Matter
GLYCOSYLATION SITES & VARIANTS	**PROCESS-RELATED IMPURITIES**
N-Glycosylation Site(s) Site Occupancy N-Glycan Profile(s) Sialylated Glycans	Host Cellular DNA Host Cell Proteins (HCPs) Upstream Residuals Downstream Residuals

'compendial' = obligatory

3 Step Process: Determining which QA's are CQA's

Step 2 of 3: Rank ALL QA's for 'Level of Criticality'

- **Risk Ranking & Filtering (RRF)**

  RISK SCORE = Impact Risk level x Uncertainty Risk level

  Impact Risk: 1 → n highest level (n can be 3,10, 20, or …)

  Uncertainty Risk: 1 → n highest level (n can be 3, 10 or …)

- **Failure Modes & Effect Analysis (FMEA)**

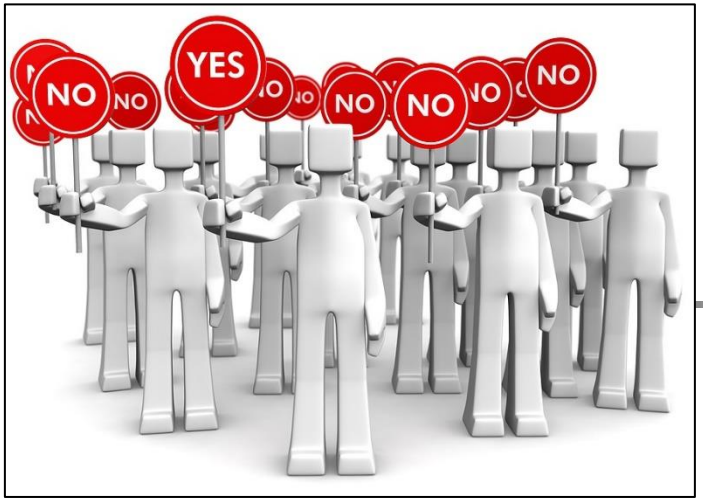
  RISK PROFILE NUMBER = Likelihood of Occurrence Risk level
  x Severity Risk level x Likelihood of Detection Risk level

  Likelihood of Occurrence Risk: 1 → 10 highest level

  Severity Risk: 1 → 10 level highest level

  Likelihood of Detection Risk: 1 → 10 level highest level

This is the most difficult step!



What is the <u>weakest link</u> in assigning level of criticality?

<u>Selection of the multi-discipline team</u>
(Development, Manufacturing, QC, QA, RA, etc.)
to decide the <u>consensus</u> on each level of risk assignment

Wrong staff involved (e.g., incompetent, inexperienced)
– wrong outcome!

- ***SUBJECTIVITY can impact every stage of a quality risk management process, especially the identification of hazards and estimates of their probabilities of occurrence, the estimation of risk reduction and the effectiveness of decisions made from quality risk management activities.***
  - ***Subjectivity can be introduced in quality risk management through differences in how risks are assessed and in how hazards, <u>harms and risks are perceived by different stakeholders</u>.***
  - ***Subjectivity can also be introduced through the use of tools with <u>poorly designed risk scoring scales</u>.***
- ***While subjectivity cannot be completely eliminated from quality risk management activities, it may be controlled by addressing bias, the proper use of quality risk management tools and maximising the use of relevant data and sources of knowledge.***
  - ***<u>ALL</u> participants involved with quality risk management activities should acknowledge, anticipate, and address the potential for subjectivity.***

ICH Q9 (R1)

If you want more than a thick book sitting on a shelf,
provide adequate resources and knowledgeable people to carry out the task!

3 Step Process: Determining which QA's are CQA's

Step 3 of 3: Set Risk Score threshold for 'Critical'

MONOCLONAL ANTIBODY Risk Ranking and Filtering CQA RISK ASSESSMENT			
Product Quality Attribute	**Impact**	**Uncertainty**	**Risk Score**
Non-Glycosylated Heavy Chain	16	5	80
High Mannose Content	16	5	80
Sialic Acid Content	12	5	60
Afucosylation	20	3	60
Aggregation	12	5	60
Galactose Content	16	3	48
Residual Host Cell Proteins	12	3	36
CQA ↑		**Non-CQA ↓**	
Residual Protein A	16	1	16
Residual Methotrexate	16	1	16
Oxidation	4	3	12
Residual Host Cellular DNA	2	3	6
C-Terminal Lysine	2	2	4
Deamidated Isoforms	2	2	4

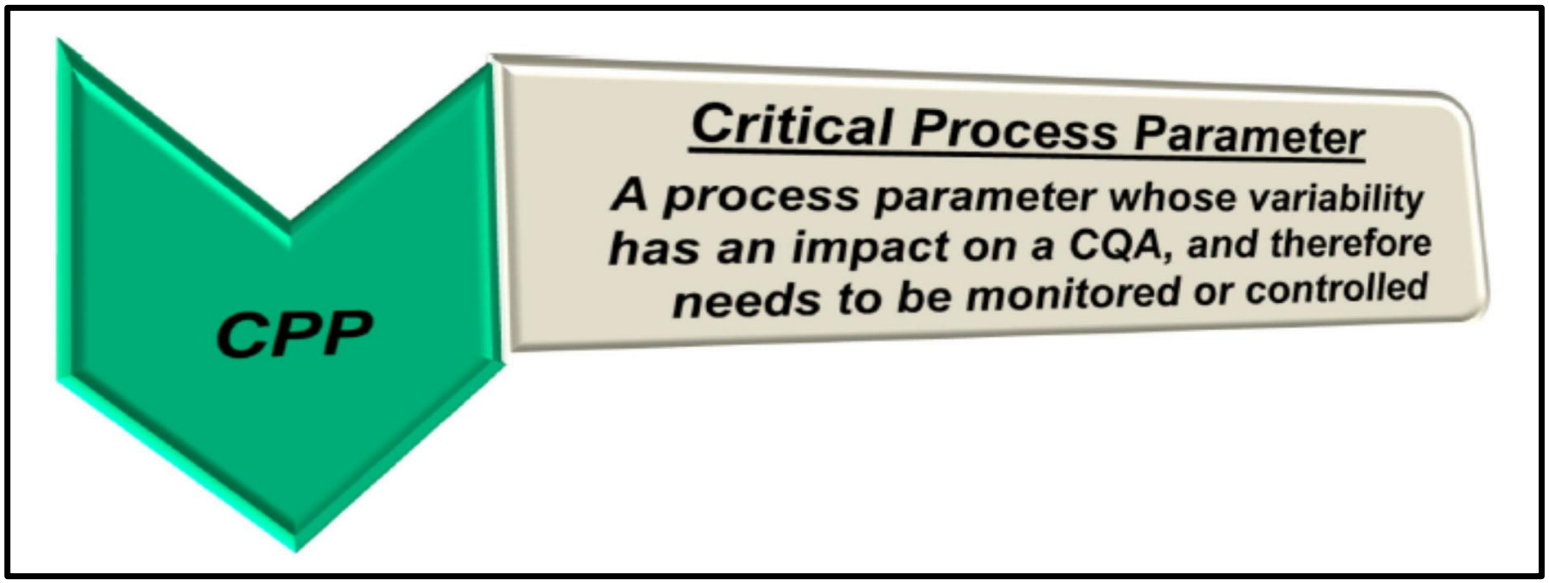
National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL): N-mAb – A Case Study to Support Development and Adoption of Integrated Continuous Bioprocesses for Monoclonal Antibodies (June2022); www.niimbl.org/Downloads/N-mAb/N-mAb_Version1.pdf

Process Parameter (PP) – an element of manufacturing process control

impact on CQAs

(changeable, not static, as scientific understanding about the process increases)

ICH Q8(R2)



CPP – forces the focus onto those manufacturing process parameters that are most important – especially those that are related to CQA control!

3 Step Process: Determining which PP's are CPP's

Step 1 of 3: Identify ALL PPs

Each manufacturing process has many process steps …

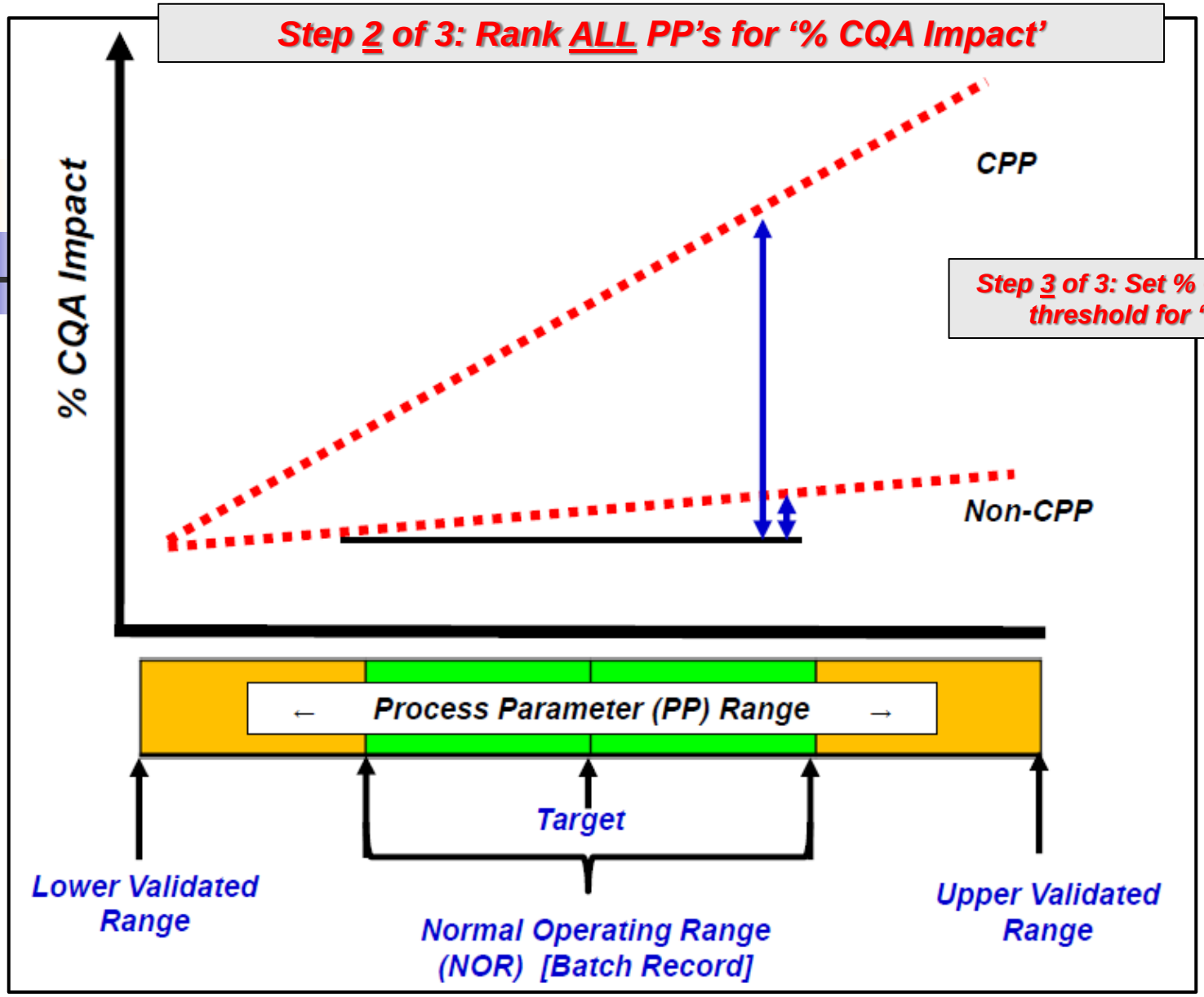
Each process step has many sub-steps …

Each sub-step has many PPs

CEX → **ELUTION**

process step	process sub-steps	process parameters (PPs)
Fixed Design	Sanitization	Process Parameters
Column Resin	Neutralization	Maximum Product Load
Bind/Elute	Equilibration	Column Length
	Loading	Eluent Composition
	Wash	Eluent pH
	Elution →	Eluent Flow Rate
	Strip	Peak Collection Start
	Equilibration	Peak Collection End
	Storage	

7 PPs for 1 sub-step of 1 process step



A must read before attempting a CQA impact study is an updated and improved mathematical approach to determining the impact ratio (i.e., the degree of change on a CQA) published by Hoffmann-La Roche/Genentech – Lamerz,J, et. al, in the PDA Journal of Pharmaceutical Science and Technology, 2022; 76(6), 497-508

Additional Guidance on Identifying CPPs for Monoclonal Antibodies

A-Mab: A Case Study in Bioprocess Development (2009) ***(free, downloadable)***

https://ispe.org/sites/default/files/initiatives/pqli/a-mab-case-study-version.pdf

Table 4.15 Low pH Inactivation

Process Parameter *CPP*	Normal Manufacturing Target or Range	Worst Case Study Conditions	Conditions used for Virus Clearance	Scientific Rationale
pH	3.5 ± 0.1	3.2	3.2 – 4.0	Lower pH is expected to result in a greater tendency of the antibody to aggregate and may also result in changes to the charge variants. The lower pH will enhance the rate inactivation. Previous univariate experiments have indicated that antibody precipitation may occur at pH 3.1 or below. Therefore pH 3.2 was chosen as the lowest pH to assure precipitation did not occur during the study. The upper limit was defined by the highest pH studied in inactivation experiments.
Time	60 - 120 minutes	0-240 minutes	15-180 minutes	Longer hold times are expected to result in greater aggregation and may result in changes to the charge variant profile. Previous experience with the platform process indicates that product quality may begin to deteriorate after 180 minutes at these conditions. In order to gain kinetic data on the stability of A-Mab, samples were taken at time points up to 240 minutes. The maximum hold time was set at the longest time the antibody could be held at this condition without loss of acceptable quality

FDA recommendation on how to communicate CPPs to them

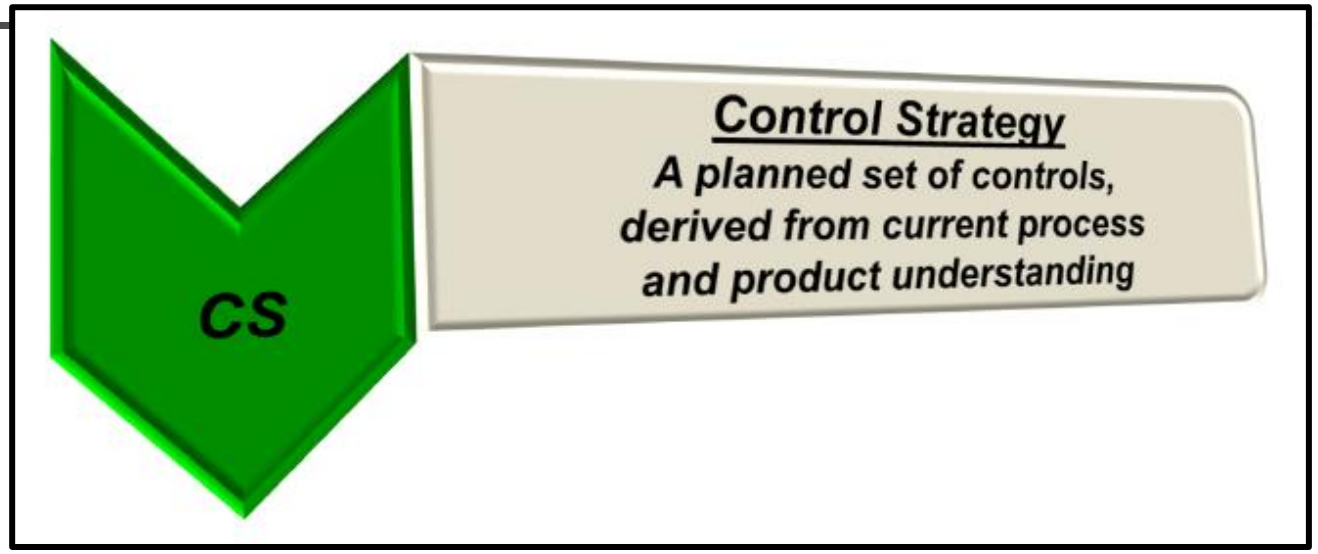
Pre-BLA Meeting Minutes – Vabysmo (bispecific, faricimab) – Genentech – March 29, 2021

1. To facilitate the Agency's review of the drug substance and drug product manufacturing process for faricimab, provide the information for all attributes, parameters, or controls proposed for routine commercial manufacturing as well as those evaluated during development and validation, in the tabular format provided below. Please provide a separate table for each unit operation. The tables should summarize information from Module 3 and may be submitted either to Module 1 or Module 3R. Note, this Table does not replace other parts of Module 3 or impact the nature or amount of information included in those parts of Module 3.

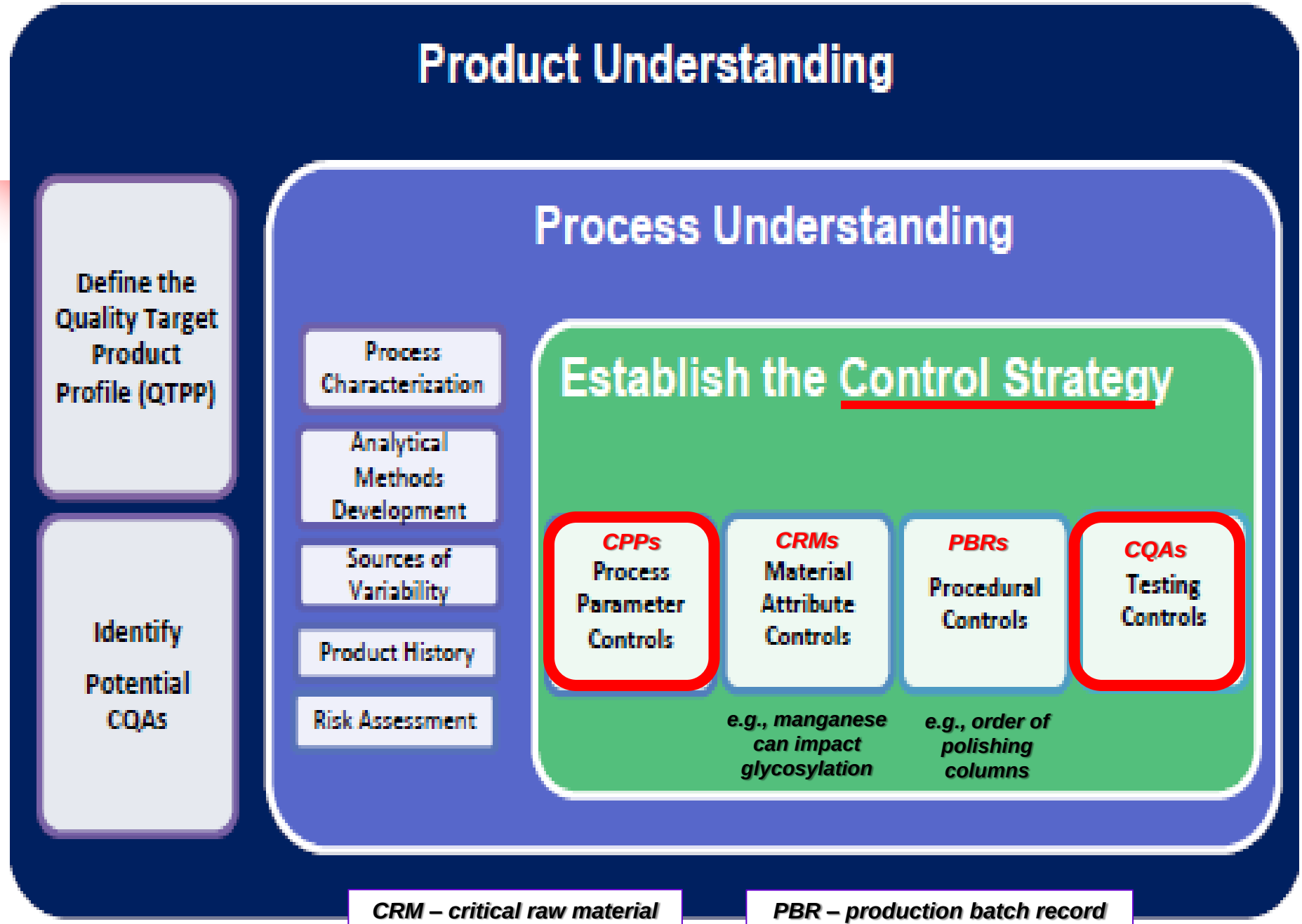
Process Parameter/ Operating Parameter/ In-Process Control (IPC)	Proposed Range for Commercial Manufacturing	Criticality Classification	Range Assessed During Process Development Studies	Validated Range	Clinical Study Range	Justification of the Proposed Commercial Acceptable Range
PP		***CPP*** ***Non-CPP***				

[1]For example, critical process parameter, key process parameter, non-critical process parameter, as described in module 3.
[2]Provide a brief summary description (e.g., "development range", "validation range", or "platform experience"). To link to additional description for justification you may additionally include a link or reference to the appropriate section of the eCTD with more detail.

ICH Q8(R2)



The Control strategy is <u>much more</u> than just product release specifications!


Product Understanding
Define the Quality Target Product Profile (QTPP)
Identify Potential CQAs
Process Understanding
Process Characterization
Analytical Methods Development
Sources of Variability
Product History
Risk Assessment
Establish the Control Strategy
CPPs
Process Parameter Controls
CRMs
Material Attribute Controls
PBRs
Procedural Controls
CQAs
Testing Controls
e.g., manganese can impact glycosylation
e.g., order of polishing columns
CRM – critical raw material
PBR – production batch record

FDA recommendation on how to communicate the Control Strategy to them

Pre-BLA Meeting Minutes – Vabysmo (bispecific, faricimab) – Genentech – March 29, 2021

2. To facilitate the Agency's review of the control strategy for faricimab, provide information for quality attributes and process and product related impurities for the drug substance and drug product in the following tabular format. The tables should summarize information from module 3 and may be submitted either to module 1 or module 3R. These tables do not replace other parts of Module 3 or impact the nature or amount of information included in those parts of Module 3. Attributes that are deemed to not be critical should also be justified in the BLA with the reasoning for that categorization.

Critical Quality Attributes (Including Process and Product Related Impurities for DS and DP)	Impact	Source	Analytical Mehtod	Proposed Control Strategy	Justification of the Proposed Control Strategy
CQA	*RISK*	*ORIGIN*			

[1]What is the impact of the attribute, e.g., contributes to potency, immunogenicity, safety, efficacy.
[2]What is the source of the attribute or impurity, e.g., intrinsic to the molecule, fermentation, protein purification column.
[3]List all the methods used to test an attribute in-process, at release, and on stability. For example, if two methods are used to test identity then list both methods for that attribute.
[4]List all the ways the attribute is controlled, e.g., in-process testing, validated removal, release testing, stability testing.
[5]Provide a brief verbal description. In addition, you may provide links or references to appropriate sections of the eCTD that provide more detail.

A taste of QBD/QRM: non-pharmaceutical illustration

QbD/QRM manufacturing of potato chips

QTPP – consistent manufactured potato chips shippable around the world without breaking

As you watch the video

SOURCE MATERIAL

_____

IDENTIFY CQAs

Texture _____

Shape _____

Thickness _____

Container _____

IDENTIFY CPPS

Pressure _____

Time in Hot Oil _____


How It's Made

QbD/QRM – the LANGUAGE of CMC communication to regulatory authorities

not mandatory during clinical development, but highly recommended ('expected') for BLA/MAA

CASE EXAMPLE ***QTPP, CQA, CPP***

Risk assessments to identify the critical quality attributes (CQAs) of bimekizumab were performed using an approach aligned with quality by design (QbD) principles described in ICH Q8, Q9, Q10, and Q11. Quality attributes were identified based on the quality target product profile (QTPP), knowledge of the bimekizumab molecule, and information gained during process development and manufacture. No design space is claimed.

Process evaluation studies using scale-down models, which were verified as representative of the large-scale manufacturing process, have been performed for the bimekizumab active substance manufacturing process, to increase process understanding, define the acceptable range for process parameters and to identify CPPs that have a significant impact on the CQAs of the product.

EUROPEAN MEDICINES AGENCY

Bimzelx UCB Pharma Assessment report 24 June 2021
bimekizumab EMA/393532/2021

Questions??

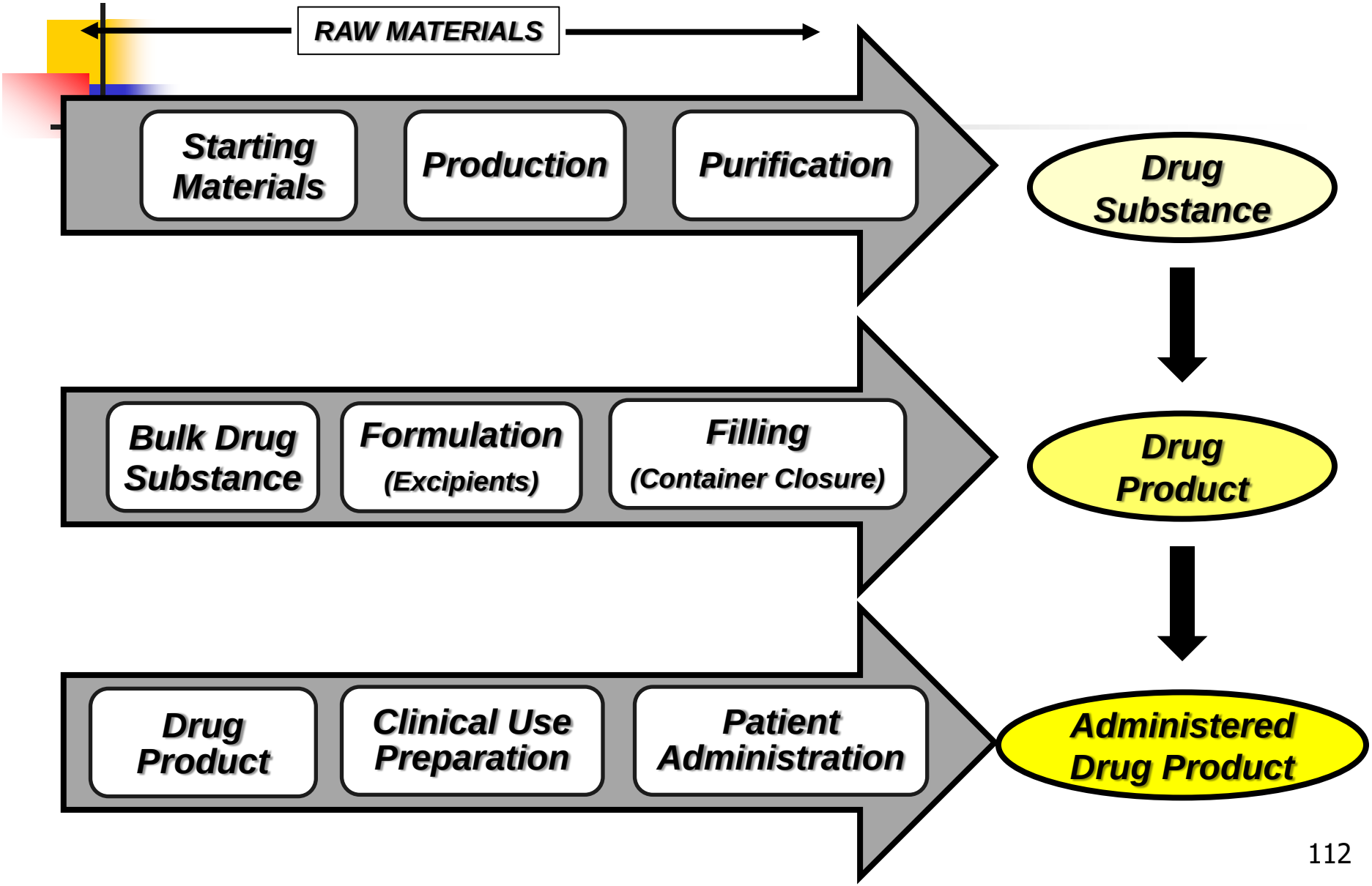
Course Outline

3. Applying the Risk-Managed CMC Regulatory Compliance Strategy

- CMC strategy applied across the manufacturing process from:
  - raw materials
  - starting materials → production → purification → drug substance
  - bulk drug substance → (formulation) → drug product
  - released labeled drug product → administered drug product

Case examples and references are from public sources
(manufacturers do not voluntarily reveal their manufacturing details;
but, FDA and EMA will, after market approval, upload to their
respective websites details of their CMC reviews)

Applied Risk-Management Across the Manufacturing Process



RAW MATERIALS

Raw materials are the reagents and components that come in contact with the product during manufacturing, but are <u>not</u> part of the final product

Examples:

<u>DS UPSTREAM PROCESS (UPS)</u>

- *cell culture media (proprietary)*
- *fetal bovine serum (FBS)*
- *enzymes (trypsin, nuclease)*
- *growth factors/cytokines (IL-2, GM-CSF)*
- *antibiotics (gentamicin, tetracycline)*
- *pH controls*
- *antifoam*
- *…*

<u>DS DOWNSTREAM PROCESS (DPS)</u>

- *surfactants (Triton X-100)*
- *purification buffer/salt solutions*
- *chromatography resins*
- *…..*

Major CMC Regulatory Compliance Concerns of Raw Materials

***Impact* from raw material *batch-to-batch variation* on the the *consistency* of the manufactured protein-based biopharmaceutical!**

***Patient safety concerns* from *contaminants* introduced into the manufacturing process by the raw materials**

***Patient safety concerns* from the raw material *residuals* remaining in the final product!**

Explains why raw materials for receive attention from regulatory authorities

RAW MATERIALS

Risk to Product Quality! Risk to Patient Safety!

(1) Listed, (2) Identified, (3) Justified Quality, (4) Suitable for Intended Use → IND/IMPD Submissions

Materials used in the manufacture of the active substance (e.g. raw materials, starting materials, cell culture media, growth factors, column resins, solvents, reagents) should be listed identifying where each material is used in the process. Reference to quality standards (e.g. compendial monographs or manufacturers' in-house specifications) should be made. Information on the quality and control of non-compendial materials should be provided. Information demonstrating that materials (including biologically-sourced materials, e.g. media components, monoclonal antibodies, enzymes) meet standards applicable for their intended use should be provided, as appropriate.

For all raw materials of human or animal origin (including those used in the cell bank generation), the source and the respective stage of the manufacturing process where the material is used should be indicated. Summaries of safety information on adventitious agents for these materials should be provided in Appendix A.2.

EUROPEAN MEDICINES AGENCY

Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials

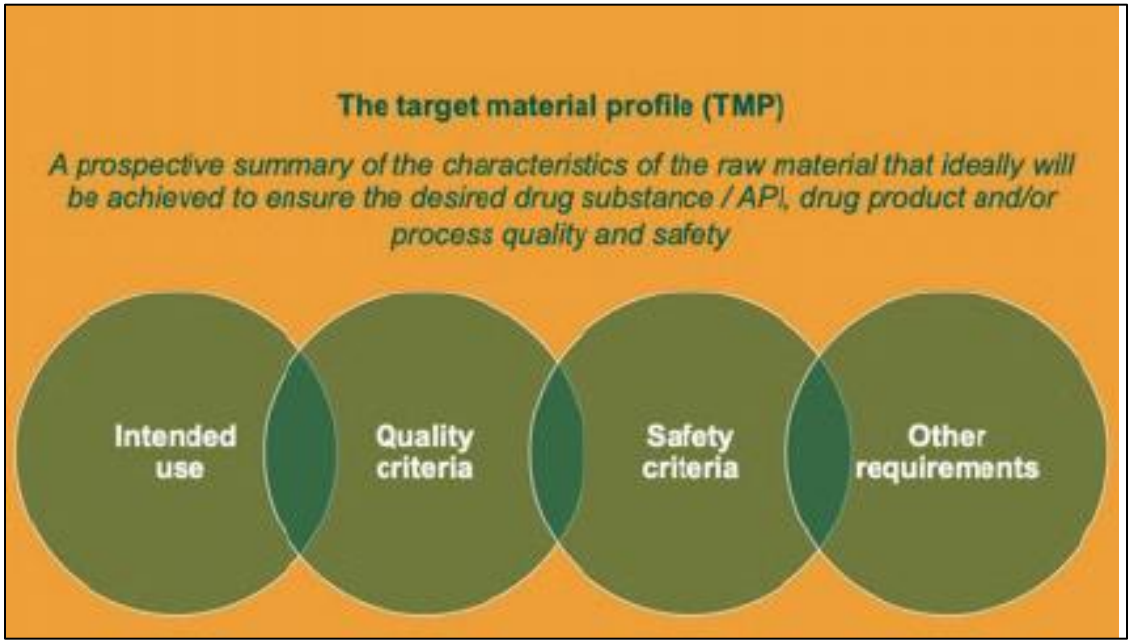
27 January 2022
EMA/CHMP/BWP/534898/2008 Rev. 2

'Trust, but Verify' your Vendors

- ***Vendor DMF cross reference (when possible or practical)***
- ***Vender Certificate of Analysis***
- ***Assess impact of lot-to-lot raw material on process performance***
- ***Assess removal of raw material residuals from final product***
- ***Audit the raw material vendor***
- ***Develop stringent internal specifications***

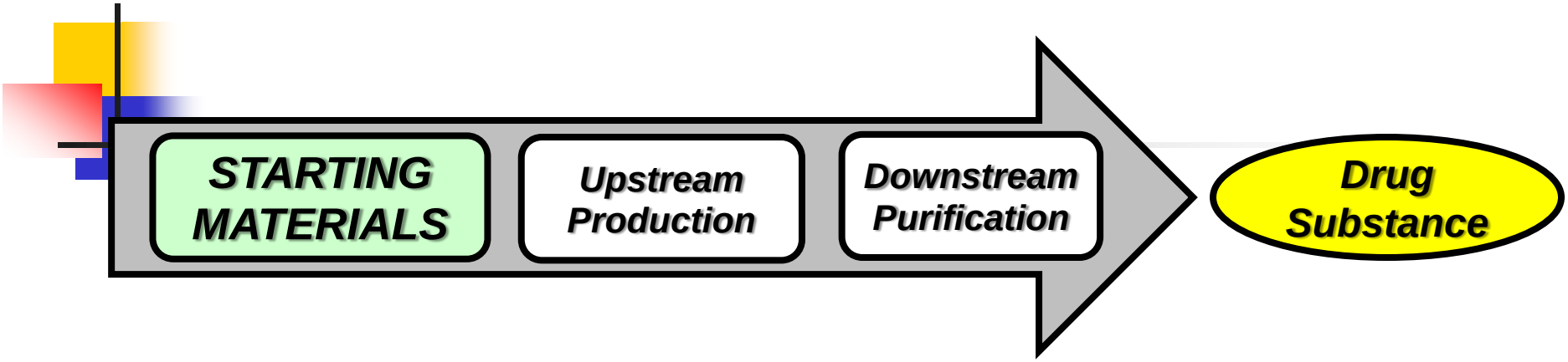
BioPhorum approach to the registration of innovative raw materials using quality by design principles

January 2022



risk assessment approach

Applied Risk-Management Across the Manufacturing Process



Chemical Drugs – ICH Q11

A starting material should be a substance of defined chemical properties and structure. Non-isolated intermediates are usually not considered appropriate starting materials. A starting material is incorporated as a significant structural fragment into the structure of the drug substance. "Significant structural fragment" in this context is intended to distinguish starting materials from reagents, solvents, or other raw materials.

Recombinant Proteins/Monoclonal Antibodies – ICH Q11

Cell banks are the starting point for manufacture of biotechnological drug substances and some biological drug substances. In some regions, these are referred to as source materials; in others, starting materials.

Cell banks contain the genetic capability of producing the biopharmceutical

Why have a cell bank?

2.2. Cell Banking

One of the most important advantages of using serially subcultivated cells to produce biotechnological/biological products is the ability to have a characterised common starting source for each production lot, i.e., the preserved bank of cells. Manufacturers may prepare their own cell banks, or may obtain them from external sources. Manufacturers are responsible for ensuring the quality of each cell bank and of the testing performed on each bank.

Development Genetics → *7-12 month process* → **Master Cell Bank (MCB)**

(get this wrong, and you have major problems!)

Development Genetics

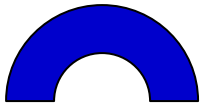
(Step 1 of 2) Stitching together the genetic components

genetic material that contains the capability of producing the desired structure/product;

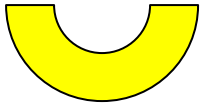
(genes can be further genetic engineered)

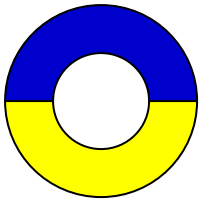
larger piece of DNA (e.g., plasmid, virus) that contains promoters, enhancers and other genetic pieces to allow the gene to function and survive within a foreign host

GENE

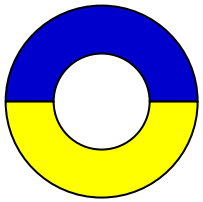


VECTOR





expression construct



expression construct

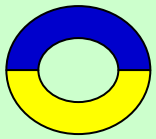
Transduction (virus)

Transfection (plasmid)

Transformation (electroporation)

LIVING HOST

Host Cells	Most Common
Bacterial	E. coli
Yeast	Pichia
Mammalian	CHO
Human	HEK293

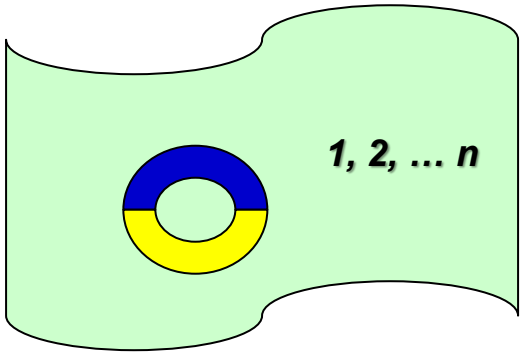


1, 2, … n

not 1 recombinant host cell, but 1000s

Development Genetics

(Step 2 of 2) Preparing the Cloned Cell Substrate



not 1 recombinant host cell, but 1000s

CLONING

Selection of 1 recombinant host cell

CLONED CELL SUBSTRATE

also called the Research Cell Bank (RCB)

expand aliquot

MCB

expand aliquot

WCB

Clonality is the regulatory authority expectation for the MCB

MCB (Master Cell Bank). An aliquot of a single pool of cells which generally has been prepared from the selected cell clone under defined conditions, dispensed into multiple containers and stored under defined conditions. The MCB is used to derive all working cell banks

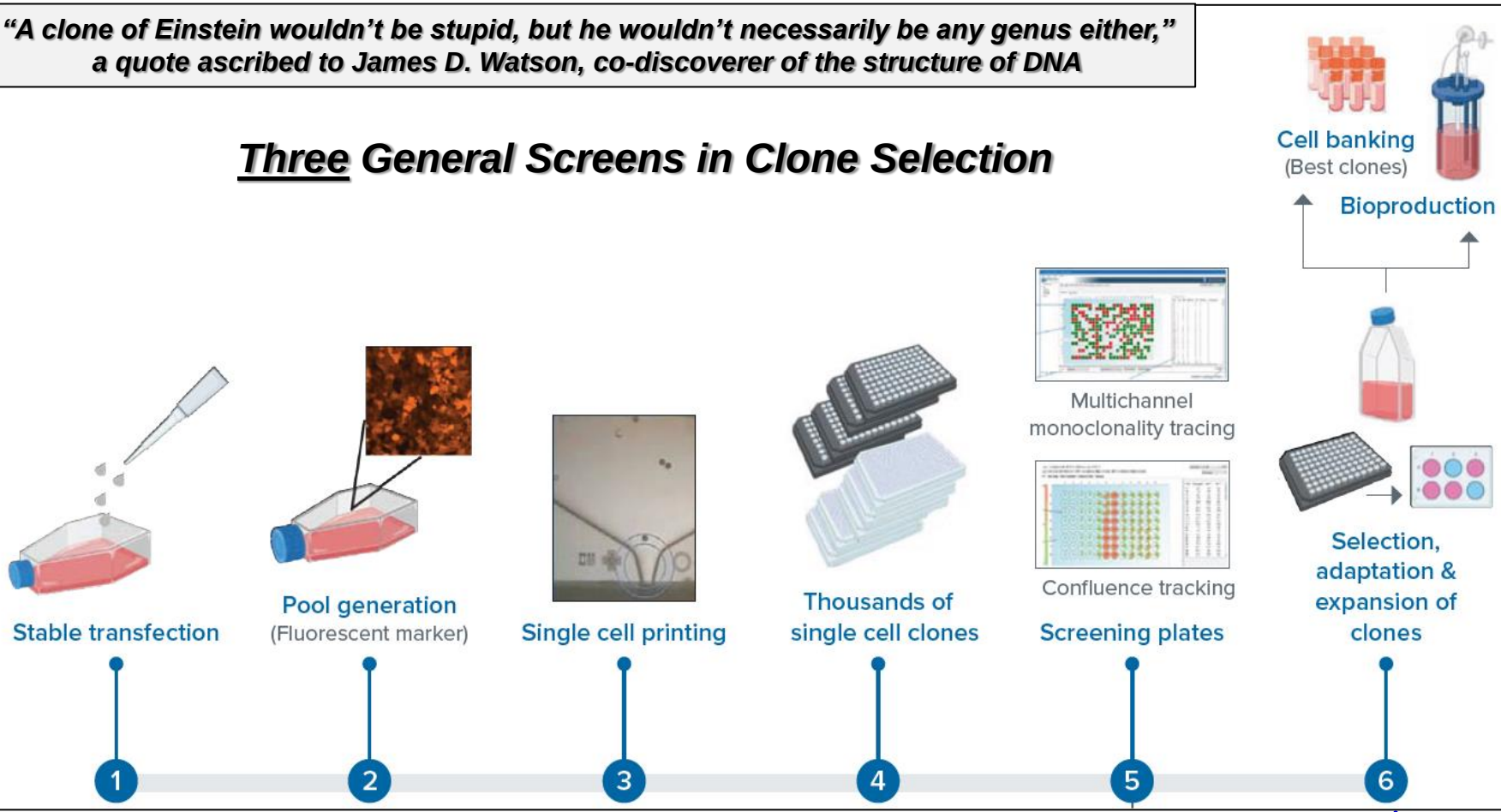
ICH Q5D (1997) ***EC GMP Annex 2 (2018)***

Using a cell line derived from a single progenitor minimizes the variability of the starting cryopreserved cell population, which would be anticipated to have the effect of minimizing product heterogeneity. However, sustained culturing of immortalized cells can result in genetic alterations, which may be further exacerbated by amplification procedures. Therefore, it is not feasible to term a population as truly genetically homogeneous following sustained culture. Despite this, the reason for generating a clonally derived cell line relates to the ability of a controlled process to produce a consistent product with minimal heterogeneity. Thus, for these reasons, any adaptations (e.g., switching to serum-free conditions) should be considered prior to cloning. In contrast, use of an entirely non-clonal cell population as a starting point may give rise to outgrowth of a subpopulation of cells that generate products with different CQAs. For instance, this could affect glycosylation, which could then impact the mechanism of action if the product is an antibody that functions by antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC). Likewise, a different population with a different integration site might have altered expression levels, growth metrics, and stability, which could have the potential to lead to drug shortages if a cell bank is no longer performing as expected. Such adverse end points could be exacerbated in conditions where cell culture parameters or raw materials have been altered in a way that places selective pressure on the system.

USP <1042> PF 47:1 (April 2023)

"A clone of Einstein wouldn't be stupid, but he wouldn't necessarily be any genus either," a quote ascribed to James D. Watson, co-discoverer of the structure of DNA

Three General Screens in Clone Selection



LIMITING DILUTION CLONING (LDC)

LDC – cells are plated at a low density, ideally <0.5 cells/well in a 96-wellplate, with the aim of obtaining only 1 cell in a well from which progeny can grow. Two rounds of LDC provide an approximately 99% probability that the cell line will be monoclonal.

AUTOMATED

Clone Plating, Image Screening, Picking

Screen 1

PRODUCITIVITY OF SINGLE CLONE

Limiting dilution (x2)
Limiting dilution (x1 + imaging)
Single cell deposition + imaging

Screen 2

QUALITY OF CLONE

Screen 3

STABILTY OF CLONE

QUESTION: Which clone would you select to replace an existing Master Cell Bank? Why?

Product Quality Attributes		MCB	Clone 1 (%)	Clone 2 (%)	Clone 3 (%)	Clone 4 (%)	Clone 5 (%)	Clone 6 (%)
Heavy Chain N-Terminal Heterogeneity [1]	Unmodified	97.0	97.6	98.0	98.1	97.9	97.7	97.7
	Pyroglutamic acid	2.5	2.4	2.0	1.9	2.1	2.3	2.1
	-3VHS	0.5	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	0.2
Heavy Chain C-Terminal Heterogeneity [1]	Unmodified	92.3	87.9	81.7	90.3	83.9	92.0	89.1
	Amidated proline	3.7	0.7	0.7	0.8	0.7	0.4	0.6
	C-terminal lysine	3.5	8.9	12.9	7.0	11.5	5.9	8.2
Light Chain N-Terminal Heterogeneity [1]	Unmodified	93.6	88.4	89.5	89.3	87.3	88.1	89.2
	-3VHS	N/A	< 0.1	< 0.1	0.1	< 0.1	< 0.1	< 0.1
	des – 1SYE	4.0	11.3	10.4	10.3	12.4	11.3	10.6
N-Glycans [2]	G0F	82.3	66.4	65.7	79.8	66.6	69.0	70.4
	G1F	7.3	22.6	21.4	15.3	23.7	24.9	21.2
	G2F	0.3	2.1	2.2	0.9	2.2	2.3	1.8
	G0	5.0	2.9	2.3	2.3	2.0	1.7	1.7
	G0F minus GlcNAc	1.0	1.1	2.1	0.3	1.0	< 0.1	0.6
	Man5	1.3	2.9	3.8	0.2	2.6	0.5	1.2
	Aglycosylated	2.8	2.0	2.5	1.2	1.9	1.6	3.1
Trisulfides [3]	One trisulfide	ND	35	36	29	31	Trace	ND
	Two trisulfides	ND	17	20	11	13	ND	ND

Pfizer WORLDWIDE RESEARCH & DEVELOPMENT
BioTherapeutics Pharmaceutical Sciences

ND = not detected
N/A = not applicable

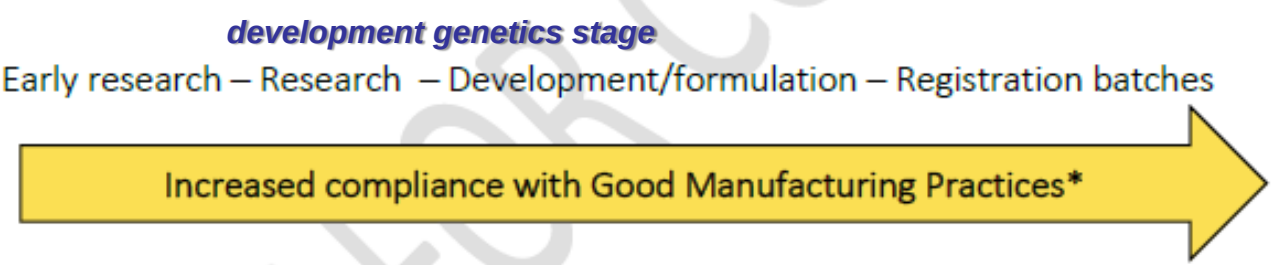
1. *Determined by LC/MS/MS-peptide mapping*
2. *Determined by LC/MS-3-part subunit analysis*
3. *Determined by LC/MS – intact mAb analysis*

'Principles of GMP' recommended during development genetics stage

(gene → cloned cell substrate)

World Health Organization

Figure 1. Application of this guide



*The principles described in this guideline are applied, based on risk management principles, in an increased manner from early research to development to registration batches

WHO good practices for research and development facilities of pharmaceutical products

Working document QAS/20.865/.Rev1
July 2021

Example of 'principles of GMP'

- ***Quality management system (rather than a Quality Unit)***
- ***Adequately trained staff***
- ***Documentation (and adequate record keeping) [emphasized by ICH Q5D]*** →
- ***Self-inspection***

basic common sense principles!

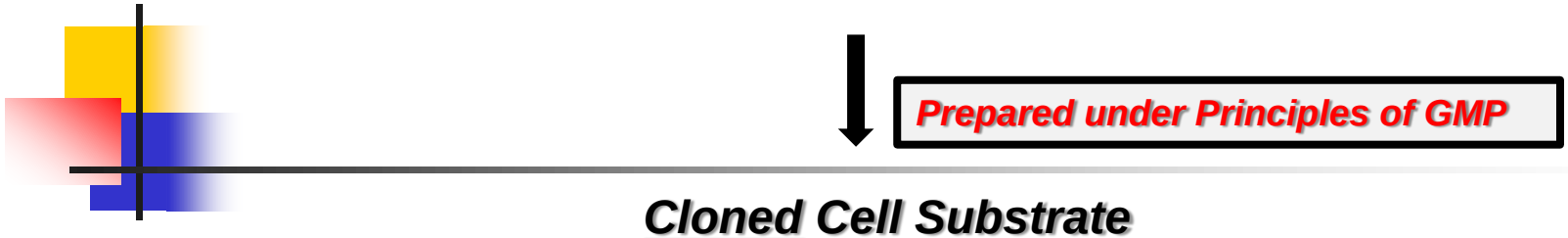
Development Genetics – Importance of Documentation!

Warning! Don't get it wrong here (long before clinical trials begin)

It is important to provide supportive documentation which describes the history of the cell substrate that is used in the manufacture of a biotechnological/biological product, as well as any parental cell line from which it was totally or partially derived. Events during the research and development phases of the cell substrate may contribute significantly to assessment of the risks associated with the use of that particular cell substrate for production. The information supplied in this regard is meant to facilitate an overall evaluation which will ensure the quality and safety of the product.

Careful records of the manipulation of the cell substrate should be maintained throughout its development. Description of cell history is only one tool of many used for cell substrate characterisation. In general, deficiencies in documented history may not, by itself, be an impediment to product approval, but extensive deficiencies will result in increased reliance on other methods to characterise the cell substrate. ***ICH Q5D***

Development Genetics is carried out by the Development Group



Prepared under Principles of GMP

Cloned Cell Substrate

Prepared under cGMP

Master Cell Bank (MCB)

the expanded cell substrate Is aliquoted into multiple containers (typically 200+ aliquots) and stored under defined long-term conditions

(MCB can provide up to 200 production batches)

Prepared under cGMP

Working Cell Bank (WCB)

1 aliquot of the MCB is expanded and then aliquoted into multiple containers (typically 200+ aliquots) and stored under defined conditions

(MCB + WCB can provide up to 40,000 production batches)

MINIMUM CMC Regulatory Compliance CONTINUUM

applied from development genetics to the Master Cell Bank (MCB)

Regulatory authority focus to enter clinical development	***Regulatory authority focus to enter market approval***

"What's the big deal?"

"Since our Master Cell Bank has been allowed by a regulatory authority to be used to manufacture our clinical trial studies, that MCB must also be acceptable for commercial manufacturing."

MINIMUM CMC Regulatory Compliance CONTINUUM

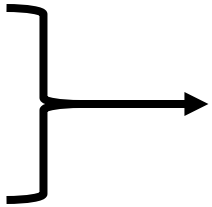
applied from development genetics to the Master Cell Bank (MCB)

Regulatory authority focus to enter clinical development	***Regulatory authority focus to enter market approval***

CMC Details Required in Filings

BRIEF description IND/IMPD

DETAILED description in BLA/MAA



Description in IND/IMPD for clinical development vs …

Source, history and generation of the cell substrate

A **BRIEF description** of the source and generation (flow chart of the successive steps) of the cell substrate, analysis of the expression vector used to genetically modify the cells and incorporated in the parental / host cell used to develop the Master Cell Bank (MCB), and the strategy by which the expression of the relevant gene is promoted and controlled in production should be provided, following the principles of ICH Q5D.

Cell bank system, characterisation and testing

A MCB should be established prior to the initiation of phase I trials.
It is acknowledged that a Working Cell Bank (WCB) may not always be established.

EUROPEAN MEDICINES AGENCY

Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials

27 January 2022
EMA/CHMP/BWP/534898/2008 Rev. 2

… vs Description in BLA/MAA for market approval

Gene Construct – A **DETAILED description of the gene** which was introduced into the host cells, including both the cell type and origin of the source material, should be provided…The complete nucleotide sequence of the coding region and regulatory elements of the expression construct, with translated amino acid sequence, should be provided, including annotation designating all important sequence features.

Vector – **DETAILED information regarding the vector and genetic elements** should be provided, including a description of the source and function of the component parts of the vector, e.g. origins of replication, antibiotic resistance genes, promoters, enhancers.

Final Gene Construct – A **DETAILED description should be provided of the cloning process** which resulted in the final recombinant gene construct. The information should include a step-by-step description of the assembly of the gene fragments and vector or other genetic elements to form the final gene construct.

FDA U.S. FOOD & DRUG ADMINISTRATION

FDA Guidance For Industry For the Submission of Chemistry, Manufacturing , and Controls Information For a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product For In Vivo Use (August 1996)

But genetic development took place before FIH studies, a long time ago – do you know where your 'detailed' information is?

MINIMUM CMC Regulatory Compliance CONTINUUM

applied from development genetics to the Master Cell Bank (MCB)

Regulatory authority focus to enter clinical development	***Regulatory authority focus to enter market approval***

CMC Details Required in Filings

brief description IND/IMPD	***detailed description in BLA/MAA***

Level of CMC Regulatory Review

limited, single CMC reviewer	***thorough, team CMC reviewers***
patient safety focus	***patient safety focus***
	+ manufactured product consistency

Level of CMC review of IND/IMPD for clinical development

Although CDER acknowledges its review responsibilities,
it does not have unlimited resources to review all submissions with the highest level of scrutiny in short time frames.
CDER review staff must prioritize
their workload and evaluate individual submissions
in the context of their place in drug development…
review of a new IND focuses primarily on SAFETY….

Patient safety focus

absence of adventitious agents
+
correct identity of genetic components (gene, vector, host)

FDA CDER Manual of Policy and Procedures (MAPP): MAPP 6030.9 – Good Review Practice: Good Review Management Principles and Practices for Effective IND Development and Review (Feb 2017)

Reviewer Considerations for Clonality at the IND stage

FDA

- At the IND stage, reviewers will do a initial assessment of the information provided about the clonality of the MCB. If significant deficiencies are noted, then the appropriate comments will be communicated.
- Lack of assurance of clonality is **not** necessarily a hold issue.

Considerations at the BLA stage

FDA

- Adequate assurance of clonality should be provided at the time of the BLA submission.
- Having low assurance of clonality of the MCB at the time of licensure does ***not*** necessarily preclude approvability of the application.
- Augmentation of the control strategy could be an acceptable approach to managing a non-clonal MCB for licensure.

***AUGMENTATION* of the Control Strategy**

(not a desired position to be in)

- Some strategies that have been implemented:
  - Adding additional specifications (LC-MS/MS for Sequence Variants, Glycosylation despite not impacting MOA, etc.)
  - Tighter limits on the limit of in vitro cell age
  - Establishing additional critical process parameters (growth parameters escalated to CPP)
  - Trending and Statistical Process Control
  - Additional risk assessment for changes in critical raw materials (media, components, etc.)
  - Tighter controls for re-qualification of a new WCB

R. Novak, CDER, WCBP 2017

CASE EXAMPLE concern about clonality of MCB

absence of documented proof at BLA review stage

Monoclonal antibody produced by CHO ***Ultragenyx***

A formal cloning procedure was conducted only once. Therefore, there is residual uncertainty for the monoclonality of burosumab MCB.

The specifications for burosumab drug substance and drug product are acceptable to ensure adequate quality and safety for the initial marketed product.

Assurance of the monoclonality of the burosumab MCB will reduce the risk of the generation of product variants and ensure the consistency of product quality throughout the product life cycle.

Conduct studies to further characterize the burosumab master cell bank (MCB) and to support the monoclonality of the MCB.

FDA Drugs – Search Drugs@FDA: FDA Approved Drug Products: Crysvita (Burosumab-twza) – Approval History, Letters, Reviews and Related Documents – Other Reviews – PMR/PMC Development Template: Product Quality (CMC) – PMC #1 (April 17, 2018)

Concern was to be resolved as a post-market approval BLA commitment

MINIMUM CMC Regulatory Compliance CONTINUUM

applied to development genetics and the Master Cell Bank (MCB)

Regulatory authority focus to enter clinical development	***Regulatory authority focus to enter market approval***
CMC Details Required in Filings	
brief description IND/IMPD	***detailed description in BLA/MAA***
Level of CMC Regulatory Review	
limited, single CMC reviewer	***thorough, team CMC reviewers***
patient safety focus	***patient safety focus + manufactured product consistency***
Assurance of Continued Product Supply	
N/A	***required***

CMC requirements for commercial manufacturing

assurance of continued supply with MCB/WCB

No upside to a regulatory authority to grant market approval if product cannot be manufactured!

> ***Manufacturers should describe their strategy for providing a continued supply of cells from their cell bank(s), including the anticipated utilization rate of the cell bank(s) for production, the expected intervals between generation of new cell banks,....***

ICH Q5D

Be cautious, assume worst case (double your calculated utilization rate!)

What is an acceptable MCB/WCB inventory level? 40, 20, 10 years, ?

CMC requirements for commercial manufacturing

assurance of long-term MCB/WCB stability

Evidence for banked cell stability under defined storage conditions will usually be generated during production of clinical trial material from the banked cells. Available data should be clearly documented in the application dossiers, plus a proposal for monitoring of banked cell stability should be provided.

The proposed monitoring can be performed at the time that one or more containers of the cryopreserved bank is thawed for production use, when the product or production consistency is monitored in a relevant way, or when one or more containers of the cryopreserved MCB is thawed for preparation of a new WCB (and the new WCB is properly qualified), as appropriate.

ICH Q5D

A WCB stability timepoint is obtained every time a WCB is thawed to initiate a cell culture batch – viability/ DS quality

But, when was the last time you checked the stability of your MCB? (before initial freeze, after initial thaw, first WCB, ????)

So how frequent should the MCB be tested for stability?

One answer

- ***There is no regulatory authority guidance on the frequency of stability testing for a MCB, so CMC consultants have typically recommended every 4-5 years (or more frequent if a short clinical development period) – the goal is to have a spread out regression line fit for the stability graphs***

- ***However, the FDA indicated their preference on the MCB frequency of stability testing in a communication to Genentech during the market approval of the CHO-produced monoclonal antibody, Perjeta:***

> ***Conduct stability studies of the Master Cell Bank at more frequent intervals than the currently proposed 10 years. Submit Interim Reports every four years and the Final Report after 20 years.***

FDA Drugs – Search Drugs@FDA: FDA Approved Drug Products: Perjeta (Pertuzumab) – Approval History, Letters, Reviews and Related Documents – Market Approval Letter (June 08, 2012)

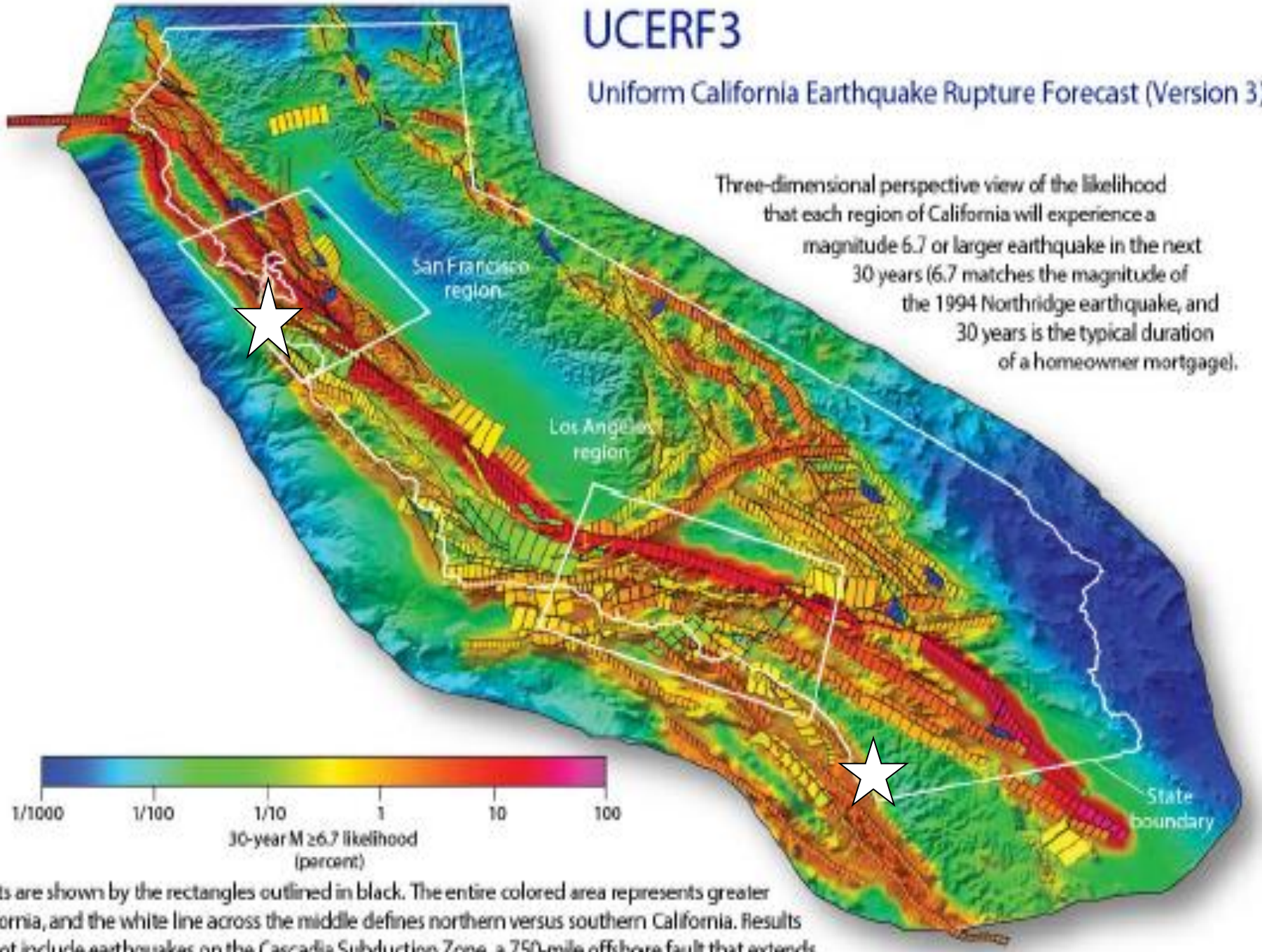
CMC requirements for commercial manufacturing

one critical GMP feature: a secure catastrophic event plan

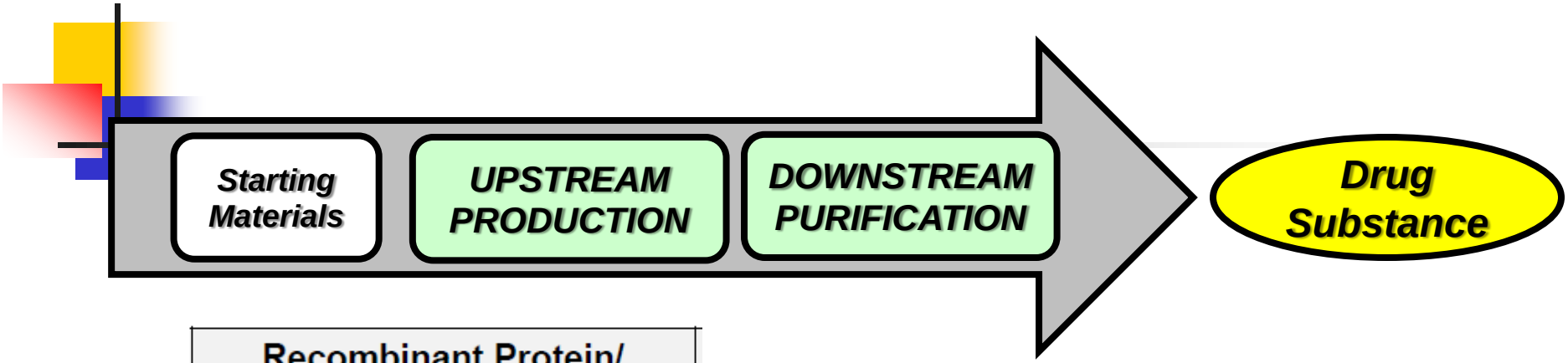
To ensure continuous, uninterrupted production of pharmaceuticals, manufacturers should carefully consider the steps that can be taken to provide for protection from catastrophic events that could render the cell bank unusable. Examples of these events include fires, power outages and human error. Manufacturers should describe their plans for such precautions; for example, these may include redundancy in the storage of bank containers in multiple freezers, use of back-up power, use of automatic liquid nitrogen fill systems for storage units, storage of a portion of the MCB and WCB at remote sites, or regeneration of the MCB.

ICH Q5D

What catastrophic event might happen where your MCB is stored?


UCERF3
Uniform California Earthquake Rupture Forecast (Version 3)
Three-dimensional perspective view of the likelihood that each region of California will experience a magnitude 6.7 or larger earthquake in the next 30 years (6.7 matches the magnitude of the 1994 Northridge earthquake, and 30 years is the typical duration of a homeowner mortgage).
San Francisco region
Los Angeles region
State boundary
1/1000
1/100
1/10
1
10
100
30-year M ≥6.7 likelihood (percent)
Faults are shown by the rectangles outlined in black. The entire colored area represents greater California, and the white line across the middle defines northern versus southern California. Results do not include earthquakes on the Cascadia Subduction Zone, a 750-mile offshore fault that extends about 150 miles into California from Oregon and Washington to the north.

Applied Risk-Management Across the Manufacturing Process



Recombinant Protein/ Monoclonal Antibody

Recombinant Cell Bank (Aliquot Thaw)

↓

Cell Expansion in Bioreactor (Increasing Size, Suspension)

↓

Induction of Protein Expression

↓

rProtein/mAb Harvest

Recombinant Protein/ Monoclonal Antibody

Harvested rProtein/mAb

↓

Chromatography/Filtration

↓

Concentration/Buffer Exchange

↓

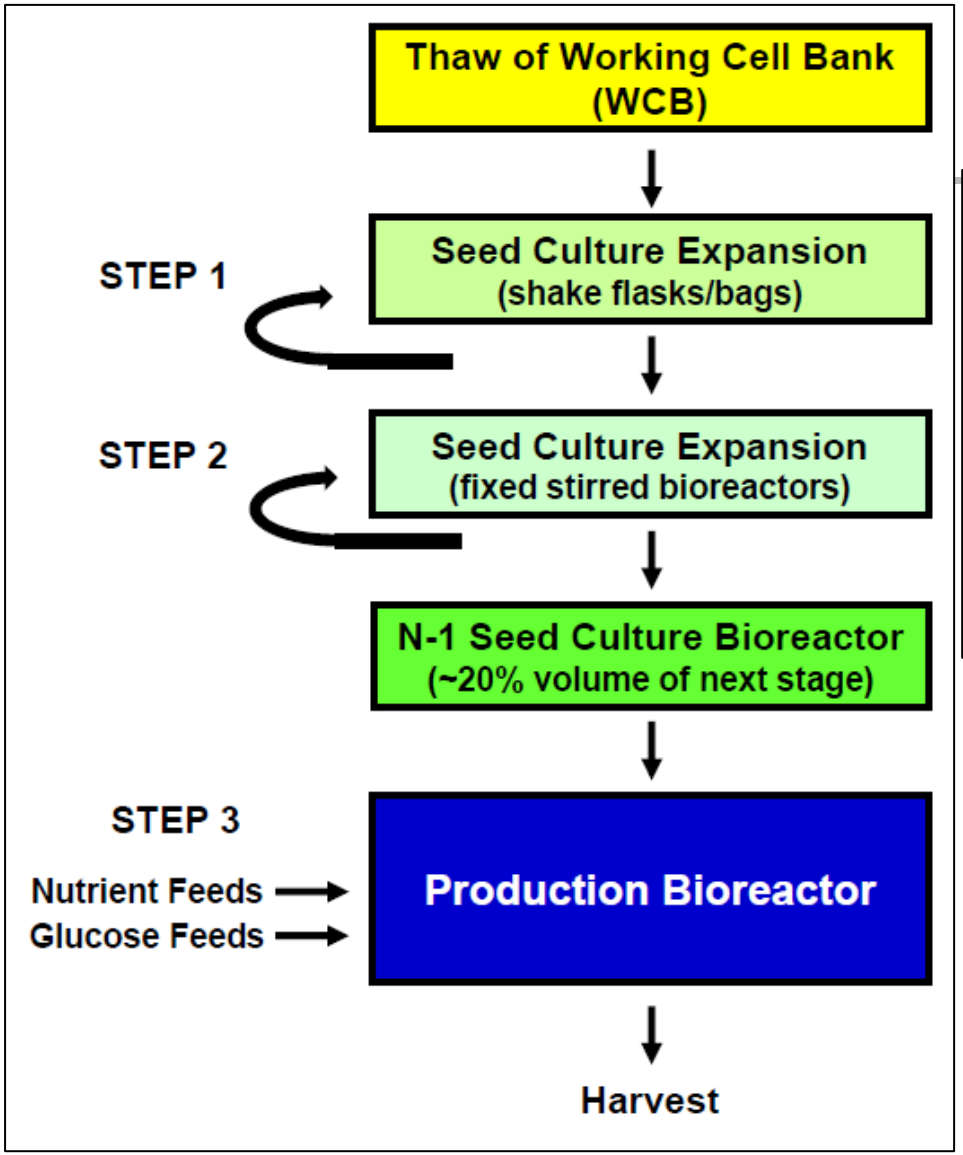
0.2 Micron Filtration

↓

Bulk Drug Substance

UPSTREAM PRODUCTION (USP) BY CELL CULTURE

Fed-Batch Cell Culture



there also is perfusion cell culture production

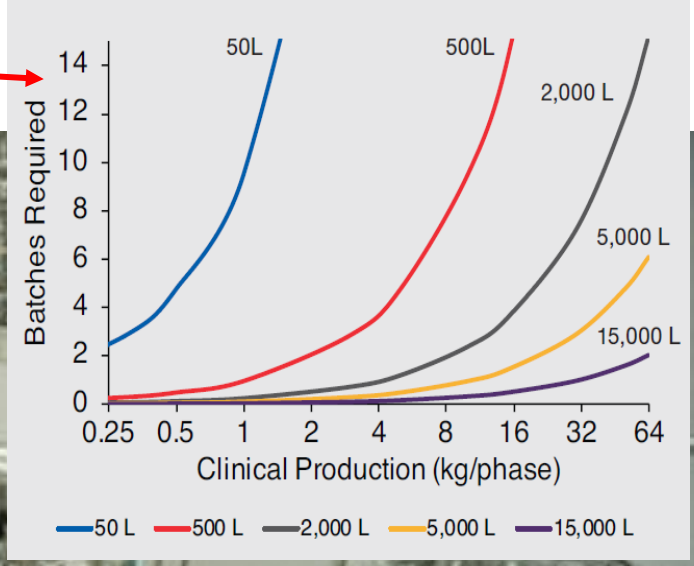
Complexity of Cell Culture media (frequently proprietary)

Inorganic salts (sodium, phosphate) to maintain osmotic balance
Amino acids for cell growth
Carbohydrates as a main source of energy for the cells
Fatty acids and lipids for cell membrane synthesis
Vitamins for cell growth
Trace elements for the growth and biological functions of cells
Anions (phosphate, nitrate, sulfate, chloride) as sources of energy
Buffering agents to maintain correct pH conditions to support optimum growth
Growth factors to promote cell growth
Peptones and hydrolysates to enhance cell growth and titer
L-glutamine to support cell growth and protein synthesis
Antibiotics to minimize contamination

Upstream Production Parameters to Vary	Upstream Production Outputs to Measure
Cell passage number	Viable cell density
Initial seeding density	Viability
Nutrient feed amount	Recombinant protein titer
Nutrient feed timing	Glucose level
pH operating range	Lactate level
Temperature operating range	Ammonia level
Temperature shift timing	Product characteristics (e.g., glycosylation)
Dissolved oxygen level	

Need more monoclonal antibody – scale up or scale out cell culture production!

or increase cell productivity

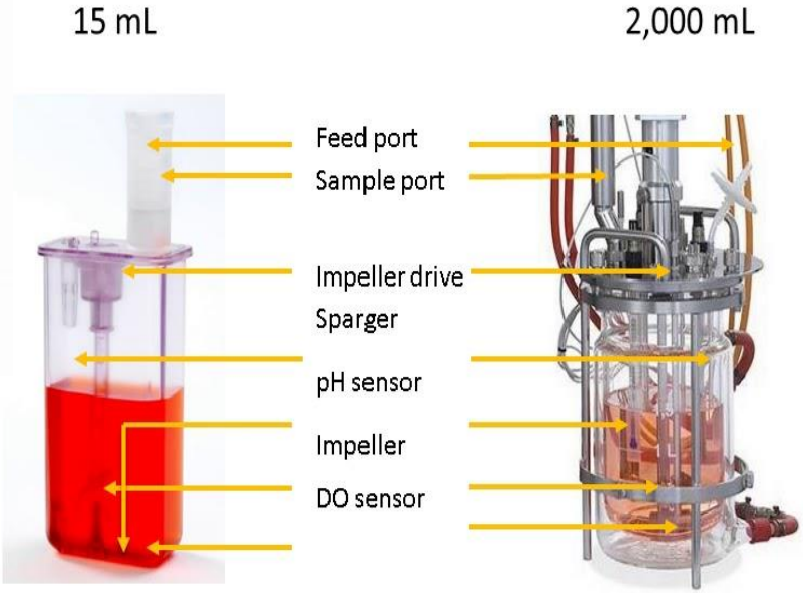


SAMSUNG BIOLOGICS

>30 15K L bioreactors

But, don't let the USP 'predictability' lull you into <u>not</u> confirming the science for <u>your</u> seed expansion → protein production culture process

ambr® 15 Vessel Features



<u>Process parameters to vary</u>: incubation temp, DO, induction day, feed times, pH, …

<u>Outputs to measure</u>: VCD, % viability, protein titer, glucose, lactate, ammonia, …

2 Challenges in Upstream Production by Living Cells

#1 Replacing a Working Cell Bank: Should there be any surprises?

MINIMUM CMC Regulatory Compliance CONTINUUM
during clinical development …

Cell bank system, characterisation and testing

A MCB should be established prior to the initiation of phase I trials. It is acknowledged that a Working Cell Bank (WCB) may not always be established.

Information on the generation, qualification and storage of the cell banks is required. The MCB and/or WCB if used should be characterised and results of tests performed should be provided. Clonality of the cell banks should be addressed for mammalian cell lines. The generation and characterisation of the cell banks should be performed in accordance with the principles of ICH Q5D.

Cell banks should be characterised for relevant phenotypic and genotypic markers so that the identity, viability, and purity of cells used for the production are ensured.

The nucleic acid sequence of the expression cassette including sequence of the coding region should be confirmed prior to the initiation of clinical trials.

As for any process change, the introduction of a WCB may potentially impact the quality profile of the active substance and comparability should be considered (see section S.2.6. Manufacturing process development).

Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials

27 January 2022
EMA/CHMP/BWP/534898/2008 Rev. 2

Not specifically what to test for, but the need to at least check for no quality impact

MINIMUM CMC Regulatory Compliance CONTINUUM

… for market approval

Replacement WCBs prepared using procedures equivalent (as described in the license) to those used to generate the previously approved WCB must meet all specified requirements [e.g., certificate of analysis (CoA) testing] but require no further evaluation under a validation protocol. When the new WCB is a "like-for-like" replacement, the WCB can be implemented after meeting the following criteria:

1. The new WCB must meet all cell bank release testing criteria, including tests for freedom from adventitious agents.
2. Prior to at-scale manufacturing, the WCB should be evaluated using scale-down cell culture tests from thaw through production culture to confirm cell culture performance. A minimum number of independent thaws should be included in the evaluation.
3. The scale-down cell culture evaluation criteria should include cell culture process key performance indicators (KPIs) and relevant product attributes and/or CQAs. For example, the KPI assessment may include specific growth rate and final viabilities for seed and inoculum train passages, final production culture viability, and final product titer. Product quality assessments may include purity, size-exclusion chromatography (SEC), and ion-exchange chromatography (IEC) assays. The evaluation criteria can be based on 95% confidence/99% probability tolerance intervals (95/99 TIs) generated using representative data available at the time the evaluation is performed (where appropriate). Results outside the evaluation criteria should be justified or further assessed using additional cell culture studies and/or product attribute testing.
4. The new WCB should produce manufacturing-scale material that meets all specified DS release testing requirements. A DS manufactured from a replacement bank may not need to be on stability protocol, but requires a CoA.

The release of batches derived from the new WCB would be predicated on successfully completing all the above-mentioned criteria and reporting the new WCB to the health authorities.

USP <1042>

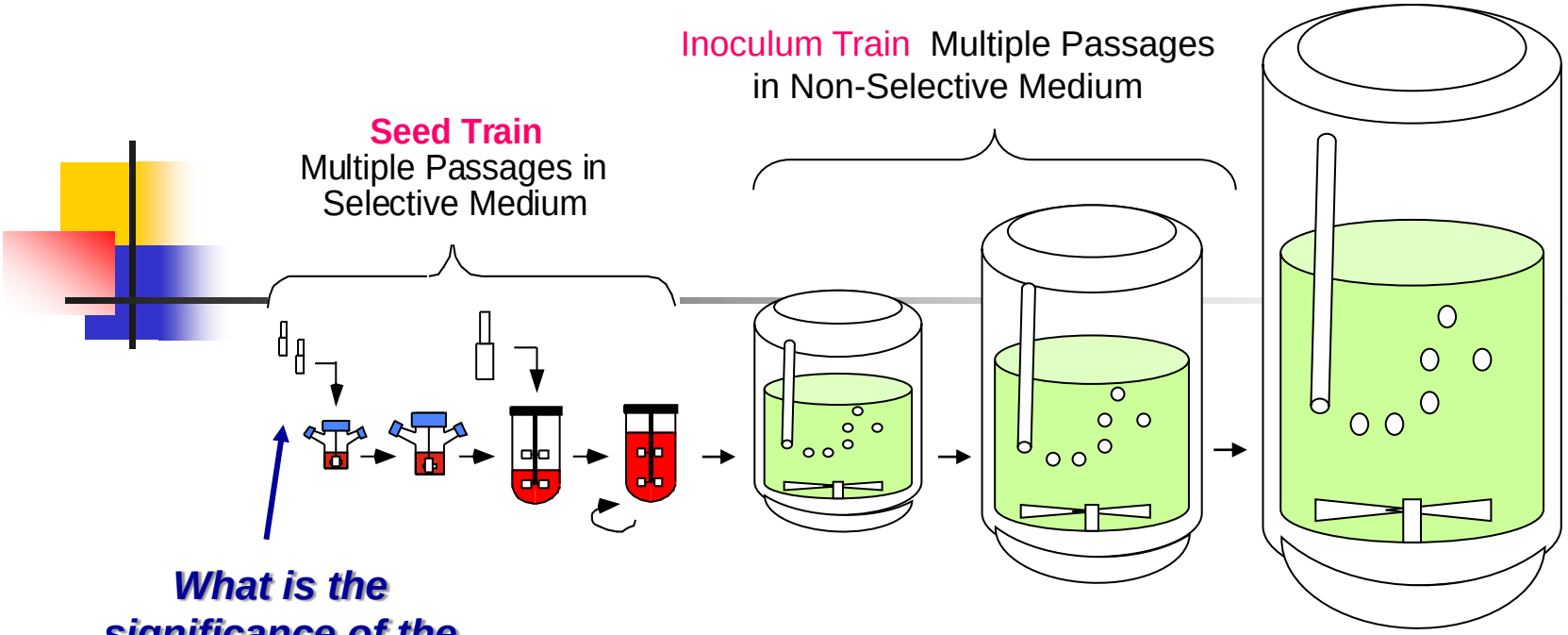
So a bit surprising that a WCB instability was not identified until the FDA was on site performing a PLI!

WCB, CHO cell line producing a mAb ***Genentech***

A pre-approval inspection (PAI) for pertuzumab drug substance manufacture was performed at the Vacaville (VV), CA facility from March 20 to March 28, 2012 by BMT reviewer Bo Chi (lead), BMT trainee Qing Zhou, product reviewers Kathryn King and Laurie Graham and an inspector from the San Francisco District, Lance DeSouza. VV is responsible for the manufacture of pertuzumab drug substance and for DS QC testing. A form 483 was issued at the end of this inspection. Observations included: 1) The environment of (b) (4) facility where pertuzumab is manufactured is not maintained in a clean and sanitary condition; 2) There is a lack of assurance that water used in (b) (4) is suitable for its intended use; 3) Equipment cleaning validation studies are inadequate; 4) There is a lack of systematic oversight of the DCS (distributed control system) used to monitor and control process performance; 5) Quality oversight of documentation is inadequate; 6) There is inadequate control of raw materials. In addition, while inspecting the facility, we discovered that the Sponsor was experiencing serious issues with the thaw and subsequent propagation of cells from WCB (b) (4) used to manufacture pertuzumab. At the time of inspection, the root cause investigation was ongoing and no root cause had been identified, although data suggested instability of WCB (b) (4) WCB (b) (4) is under the

The 483 items cited on this inspection could generally be classified as VAI (voluntarily action indicated), BUT the deviation and follow up data supplied from the firm related to their inability to successfully thaw and grow cultures from their working cell bank lead us to concur with the recommendation to withhold on this application by Division of Monoclonal Antibodies.

FDA CDER – Drugs@FDA: FDA Approved Drug Products: PERJETA (Pertuzumab) – Approval Date(s) and History, Letters, Labels, Reviews for BLA 125409 – Review: Chemistry Review(s) – Product Quality Review Data Sheet (May 31, 2012)



Summary Review for Regulatory Action

The initial and continued major concern in regard to this issue is whether Genentech has a validated process and can consistently manufacture pertuzumab with product quality characteristics comparable to that used in their clinical trials. Given the ongoing failures with the current working cell bank, Genentech has not yet demonstrated a consistent process that would ensure continued supply of commercial material.

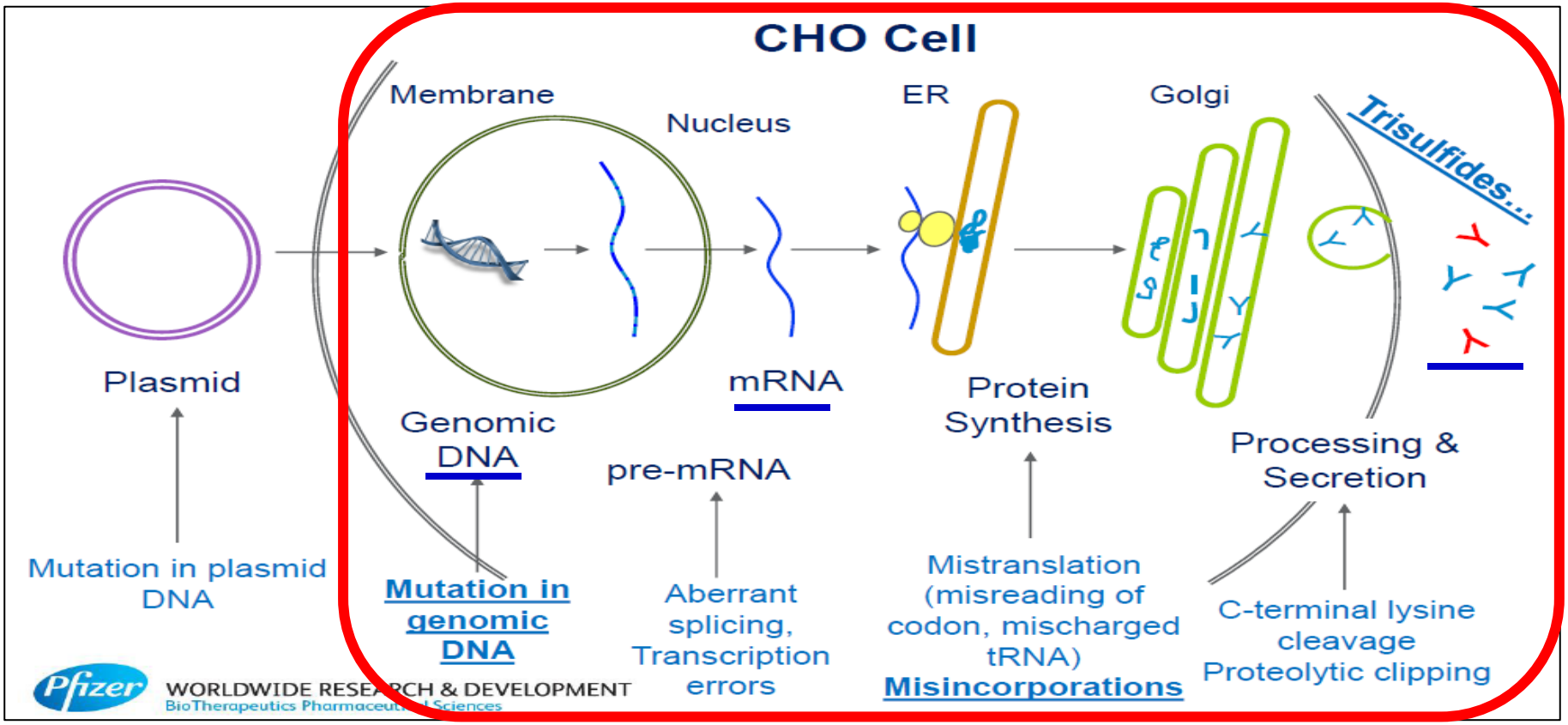
CHEMISTRY REVIEW(S)

Based on the understanding that the applicant has refused to make this product more widely available to patients prior to licensure while the manufacturing issues are being addressed, the clinical review office has indicated their intent to approve this product within a time frame consistent with the PDUFA deadline and to resolve outstanding manufacturing issues post-licensure. To the knowledge of the CMC review team, the initial licensure of a biological product under a BLA without concurrent approval of the manufacturing facility and the manufacturing process is unprecedented. This approach was agreed upon by the CDER Director. Therefore, DMA participated in the drafting of PMRs as the only mechanism available to mitigate risks to product quality from a process which lacks adequate validation.

2 Challenges in Protein Production by Living Cells

#2 Sequence Variants and LIVCA: Genetic Instability Happens!

Central Dogma of Molecular Biology → not 100% fidelity within the living cell!



Genetic infidelity is more common than previously thought!

Biopharmaceutical Industry Practices for Sequence Variant Analyses of Recombinant Protein Therapeutics

JOHN VALLIERE-DOUGLASS[1]*, LISA MARZILLI[2], APARNA DEORA[3], ZHIMEI DU[4], LUHONG HE[5], SAMPATH R. KUMAR[6], YAN-HUI LIU[4], HANS-MARTIN MUELLER[7], CHARLES NWOSU[6], JOHN STULTS[8], YAN WANG[10], SAM YAGHMOUR[11], and YIZHOU ZHOU[9]

[1]Seattle Genetics Inc., Bothell, WA; [2]Pfizer Inc., Andover, MA; [3]Pfizer Inc., Chesterfield, MO; [4]Merck & Co., Inc., Kenilworth, NJ; [5]Eli Lilly & Company, Indianapolis, IN; [6]Takeda Pharmaceuticals, Cambridge, MA; [7]Merck Sharp & Dohme AG, Lucerne, Switzerland; [8]Genentech Inc., South San Francisco, CA; [9]Biogen Inc., Cambridge, MA; [10]Takeda Pharmaceuticals, Lexington, MA; and [11]Amgen Inc., Thousand Oaks, CA

PDA J Pharm Sci and Tech **2019**, *73* 622-634

frequency of transgene mutation

plasmid → genomic DNA
(5-20%)

frequency of misincorporation

mRNA codon → amino acid
(5-30%)

amino acid supplementation during cell culture). When respondents were asked about the frequency with which cell lines (clones) were found to carry genetic mutations in the recombinant transgene, the range in the responses varied considerably, from 5% to 20%. Similarly, when asked about the frequency with which misincorporation was observed in samples submitted for SVA, respondents indicated that it (misincorporation) was observed in 5%–30% of samples that were analyzed. As indicated previously, 6 of 11 respondents used NGS to detect mutations in the DNA of the recombinant protein/transgene. Although NGS is not

According to the industry survey –

What if protein sequence variants are detected?

If in new cell line at > 1% protein sequence variants – discard

If in established cell line , need to develop a robust strategy to address any quality issue

Case Examples

Samsung Biosimilar to Avastin (Genentech) **Aybintio** bevacizumab EPAR 25 June 2020 EMA/380645/2020

> Of importance, the presence of additional C- and N-terminal sequence variants was observed in SB8, but not in EU Avastin. It was highlighted that the presence of sequence variants at low levels may have unanticipated safety consequences that were not apparent in the clinical studies. Consequently, potential safety risks from these sequence variants have been discussed by the Applicant. Thus, these sequence variants are considered as product-related impurities which need to be strictly controlled by an appropriate control system, and the recommendations regarding the control strategy were given.

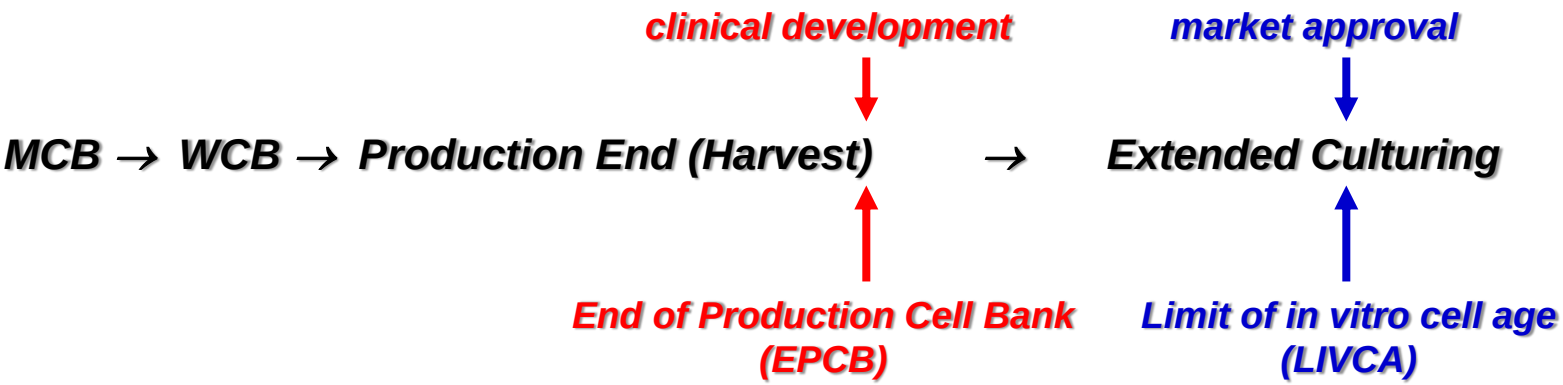
(IgG1) based bispecific antibody **Rybrevant** amivantamab EPAR 14 October 2021 EMA/629045/2021

> A sequence variant (due to a point mutation) was detected in the anti-MET LC. It exists in the MCB, the WCB and the end-of-production cell bank (EPCB) at levels close to the limit of detection. Based on the totality of information regarding the sequence variant throughout the dossier, it is considered well controlled at low levels. This is acceptable.

Required to check for genetic instability!

MINIMUM CMC Regulatory Compliance CONTINUUM

during clinical development *for market approval*



Check for:

- *Identification of any change in the amino acid sequence of the expressed protein*
- *Identification of any change in the nucleic acid sequence of the transgene DNA/RNA*

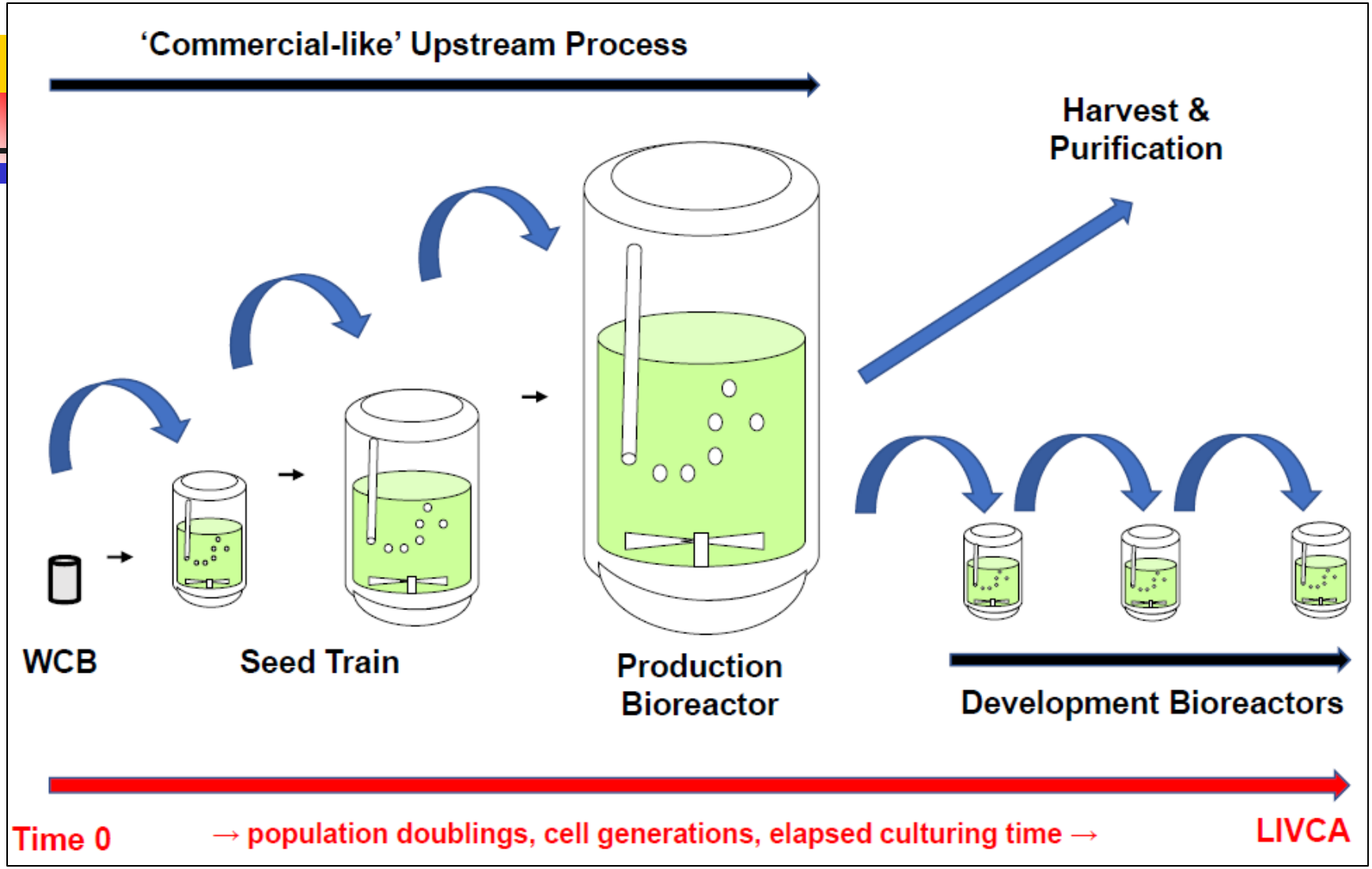
ICH Q5B/Q5D

- *+ Confirmation of absence of latent virus induction (insect/mammalian/human cells)*

  (e.g., chickenpox → shingles in humans – especially as we age)

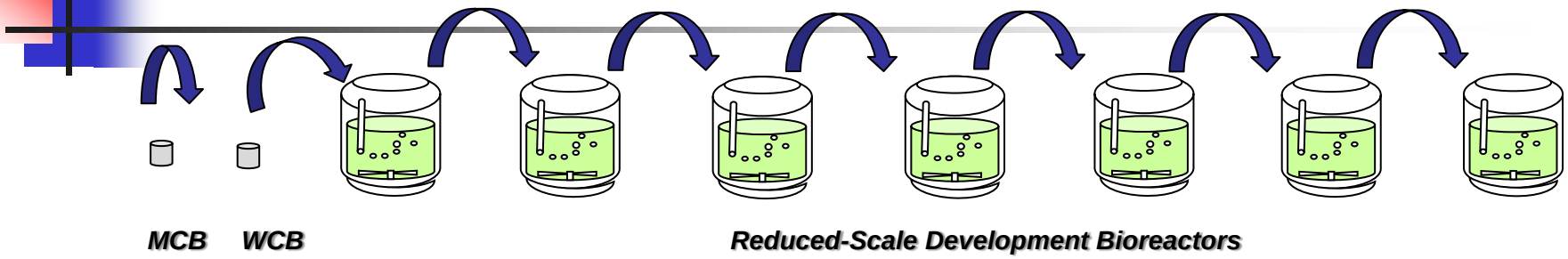
ICH Q5A(R1)

***Traditional* & *Expected* approach to LIVCA determination**



***Non-traditional* approach to LIVCA determination**

expect regulatory authority hesitancy!



11. Conduct a study using end of production cells from commercial scale manufacturing that tests for *in vivo* adventitious viruses and genetic consistency. Submit the Final Report as a PAS.

The timetable you submitted on June 1, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	08/2012
Study Completion:	12/2012
Final Report Submission:	02/2013

Rationale for PMC:
The data in the submission for this testing was performed using cells from reduced scale models. Because of concerns regarding the models not being representative of the commercial process, it was determined that this testing would need to be done on cells from the commercial scale process.

Genentech Perjeta mAb FDA Market Approval Letter Post-Market Commitment June 2012

[Genentech tried similar approach in Feb 2004 with Avastin mAb – same FDA response]

CASE EXAMPLE Genetic Instability

Chromosomal gene translocation ('jumping genes')

Merck Serono SA

ABSTRACT: During the validation of an additional working cell bank derived from a validated master cell bank to support the commercial production continuum of a recombinant protein, we observed an unexpected chromosomal location of the gene of interest in some end-of-production cells. This event—identified by fluorescence in situ hybridization and multicolour chromosome painting as a reciprocal translocation involving a chromosome region containing the gene of interest with its integral coding and flanking sequences—was unique, occurred probably during or prior to multicolour chromosome painting establishment, and was transmitted to the descending generations. Cells bearing the translocation had a transient and process-independent selective advantage, which did not affect process performance and product quality. However, this first report of a translocation affecting the gene of interest location in Chinese Hamster Ovary cells used for producing a biotherapeutic indicates the importance of the demonstration of the integrity of the gene of interest in end-of-production cells.

CQAs → no impact **KPPs → no impact**

Reciprocal Translocation Observed in End-of-Production Cells of a Commercial CHO-Based Process

PDA J Pharm Sci and Tech **2015**, *69* 540-552

CANCER GENETICS

DNA replication timing directly regulates the frequency of oncogenic chromosomal translocations

Mihaela Peycheva, Tobias Neumann, Daniel Malzl, Mariia Nazarova, Ursula E. Schoeberl, Rushad Pavri*

SCIENCE science.org

16 SEPTEMBER 2022 • VOL 377 ISSUE 6612 **1277**

DOWNSTREAM PURIFICATION (DSP) BY CHROMATOGRAPHY AND FILTRATION

Multiple Chromatographic Systems to Consider

Affinity Chromatography
Ion Exchange Chromatography
(Cation Exchange, Anion Exchange)
Hydrophobic Interaction Chromatography
Size Exclusion Chromatography

Filtration Systems to Consider

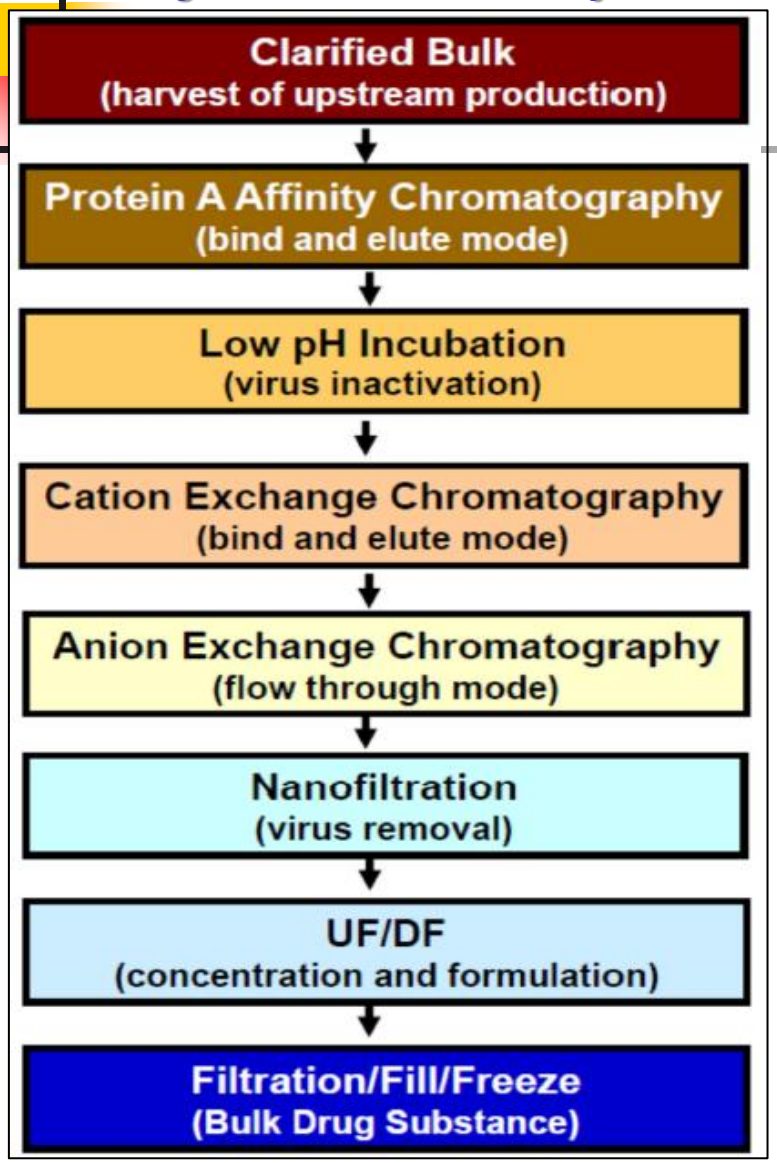
<u>Normal Flow Filtration</u> ('dead end')
0.2 micron (microbes)
0.1 micron (mycoplasma)
0.05 micron (viruses)

[protein size < 0.01 micron]

<u>Tangential Flow Filtration</u>, TFF ('cross flow")
ultrafiltration/diafiltration (UF/DF)
choice of MW cutoff of protein to contain

PURIFICATION BY CHROMATOGRAPHY AND FILTRATION

IgG Monoclonal Antibody



Platform approach today

2 Challenges in Purification of Protein from Living Cells

#1 Complexity of the Impurity Profile - Don't Underestimate!

Removal of Process-Related Impurities

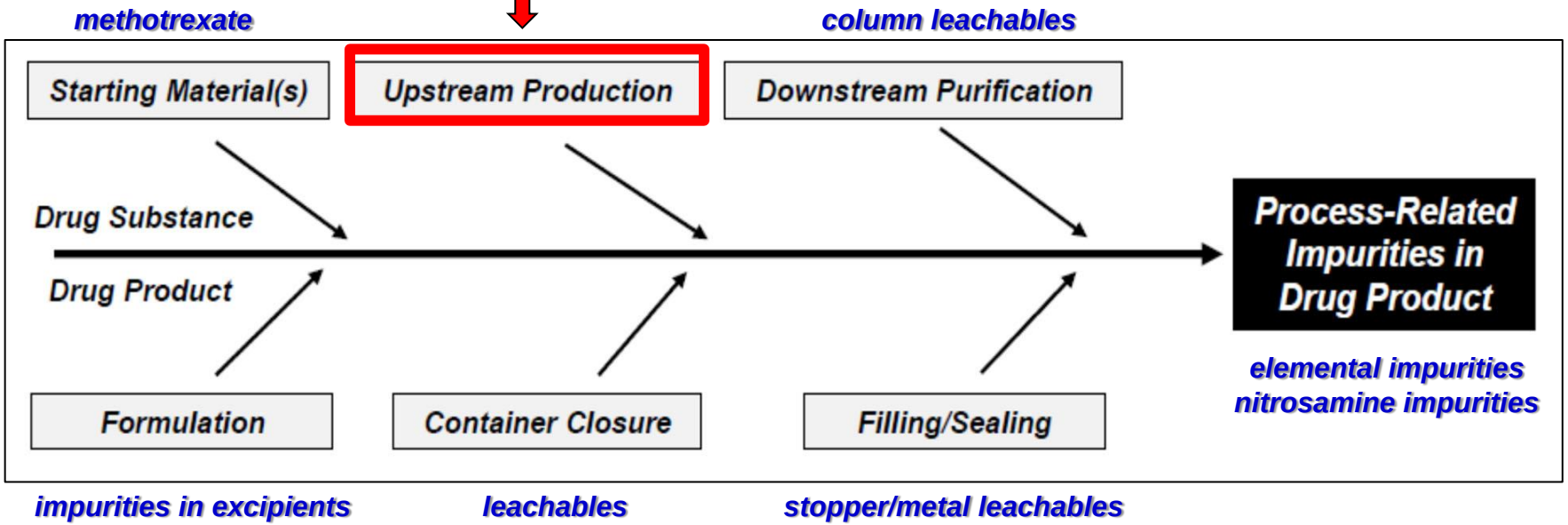
Media-derived Impurities
- growth factors (e.g., IGF)
- lipids (e.g., cholesterol)
- antibiotics antifoam

Cell-derived Impurities
- host cellular DNA
- host cell proteins (HCPs)
- putative viruses

'We recommend that you limit the amount of residual DNA for continuous nontumorigenic cells to less than 10 ng/dose and the DNA size to below approximately 200 base pairs.'
qPCR dPCR

residual level/ID by ELISA and/or LC/MS

clearance confirmed by viral safety evaluation



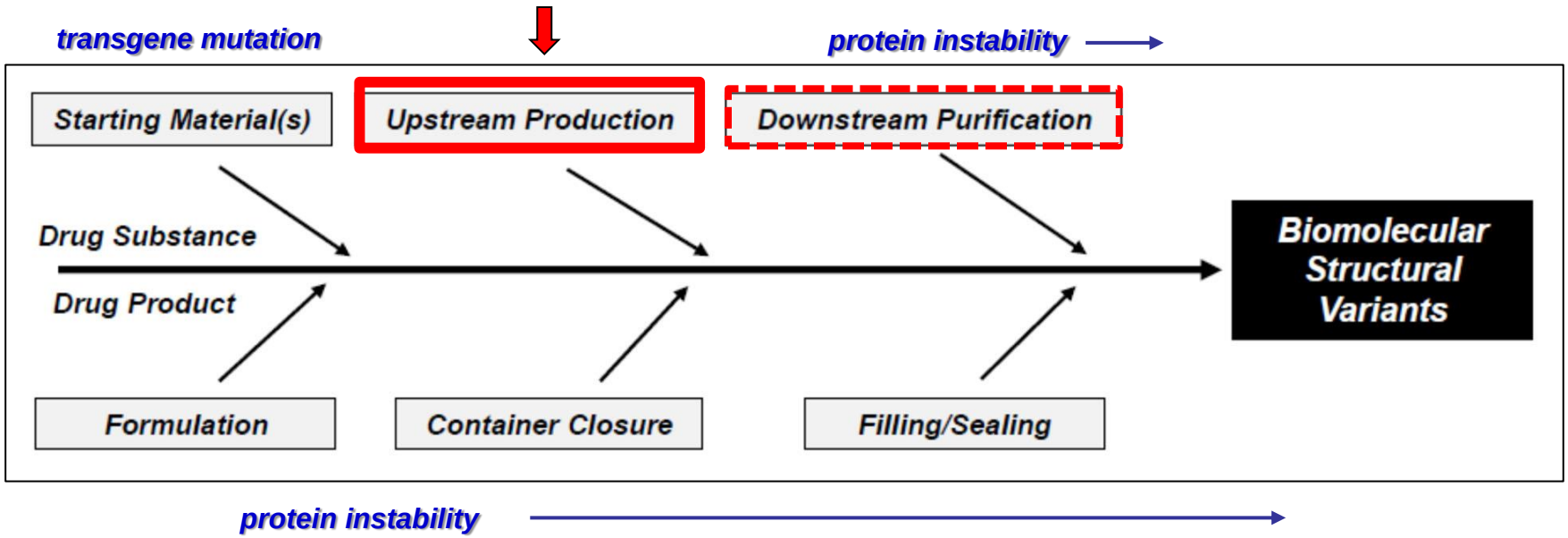
***Product-Related Substances*. Molecular variants of the desired product which are active and have no deleterious effect on the safety and efficacy of the drug product.**

***Product-Related Impurities*. Molecular variants of the desired product which do not have properties comparable to those of the desired product with respect to activity, efficacy, and safety.**

Removal of Product-Related Impurities

Misincorporation
mRNA → amino acid
Post-translational modifications
Undesired Glycosylation/Glycation

Truncation (N-terminus, C-terminus)
Hydrolytic fragmentation
Oxidation
Deamidation
Disulfide scrambling
Aggregation



MINIMUM CMC Regulatory Compliance CONTINUUM

during clinical development …

S.3.2. Impurities

Process related impurities (e.g. host cell proteins, host cell DNA, media residues, column leachables) and product related impurities (e.g. precursors, cleaved forms, degradation products, aggregates) should be addressed. Quantitative information on impurities should be provided including maximum amount for the highest clinical dose. For certain process-related impurities (e.g. antifoam agents), an estimation of clearance may be justified. In case only qualitative data are provided for certain impurities, this should be justified.

S.4.1. Specification

Upper limits, taking into account safety considerations, should be set for the impurities.

P.5.1. Specification

Upper limits, taking safety considerations into account, should be set for impurities. They may need to be reviewed and adjusted during further development. For the impurities not covered by the active substance specification, upper limits should be set, taking into account safety considerations.

EUROPEAN MEDICINES AGENCY

Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials

27 January 2022
EMA/CHMP/BWP/534898/2008 Rev. 2

MINIMUM CMC Regulatory Compliance CONTINUUM

…for market approval

The capacity of the proposed purification procedures to deliver the desired product and to remove product and process-related impurities (e.g. unwanted variants, HCPs, nucleic acids, media components, viruses and reagents used in the modification of the protein) to acceptable levels should be thoroughly evaluated. This generally includes establishment of adequate analytical methods required for respective impurity detection and an estimation of the concentrating or removing capacity for each unit operation followed by the determination of appropriate acceptance criteria. For certain process-related impurities (e.g. HCP, DNA, antibiotics) scale-down spiking experiments may be required to determine the removal capacity of the individual purification steps. Evaluation of purification steps for which high impurity clearance are claimed, operating in worst case and/or non-standard conditions (e.g. process hold times, spiking challenge) could be performed to document the robustness of the process. For some components (e.g. low-molecular weight media components), a risk-based approach is acceptable showing that no safety concerns like immunogenicity or toxicity are present.

EUROPEAN MEDICINES AGENCY

Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission

28 April 2016
EMA/CHMP/BWP/187338/2014

CASE EXAMPLE

Trouble with obtaining market BLA approval due to insufficient evaluation and control of the impurity profile!

Portola Pharmaceuticals
Recombinant coagulation factor Xa

BLA filed with FDA; after 6 month priority review, received a CRL *(12 of 18 major issues were CMC-related)*

We acknowledge that ANDEXAA is a breakthrough therapy developed for an indication that addresses an urgent unmet medical need. As such, FDA is committed to working with Portola to advance your manufacturing program…The data you provided in your responses to the Form FDA 483 issued on do not adequately address the deficiencies in the validation of the ANDEXXA manufacturing process that were identified during the Pre-License Inspection (PLI) of the facility.

The ANDEXXA process is not validated to assure reasonable control of sources of variability that could affect production output and to assure that the process is capable of consistently delivering a product of well-defined quality.

Complete the validation studies for the clearance of all impurities and submit the final study reports to demonstrate identification and control of these impurities. This is needed to assure process consistency and establish a process control strategy which will ensure the quality of the commercially manufactured product.

Please note that impurity clearance studies are considered critical to the process qualification stage of process validation (reference is made to the 2011 FDA Guidance on Process Validation) and therefore prior to submission to FDA these studies should be reviewed and approved by your quality assurance unit to document the use of sound scientific methodology and principles with adequate data to support the conclusions.

(2 year delay in BLA approval, 2018)

FDA CBER, Vaccines, Blood & Biologics: Licensed Biological Products with Supporting Documents: ANDEXXA (Coagulation factor Xa, recombinant, inactivated zhzo) – Approval History, Letters, Reviews and Related Documents 2 – BLA Complete Response Letter (August 17, 2016)

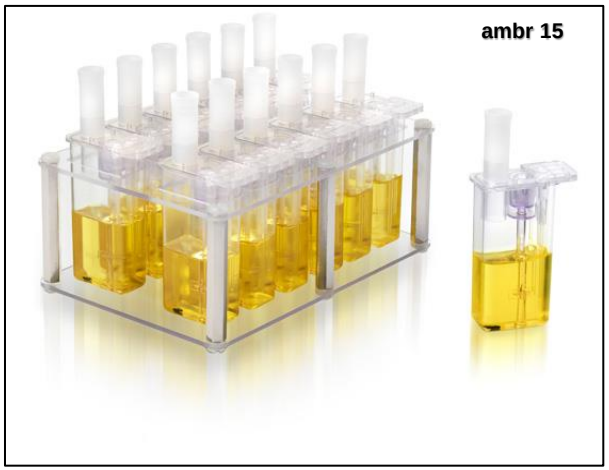
2 Challenges in Purification of Protein from Living Cells

#2 Reduced-Scale Studies: Be Aware of Limitations!

A challenge in 'visualization' of comparability

Manufacturing Scale

Reduced Scale



Reduced-scale studies are absolutely necessary for biopharmaceuticals!

- ***Some Studies Cannot be Carried Out in a GMP Facility***
  - ***ill advised to contaminate a GMP process step in the manufacturing facility (e.g., spiking excess HCPs onto a GMP chromatography column)***
- ***Some Studies Would Expose Workers to Unsafe Conditions***
  - ***large quantities of live viruses would be needed for virus clearance spiking studies onto manufacturing scale columns***
- ***Large-Scale Studies Are Costly***
  - ***expensive tying up a commercial manufacturing facility***

But, reduced-scale studies also have limitations!

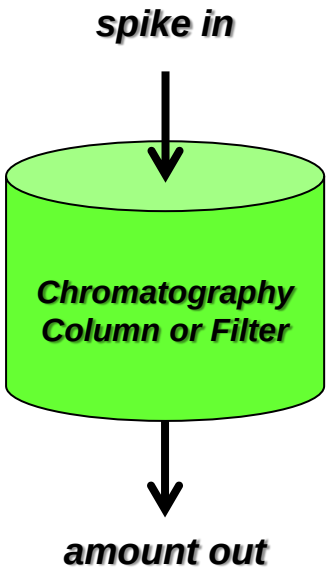
> ***"Now it would be very remarkable if any system existing in the real world could be exactly represented by any simple model. However, cunningly chosen parsimonious models often do provide remarkably useful approximations."***

'parsimonious' – frugal, stingy

British mathematician and statistician George E P Box

Typical reduced-scale studies for biopharmaceuticals!

Downstream Purification Process for Recombinant Proteins and Monoclonal Antibodies	
Reduced-Scale Study	**Comments**
Virus Clearance Evaluation (inactivation, removal)	Virus spiking studies across the individual chromatography columns and nanofiltration step; obtaining $\log_{10}$ virus reduction factors
Process-Related Impurities	Impurity spiking studies across the individual chromatography columns, obtaining reduction factors • Host cell DNA • Host cell protein (HCP) • Protein A leachables • Media components of concern
Product-Related Impurities	Tracking clearance across the individual chromatography columns, obtaining reduction factors • Aggregates • Molecular variants of concern
Intermediate Hold Times	Product stability upon holding *(will have to be confirmed at full commercial-like scale, both for protein stability as well as control of endotoxin and bioburden buildup)*
Chromatographic Column Resin Use Life	Determination of maximum number of re-uses for each chromatography resin in the purification process *(will have to be confirmed the end of commercial column resin use cycle)*



LRF – log reduction factor

Robust step = ≥ 4 $\log_{10}$ removal

Regulatory authorities EXPECT JUSTIFICATION of reduced-scale studies compared to the manufacturing process!

The contribution of data from small-scale studies to the overall validation package will depend upon demonstration that the small-scale model is an appropriate representation of the proposed commercial-scale. Data should be provided demonstrating that the model is scalable and representative of the proposed commercial process. Successful

DEVELOPMENT AND MANUFACTURE OF DRUG SUBSTANCES
(CHEMICAL ENTITIES AND BIOTECHNOLOGICAL/BIOLOGICAL ENTITIES)

ICH Q11 (2012)

Small scale models are important tools in the development and evaluation of biopharmaceutical manufacturing processes. During process evaluation, small scale models enable evaluation of input material and parameter variability to an extent that may not be feasible at manufacturing scale.

A small scale model must be designed and executed, and ultimately justified, as an appropriate representation of the manufacturing process.

Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission

28 April 2016
EMA/CHMP/BWP/187338/2014

Example of MINIMUM CMC Regulatory Compliance CONTINUUM
Reduced-Scale Study of Viral Clearance

Minimum Requirements for Viral Clearance Safety Evaluation	
Clinical Development Stage (FIH onward)	**Market Approval Stage**
Validation of virus clearance to be completed and included in clinical trial application	Full validation of virus clearance to be completed and included in market application
Studies should include two orthogonal steps that complement each other in their mode of action studies; the reproducibility to be demonstrated by at least two independent studies	Studies should include two distinct effective orthogonal steps that complement each other in their mode of action – an 'effective' virus removal step gives reproducible reduction of virus load in the order of 4 logs or more, shown by at least two independent studies
Clearance to be demonstrated for more than one manufacturing process step	Clearance to be demonstrated across the manufacturing process steps; one of the manufacturing steps should effectively clear non-enveloped viruses [*typically, all process steps that may contribute significantly to virus clearance are studied*]
Clearance to be demonstrated for both an enveloped and a non-enveloped virus (preferably a parvovirus)	Clearance to be demonstrated for a range of other potential virus types – different genomes (DNA, RNA), different physical sizes, enveloped/non-enveloped [*typically, 4 virus types studied*]
N/A	Chromatography media/resin lifetime use defined [*confirmed by reduced scale; concurrent validation at full scale*]

GUIDELINE ON VIRUS SAFETY EVALUATION OF BIOTECHNOLOGICAL INVESTIGATIONAL MEDICINAL PRODUCTS

London, 24 July 2008
EMEA/CHMP/BWP/398498/2005

VIRAL SAFETY EVALUATION OF BIOTECHNOLOGY PRODUCTS DERIVED FROM CELL LINES OF HUMAN OR ANIMAL ORIGIN ICH Q5A(R2) (2022)

Applying the Minimum CMC Regulatory Compliance Continuum

Manufacturing Process Control

Stage 1 ***Process Design*** ***Process Characterization***

GOAL: during clinical development, establish a manufacturing process suitable for eventual commercial manufacturing that can consistently deliver a defined product that meets its quality attributes (identify CQAs and CPPs, establish control system; scale-up)

Process Validation: General Principles and Practices

January 2011

Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission

28 April 2016
EMA/CHMP/BWP/187338/2014

S.2.5. Process validation

Process validation data should be collected throughout development, although they are not required to be submitted in the IMPD.

For manufacturing steps intended to remove or inactivate viral contaminants, the relevant information should be provided in the section A2, Adventitious agents safety evaluation.

Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials

27 January 2022
EMA/CHMP/BWP/534898/2008 Rev. 2

EUROPEAN MEDICINES AGENCY

Applying the Minimum CMC Regulatory Compliance Continuum

Manufacturing Process Control

Stage 1 — *Process Design* — *Process Characterization*

GOAL: during clinical development, establish a manufacturing process suitable for eventual commercial manufacturing that can consistently deliver a defined product that meets its quality attributes (identify CQAs and CPPs, establish control system; scale-up)

Stage 2 — *Process Qualification* — *Process Verification*

GOAL: implement the control strategy and confirm that the final manufacturing process performs effectively in routine manufacture and is able to produce a commercial product of the desired quality (process validation and PPQ batches)

Stage 3 — *Continued Process Verification* — *Ongoing Process Verification*

GOAL: ongoing assurance of the controlled manufacturing process

Process Validation: General Principles and Practices

January 2011

Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission

28 April 2016
EMA/CHMP/BWP/187338/2014

Adequate Risk-Based Process Control at Stage 2

(focused on patient safety + consistency of manufacturing process

3.2.S.2.5 Process Validation and/or Evaluation (name, manufacturer)

Process validation and/or evaluation studies for aseptic processing and sterilisation should be included.

Biotech:

Sufficient information should be provided on validation and evaluation studies to demonstrate that the manufacturing process (including reprocessing steps) is suitable for its intended purpose and to substantiate selection of critical process controls (operational parameters and in-process tests) and their limits for critical manufacturing steps (e.g., cell culture, harvesting, purification, and modification).

The plan for conducting the study should be described and the results, analysis and conclusions from the executed study(ies) should be provided. The analytical procedures and corresponding validation should be cross-referenced (e.g., 3.2.S.2.4, 3.2.S.4.3) or provided as part of justifying the selection of critical process controls and acceptance criteria.

For manufacturing steps intended to remove or inactivate viral contaminants, the information from evaluation studies should be provided in 3.2.A.2.

QUALITY OVERALL SUMMARY OF MODULE 2
MODULE 3 : QUALITY
ICH HARMONISED TRIPARTITE GUIDELINE

M4Q(R1) 2002

Special Note: *Level of Quality Unit 'oversight' for process validation studies*

Although often performed at small-scale laboratories, most viral inactivation and impurity clearance studies cannot be considered early process design experiments. Viral and impurity clearance studies intended to evaluate and estimate product quality at commercial scale should have a level of quality unit oversight that will ensure that the studies follow sound scientific methods and principles and the conclusions are supported by the data.

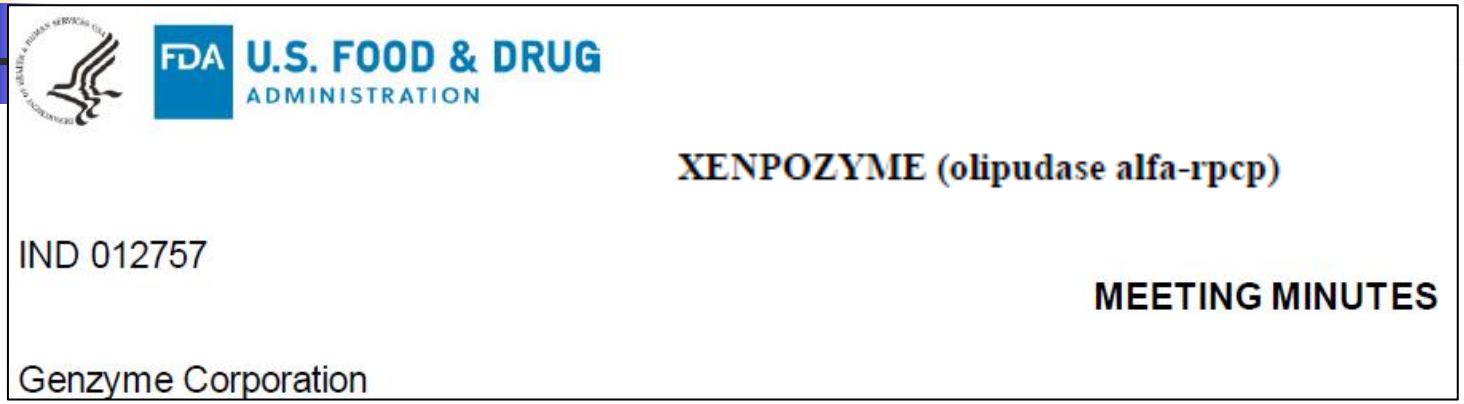
FDA Gfl Process Validation: General Principles and Practices (2011)

The Quality Unit should provide appropriate oversight and approval of process validation studies required under GMPs. Although not all process validation activities are performed under GMPs (for example, some Stage 1 – Process Design studies) *(4)*, it is wise to include the Quality and Regulatory representatives on the cross-functional team. The degree and type of documentation required varies during the validation lifecycle, but documentation is an important element of all stages of process validation. Documentation requirements are greatest during the process qualification and verification stages. Studies during these stages should conform to GMPs and be approved by the Quality Unit.

PDA Technical Report #60 Process Validation: A Lifecycle Approach (2013)

***Pre-BLA submission meetings*: FDA, in order to stress to a company the importance of process validation, frequently attaches to the meeting minutes, a "hot topic" list of frequently encountered deficiencies in biopharmaceutical process validation**

Case Example



U.S. FOOD & DRUG ADMINISTRATION

XENPOZYME (olipudase alfa-rpcp)

IND 012757

MEETING MINUTES

Genzyme Corporation

Meeting Type:	B
Meeting Category:	Pre-BLA
Meeting Date and Time:	March 24, 2021; 11:15AM – 12:15PM EST
Meeting Location:	Teleconference
Application Number:	012757
Product Name:	GZ402665

www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761261Orig1s000AdminCorres.pdf

Process validation expectations for the filed BLA, stated by the FDA

- Bioburden and endotoxin data obtained during manufacture of three process qualification (PPQ) lots (3.2.S.2.5).
- Microbial data from three successful product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).
- Chromatography resin and UF/DF membrane lifetime study protocols and acceptance criteria for bioburden and endotoxin samples. During the lifetime studies, bioburden and endotoxin samples should be taken at the end of storage prior to sanitization (3.2.S.2.5).
- Information and summary results from the shipping validation studies (3.2.S.2.5).
- In-process microbial controls and hold times. Three successful product intermediate hold time validation runs should be performed at manufacturing scale, unless an alternative approach can be scientifically justified. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.
- Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Describe the environmental and personnel monitoring procedures followed during media fills and compare them to the procedures followed during routine production.

What is the origin of the number 3? ***Monte Python, 'Search for the Holy Grail'***

Monty Python – 'Search for the Holy Grail' – Bridge of Death

The '3 Run' PV Rule is Gone!

FDA

5. Do CGMPs require three successful process validation batches before a new active pharmaceutical ingredient (API) or a finished drug product is released for distribution?

No. Neither the CGMP regulations nor FDA policy specifies a minimum number of batches to validate a manufacturing process…. The manufacturer is expected to have a sound rationale for its choices in this regard. The agency encourages the use of science based approaches to process validation."

FDA Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance – Production and Process Controls; FDA website

ICH ***EMA***

Generally, process validation includes the collection of data on an appropriate number of production batches (see ICH Q7, Section 12.5). The number of batches can depend on several factors including but not limited to: (1) the complexity of the process being validated; (2) the level of process variability; and (3) the amount of experimental data and/or process knowledge available on the specific process.

ICH Q11

Process Performance Qualification (PPQ)

Factors to consider in the calculation of how many batches to run

Manufacturing Process Understanding	Biologic Product Knowledge	Manufacturing Experience
Are all CPPs identified?	Are all CQAs identified?	Level of batch-to-batch variation?
How comprehensive is the control strategy?	How robust is the product stability profile?	Process capability knowledge?

Table 8: Calculating the number of PPQ runs by the PpK method using an MS Excel spreadsheet for sample sizes >25

1	E	F	G	H
3	Symbol	Description	Value	Formula
4	X_{avg}	Sample average	97.77	=AVERAGE(sample data)
5	s	Sample standard deviation	1.91	=STDEV.S(sample data)
6	LSL	Lower specification limit	95	User defined
7	USL	Upper specification limit	105	User defined
8	P_{pK}	Estimated process capability	1.762496	=MIN((G7-G4)/3*G5,(G4-G6)/3*G5)
9	LCCI	Target, lower bound process capability	1	Default set to 1
10	$1-\alpha$	Confidence	0.97	User defined based on risk assessment
11	α	Acceptable risk	0.03	=1-G10
12	n	Number of PPQ runs	11	=((NORM.S.INV(G11))^2)*((1/(9*G8))+0.5)/((1-(G9/G8))^2)

BioProcess International 21(5) MAY 2023

Determine overall residual risk level

Translate into number of PPQ batches to run

QUESTION: So how many PPQ batches will you run?

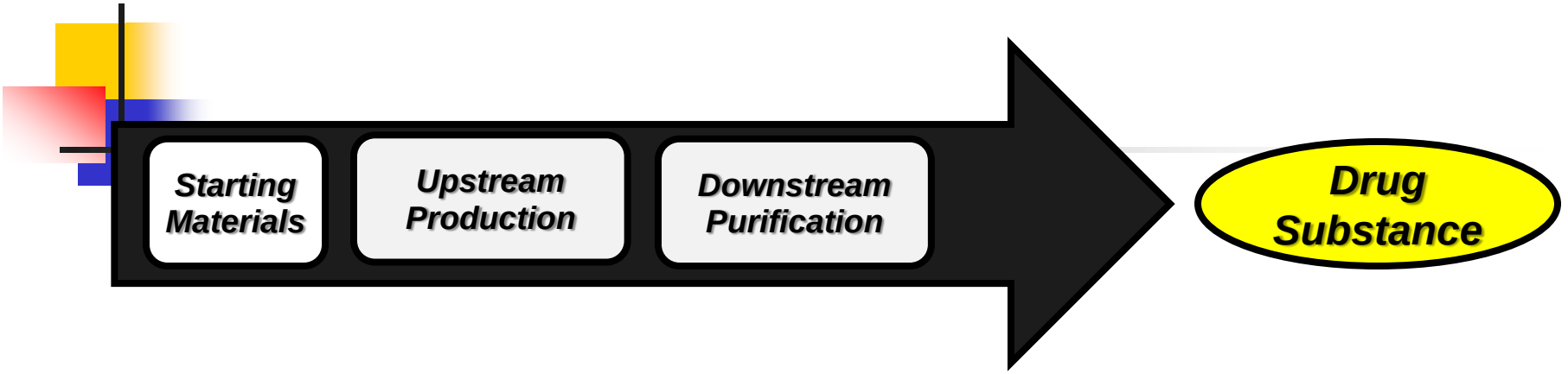
Case Example *Successful Process Validation in MAA*

Samsung Bioepis **Epysqli** eculizumab 30 March 2023 EMA/203468/2023 EPAR

Process validation included a number of studies which investigated a) process performance qualification (PPQ) of both the cell culture and the purification process, b) impurity clearance to show that the intended purification process is able to reduce the impurities to acceptable levels in accordance with the pre-determined acceptance criteria, c) hold times for process intermediates, d) resin lifetime to demonstrate that the chromatography column resins are capable of maintaining acceptable performance characteristics over extensive cycling, and e) the shipping qualification.

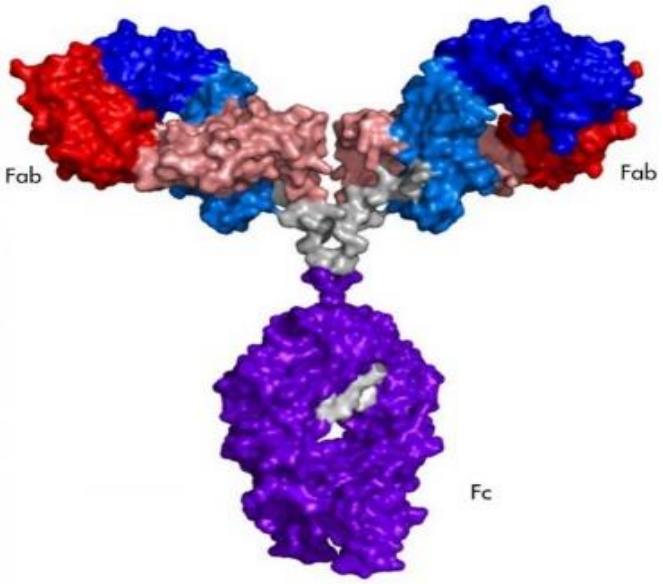
Several PPQ batches had been produced, and met the acceptance criteria. Based on the results of the process validation, the manufacturing process is considered validated for active substance commercial manufacturing. However, a single batch was terminated due to the presence of microbial contaminants. Since there was no breach of GMP practice with low possibility of recurrence and immediate detection of the event was performed, the risk category was determined as low with the requirement of an investigation for root cause analysis. A detailed summary of the conducted root cause investigation of this microbial contamination during process validation has been submitted. Based on the investigation results, it was concluded that there was no process or product impact due to termination of the certain batch. An alternative batch was started as a replacement batch and met all pre-determined specification.

Applied Risk-Management Across the Manufacturing Process



Many times, at the last purification step (DF), the formulation excipients are introduced

When aliquoted and frozen → Bulk Drug Substance



CQA Category

Appearance
Identity
Quantity
Safety
General

Purity/impurities
Potency

compendial requirements and test methods listed in USP and Ph. Eur.

CQA Category and Description	
Appearance	**Visual – physical state, color, clarity** **Particulate Matter (~~extrinsic~~, intrinsic)**
Quantity	**amount, content (e.g., mg/vial, mg/mL)**
Safety	**Absence of virus and mycoplasma (unprocessed bulk)** **Endotoxin, Bioburden**
General	**pH, osmolarity, …**

CQA Category and Description	
Identity	**must be 'highly specific' and 'based on unique aspects of its molecular structure and/or other specific properties' – [peptide map, ELISA]**

compendial requirement, with specific emphasis of ICH Q6B

"Not everything that can be counted counts, and not everything that counts can be counted"
William Bruce Cameron, sociologist

PRODUCT PURITY + PRODUCT-RELATED IMPURITIES

Known Structural Variants for Protein-Based Biopharmaceuticals	
Protein Sequence Sequence variants Mis-incorporated amino acids N-terminal variants C-terminal variants Protein hydrolysis variants	**Molecule Protein Properties** Acidic charge variants Basic charge variants Low molecular weight variants High molecular weight variants Monomer/Aggregation size variants
Individual Amino Acid Instability Oxidation variants Deamidation variants Disulfide scrambling variants	**Higher Order Structures** Secondary structural variants Tertiary structural variants
Molecule Carbohydrate Properties Site variants Site occupancy variants N-glycan structural variants	**Glycosylation** Afucosylation variants Galactosylation variants Sialyation variants

→

PROCESS-RELATED IMPURITIES

Host Cellular DNA
Host Cell Proteins (HCPs)
Upstream Media Impurities
Downstream Impurities (resins)

possible to control these through a 'process validation' approach

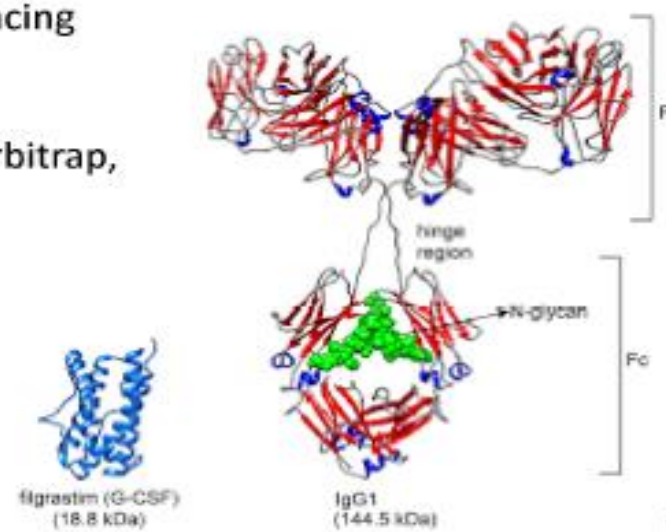
***Mature* test method tool box for characterization of mAbs**

The Current Analytical Tool Box

1° Sequence/PTMs
AA analysis
N- and C-term Sequence
Peptide Mapping and Sequencing
  LC-MS/MS
Free sulfhydryls
MALDI-TOF, ESI-QTOF-MS, orbitrap, etc....

HOS
Near- and Far-UV CD
FTIR
DSC
HDX-MS
X-ray
NMR

Glycan Analysis
ESI- MS
MALDI-TOF MS
Labeled, PNGaseF released
  HPAEC-PAD
  HPLC-FD
  HILIC (HPLC, UHPLC)
CE-LIF (MS)



Japelj et al Sci Reports 2016

Charge
cIEF
icIEF
ICE
IEX- HPLC
CZE

Process Related Impurities
DNA, HCP, Protein A, etc.

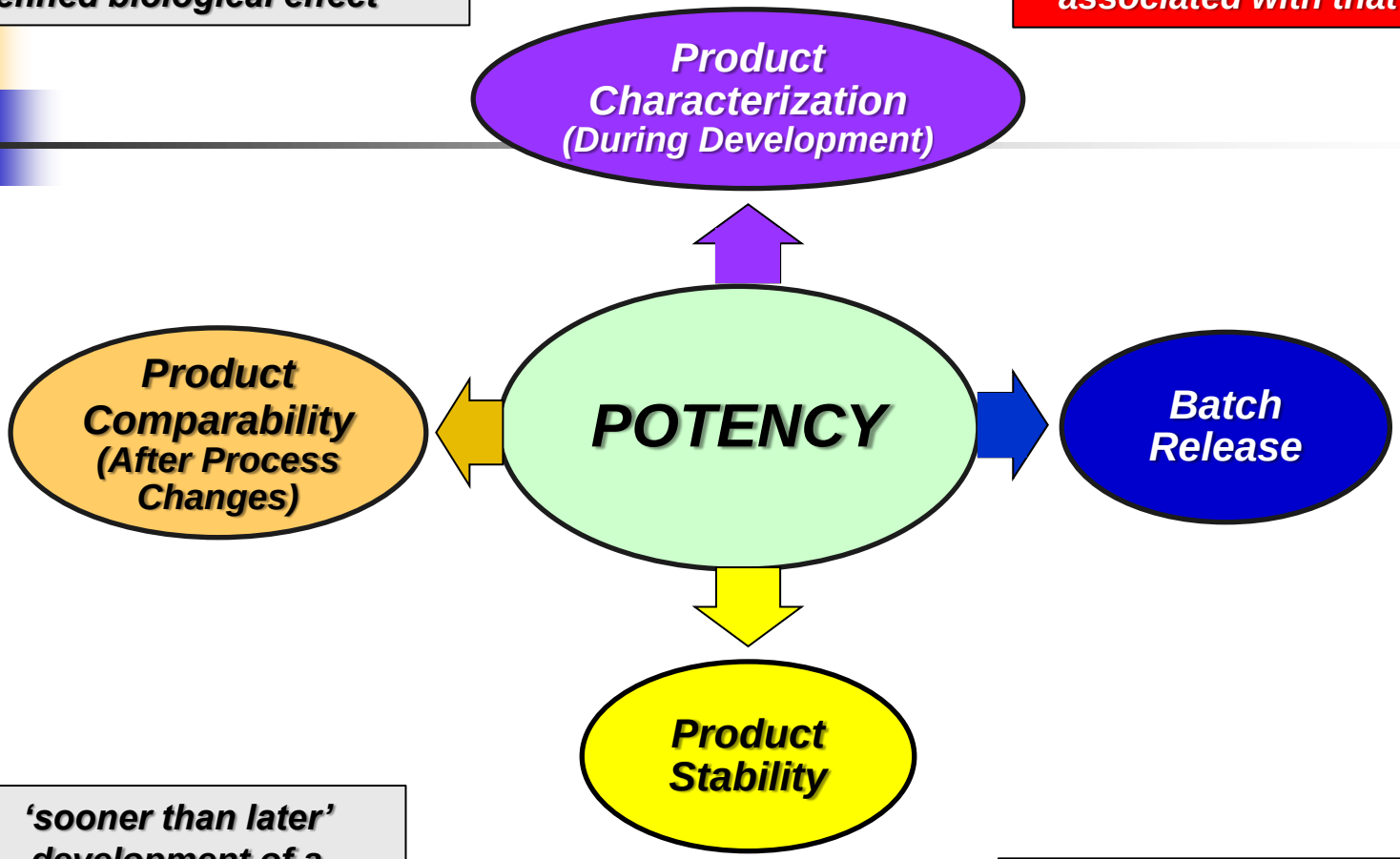
Size/ Purity
SEC-HPLC
HIC-HPLC
RP-HPLC
CE-SDS
CGE
AUC
A4F

Activity
In vitro Bioassays
  Reporter gene assays
Ag/Receptor Binding assays
  (mAbs – FcR, C1q)
SPR
Strength (UV A280)

Safety
Bioburden
Sterility
Endotoxin
  LAL
  KT

'The specific ability or capacity of the product to achieve a defined biological effect'

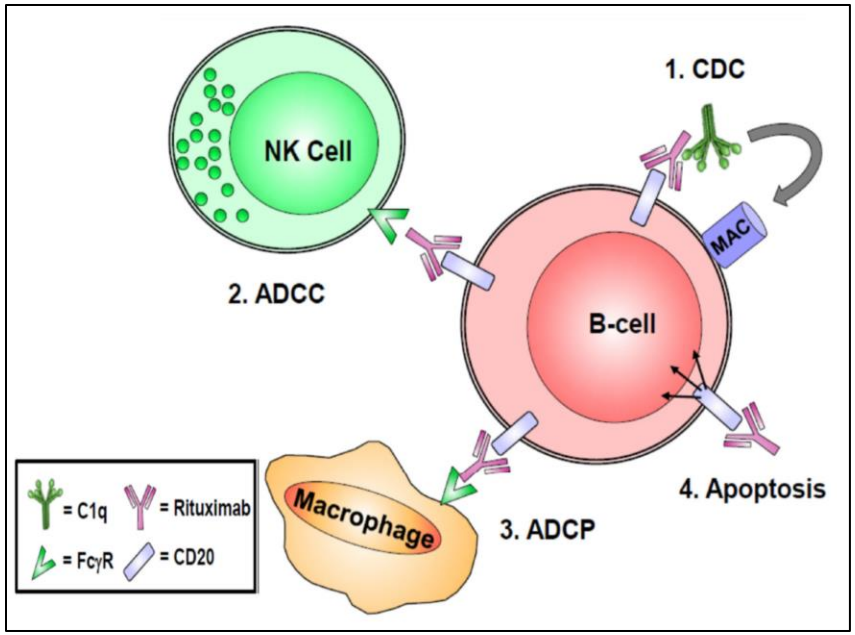
Not the amount of the API, but the biological activity associated with that amount!



'sooner than later' development of a cell-based bioassay strongly recommended

Determination of potency is one of the most important critical quality attributes (CQAs) for a biopharmaceutical

Many biopharmaceuticals have multiple 'biological properties', which require a potency assay matrix approach



rituximab potency video

DS Specifications (CQAs)

The specification for the batch(es) of active substance to be used in the clinical trial should define acceptance criteria together with the tests used to exert sufficient control of the quality of the active substance. Tests and defined acceptance criteria are mandatory for quantity, identity and purity and a limit of 'record' or 'report results' will not be acceptable for these quality attributes. A test for biological activity should be included unless otherwise justified. Upper limits, taking into account safety considerations , should be set for the impurities. Microbiological quality for the active substance should be specified.

As the acceptance criteria are normally based on a limited number of development batches and batches used in non-clinical and clinical studies, they are by their nature inherently preliminary and may need to be reviewed and adjusted during further development.

Product characteristics that are not completely defined at a certain stage of development (e.g. glycosylation, charge heterogeneity) or for which the available data is too limited to establish relevant acceptance criteria, should also be recorded. As a consequence, such product characteristics could be included in the specification, without pre-defined acceptance limits. In such cases, a limit of 'record' or 'report results' is acceptable. The results should be reported in the Batch Analyses section (S.4.4).

ILLUSTRATION: 'minimum CMC regulatory compliance continuum'

assignment of specifications

Early Stage Clinical Development

The manufacturer should establish acceptance criteria for specified attributes on each material. For some materials, all relevant attributes or acceptance criteria may not be known at the phase 1 stage of product development. However, attributes and acceptance criteria selected for assessment should be based on ***scientific knowledge*** *and* ***experience*** *for use in the specific phase 1 investigational drug.*

U.S. FOOD & DRUG ADMINISTRATION

Guidance for Industry
CGMP for Phase 1 Investigational Drugs
July 2008

Critical Quality Attribute	Early Stage Clinical Specification	Justification
Purity by CGE	≥ 95%	'Industry Standard'
Monomer by SEC-HPLC	≥ 95%	'Industry Standard'
Endotoxin by LAL	NMT 5 EU/dose/hour	USP Safety Limit
Residual Host Cellular DNA	NMT 10 ng/dose	WHO Safety Limit
Residual Host Cell Proteins (HCPs)	NMT 100 ng/mg (ppm)	Experience

Late Stage Clinical Development

Acceptance criteria should be established and justified based on ***data obtained from lots*** *used in preclinical and/or clinical studies, data from lots used for demonstration of manufacturing consistency and data from stability studies, and relevant development data.*

SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS
ICH Q6B
10 March 1999.

Critical Quality Attribute	Late Stage Clinical Specification
Purity by CGE	Based on statistical analysis of manufactured batches
Monomer by SEC-HPLC	
Endotoxin by LAL	
Residual Host Cellular DNA	
Residual Host Cell Proteins (HCPs)	

FDA recommendation on how to communicate Release Specs to them

Pre-BLA Meeting Minutes – Vabysmo (bispecific, faricimab) – Genentech – March 29, 2021

Release Specification for Faricimab Drug Product

Attribute	Analytical Method	Proposed Commercial Release acceptance criteria	Release results for nonclinical and developmental DP batches (n=?) (min-max)	Release results for clinical DP batches[a] (n=?) (min-max)	Release results for DP PPQ batches (n=?) (min-max)	Release results for all batches[b] made using commercial process (n=?) (min-max)	Justification of specification (e.g. clinical experience, manufacturing capability, etc.)

a. Include all batches used in any clinical testing, regardless of scale, process, or manufacturing location, etc. List each of the batch numbers included as footnote in the table.

b. Include all batches with available release data that were manufactured following the proposed commercial process. Include a list of the batch numbers included in analysis as a footnote in the table.

Similar table for the release specs of Drug Substance

The tables should summarize information from module 3 and may be submitted either to module 1 or module 3R

DS Stability

A stability protocol covering the proposed storage period of the active substance should be provided, including specification, analytical methods and test intervals. The testing interval should normally follow the guidance given in ICH Q5C.

The quality of the batches of the active substance placed into the stability program should be representative of the quality of the material to be used in the planned clinical trial.

The active substance entered into the stability program should be stored in a container closure system of the same type and made from the same materials as that used to store active substance batches to be used in the clinical trial. Containers of reduced size are usually acceptable for the active substance stability testing.

Studies should evaluate the active substance stability under the proposed storage conditions. Accelerated and stress condition studies are recommended as they may help understanding the degradation profile of the product and support an extension of the shelf-life.

A re-test period (as defined in ICH Q1A guideline) is not applicable to biological / biotechnology derived active substances.

EU requires shelf-life assignment; FDA places product stability under PQS

EUROPEAN MEDICINES AGENCY

Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials

27 January 2022
EMA/CHMP/BWP/534898/2008 Rev. 2

FDA recommendation on how to communicate Stability Specs to them

Pre-BLA Meeting Minutes – Vabysmo (bispecific, faricimab) – Genentech – March 29, 2021

Stability Specification for Faricimab Drug Substance

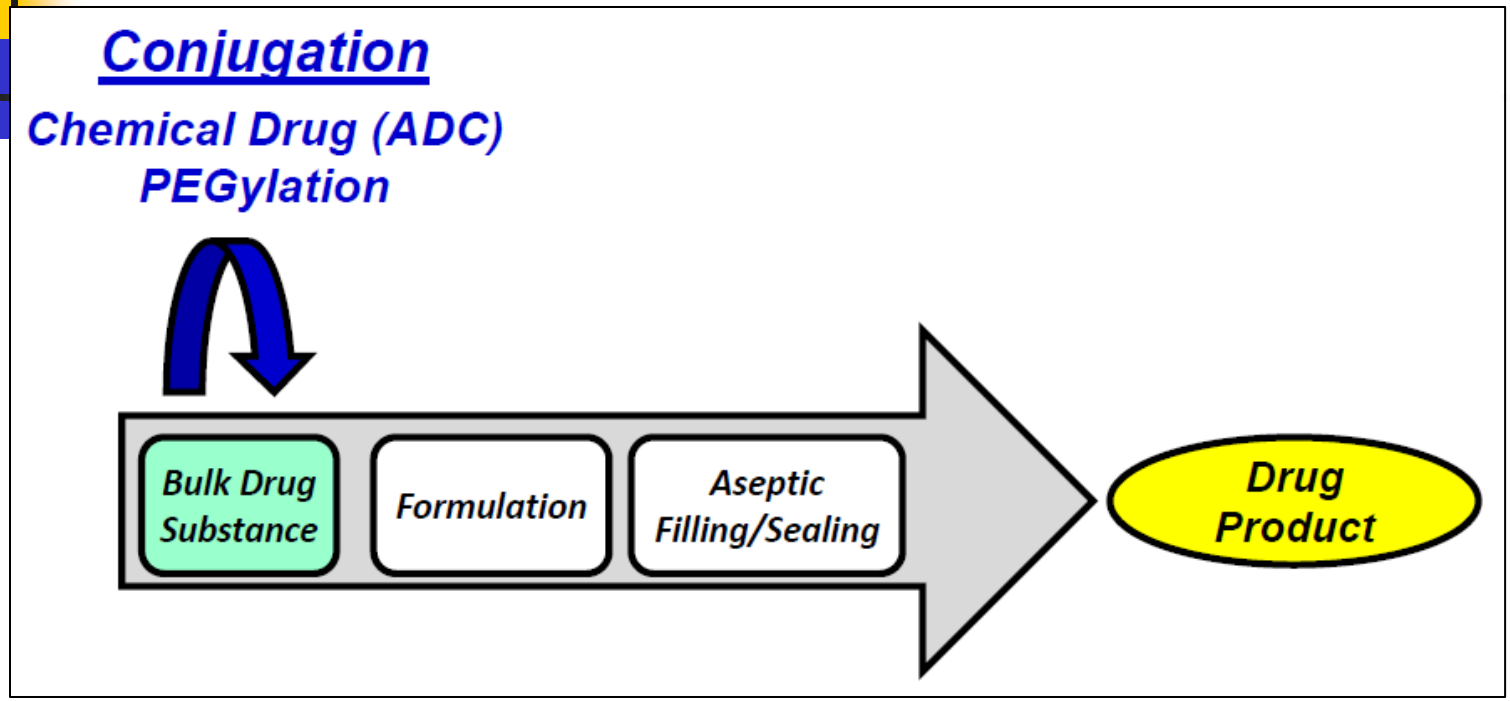
Attribute	Analytical Method	Stability acceptance criteria	Stability results for batches stored at recommended condition (n=?) [a] Min – Max (Range for all data from time 0 to the proposed end of shelf life or currently available)	Justification of specification (e.g. clinical experience, manufacturing capability, etc.)

a. Include a list of the batch numbers that were used in each assessment.

Similar table for the release specs of Drug Product

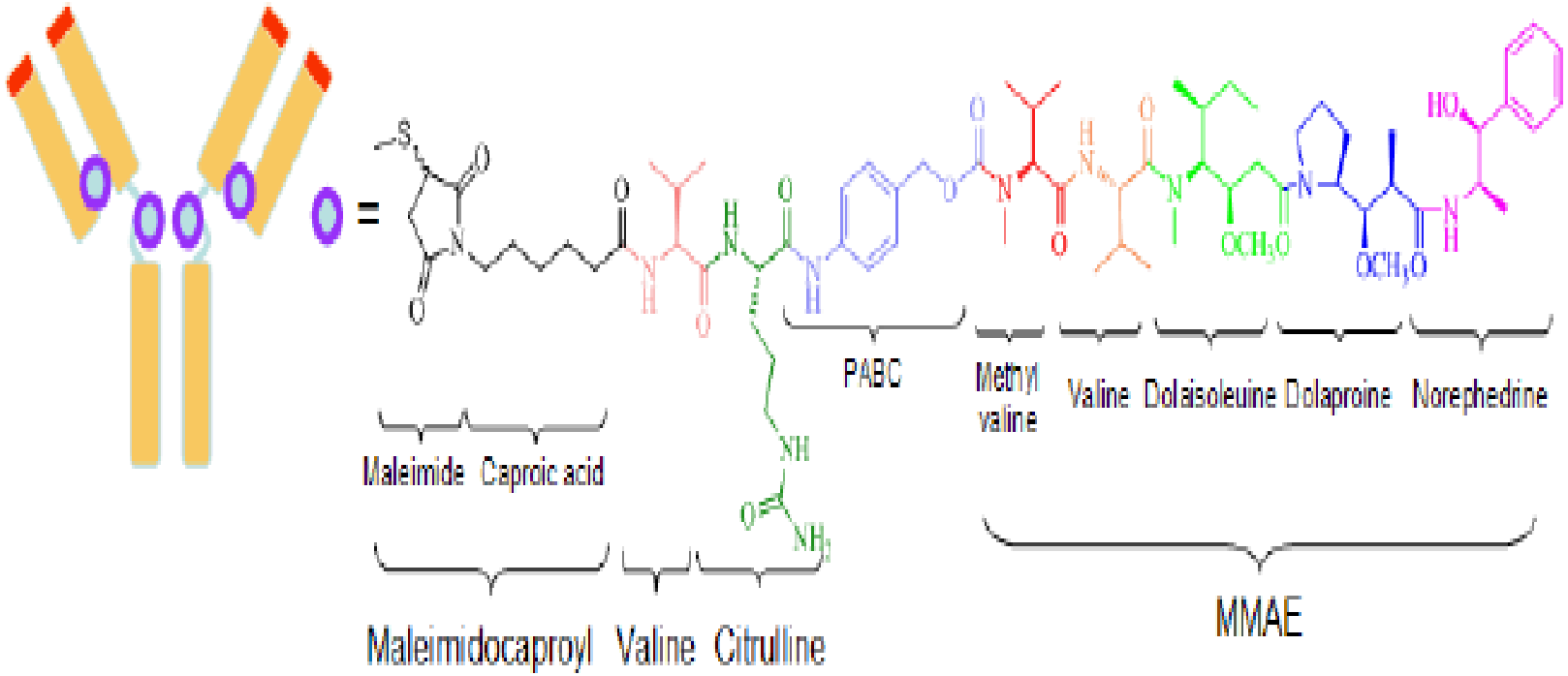
The tables should summarize information from module 3 and may be submitted either to module 1 or module 3R

Applied Risk-Management Across the Manufacturing Process



ADCs bring together all of the controls and concerns for the biopharmaceutical, as well as the chemical drug!

What are ADCs?

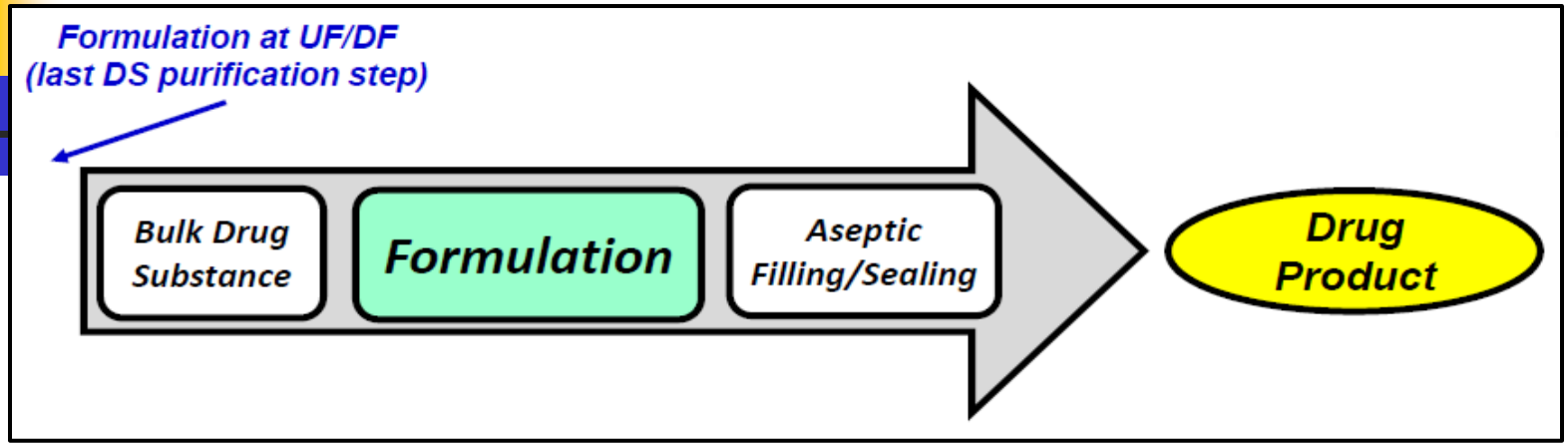


DAR: ~ 4 MMAE chemical molecules linked to each mAb molecule

CMC Concerns for the Manufacture of the Monoclonal Antibody Intermediate			
Process Stage	*CMC Manufacturing/Quality Concerns*		
Starting Material	Recombinant Master Cell Bank (MCB)		
Purified Drug Substance	Cell culture production of mAb Purification of mAb drug substance		
CMC Concerns for the Manufacture of the Drug-Linker Intermediate			
Process Stage	*CMC Manufacturing/Quality Concerns*	*Chemical Linker*	*Chemical Toxin*
Starting Materials	Starting material consistency Control of the chemical manufacturing process Chemical-related residual impurities (Organic Solvents, Elements, Mutagenic)	✓ ✓ ✓	✓ ✓ ✓
Linker-Toxin Intermediate	Control of the chemical reaction of Drug-Linker Chemical drug related residual impurities (free toxin)	✓ ✓	
CMC Concerns for the Manufacture of the ADC Drug Substance			
Process Stage	*CMC Manufacturing/Quality Concerns*		
Chemical Reaction	Control of the chemical reaction of mAb + Drug-Linker (DAR – drug-to-antibody ratio)		
Purified ADC Drug Substance	Control of the purification of the synthesized ADC (removal of unbound drug and drug-linker)		

DAR →

Applied Risk-Management Across the Manufacturing Process



- ***Pharmacopeia excipients*: lowest risk – specific monograph quality testing**
- ***Animal-derived excipients*: introduce the potential risks of contaminating adventitious agents**
- ***'Novel excipients' are either (1) an ingredient that is used for the first time in a drug product in a specific regulatory region, or (2) a substance that is used for the first time in the intended route of patient administration – highest risk because of the unknown safety risk to patients**

The higher the perceived risk of the excipient, the more detailed CMC information in the submissions required by the regulatory authorities for their safety review

Novel excipients frequently require extended animal toxicology studies

***Each* added excipient should have 'value':**
solubility, stability, minimization of variant formation, etc.

Formulation Changes occur during clinical development and post-market approval

Change due to clinical need: IV → SC

Formulations of Rituximab	
Rituxan/MabThera IV Administration	Rituxan Hycela/MabThera SC SC Administration
Rituximab (10 mg/mL) Sodium chloride Sodium citrate Polysorbate 80 pH 6.2 - 6.8 Osmolality 324-396 mOsmol/kg	Rituximab (120 mg/mL) Hyaluronidase human L-Histidine L-Methionine Trehalose Polysorbate 80 pH 5.2 - 5.8 Osmolality 300-400 mOsmol/kg

Change due to development data generated

Formulations of Adalimumab, HUMIRA and Its Many Biosimilars			
HUMIRA	ABRILADA	IDACIO	HULIO
Adalimumab Sodium chloride Sodium phosphate Sodium citrate Mannitol Polysorbate 80 pH 5.2	Adalimumab EDTA L-Histidine L-Methionine Sucrose Polysorbate 80 pH 5.5	Adalimumab Sodium chloride Glacial acetic acid Trehalose Polysorbate 80 pH 5.2	Adalimumab L-Methionine Na Glutamate Sorbitol Polysorbate 80 pH 5.2

Sometimes 'novel excipients' are absolutely required!

('Novel excipient' – an excipient being used for the first time in a drug product, or by a new route of administration or new to a specific regulatory region)

Novo Nordisk

Ozempic, SC Injectable Recombinant GLP-1 Peptide

Formulation: sodium phosphate, propylene glycol, phenol

Rybelsus, Oral Tablet Recombinant GLP-1 Peptide

Formulation: SNAC, povidone K90, magnesium stearate, cellulose

EMA 2020

Novel Excipient: SNAC

(salcaprozate sodium) – critical in transporting the peptide across the epithelium of the gastrointestinal tract

SNAC – required a 2 year tox study!

BLA also included detailed CMC information on SNAC structure, general properties, manufacturer, manufacturing process and controls, characterization, specifications, analytical methods, batch data, container and stability!

But … biopharmceutical formulation changes are considered 'high risk'

(formulation components can alter the protein effect in the human body, sometimes at very low frequency in patients)

The 'high risk' comes from the low ability to detect a potential human safety issue if the new formulation impacts only a small portion of patients

Sometimes it can take years for a new formulation to be on the market before enough patients show up on the radar screen as having a new adverse event issue

Well Known Case Example (1998)

- ***J&J changed from a glass vial presentation to a pre-filled syringe presentation for its anemia drug erythropoietin***
- ***To accomplish the switch, the formulation was changed – HSA was removed and polysorbate 80 added to the pre-filled presentation***
- ***After ~2 years on the market, a new adverse event appeared – PRCA – pure red cell aplasia – (severe anemia)***
- ***Polysorbate 80 (a detergent) was dissolving the rubber septum in the pre-filled syringe – the leachables were associated with the risk in PRCA***

Another Case Example → ***Dash of EDTA!***

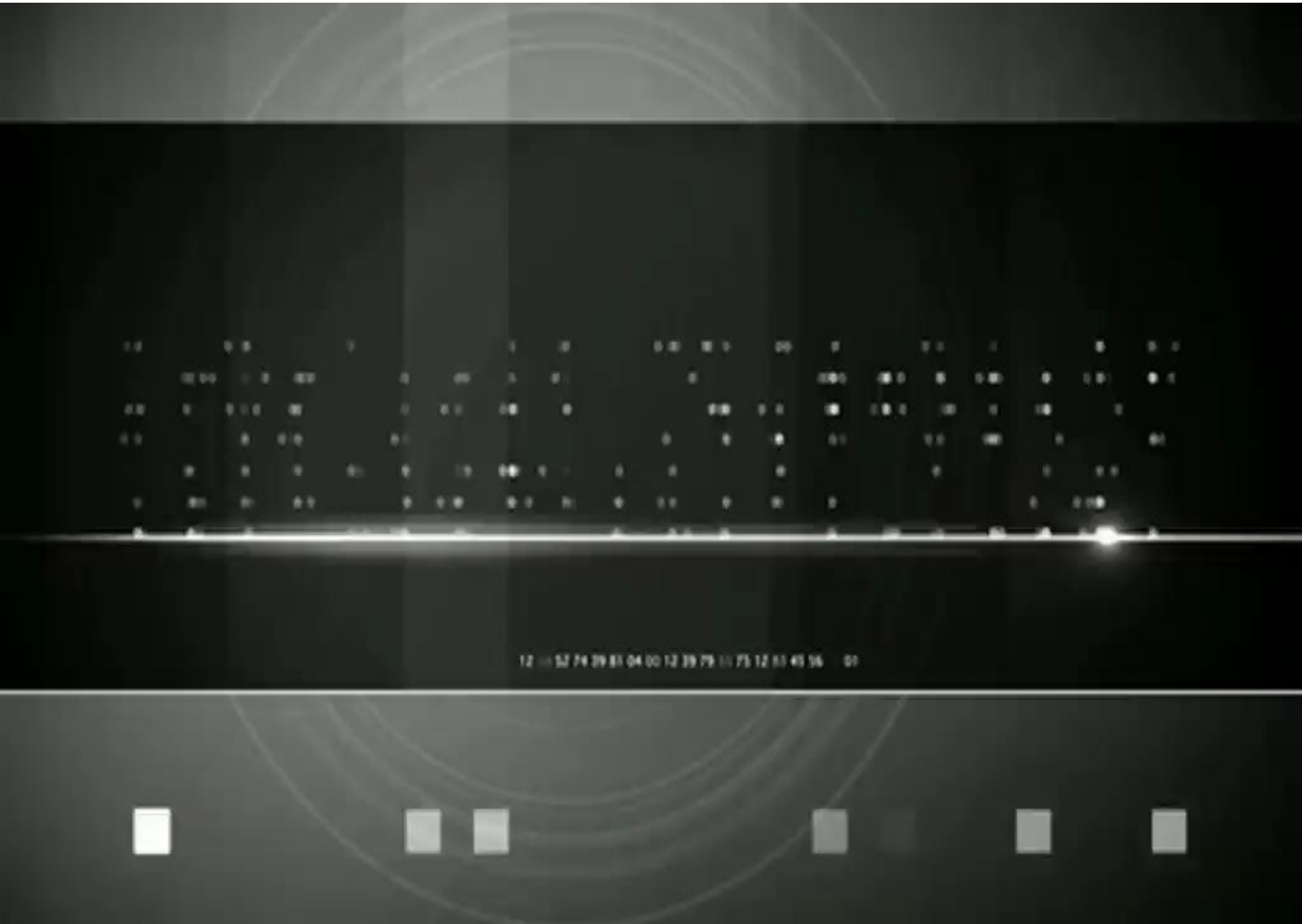
Dash of EDTA!

A 'small change' in formulation that took 2 years to detect as a new adverse event!

- ***Immunex's Leukine – developed liquid formulations of rGM-CSF [I was VP Q at the time]***
  - ***Had a choice between 2 liquid formulations (one with EDTA, one without) (no concern from FDA/EMA, but Japan said no to added EDTA – caused fainting)***
  - ***Immunex dropped liquid formulation with EDTA because of regulatory finding***
  - ***FDA approved new formulation without EDTA in 1996***
- ***2002 Amgen acquired Immunex (and Leukine)***
  - ***Sold off Leukine to company A, who sold it to company B, who finally sold it to Bayer***
  - ***How effective do you think was the CMC Knowledge Management (ICH Q10) transfer?***
- ***2006 Bayer received FDA approval to add a 'touch' of EDTA to the liquid formulation***
  - ***EDTA, a chelating agent, traps metal impurities and thereby can extend the shelf life***
  - ***Analytical testing showed that Leukine with and without EDTA was comparable***
- ***But after 2 years in the marketplace, enough pharmacovigilance data confirmed that the liquid Leukine with added EDTA had a new patient adverse event - SYNCOPE***

January 2008, recall due to syncope

1 min



Investigation revealed cause of syncope (fainting): ***(A+ to R&D)***

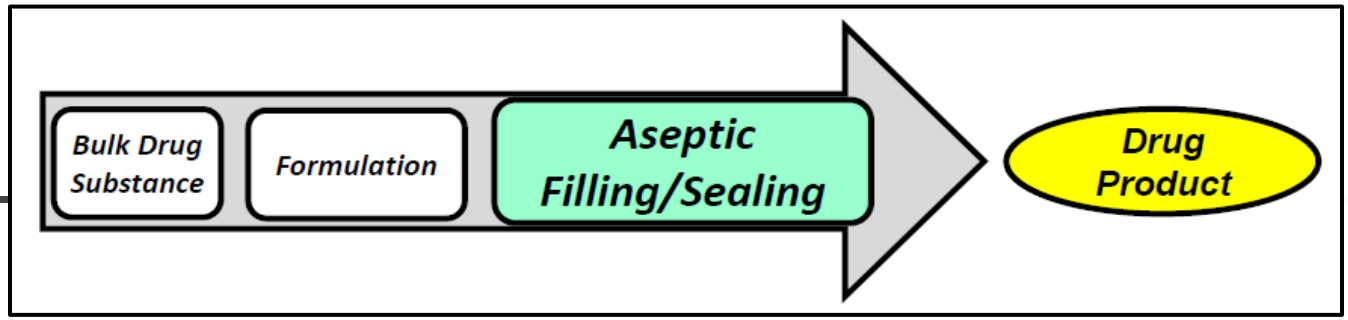
- ***"The addition of EDTA appears to increase the absorption rate of GM-CSF, the active ingredient in Leukine, and may result in a temporary increase in plasma concentration of GM-CSF shortly after administration"***
- ***Sudden protein burst caused body to go into defense mode***
- ***Fainting is part of the body's defense system***

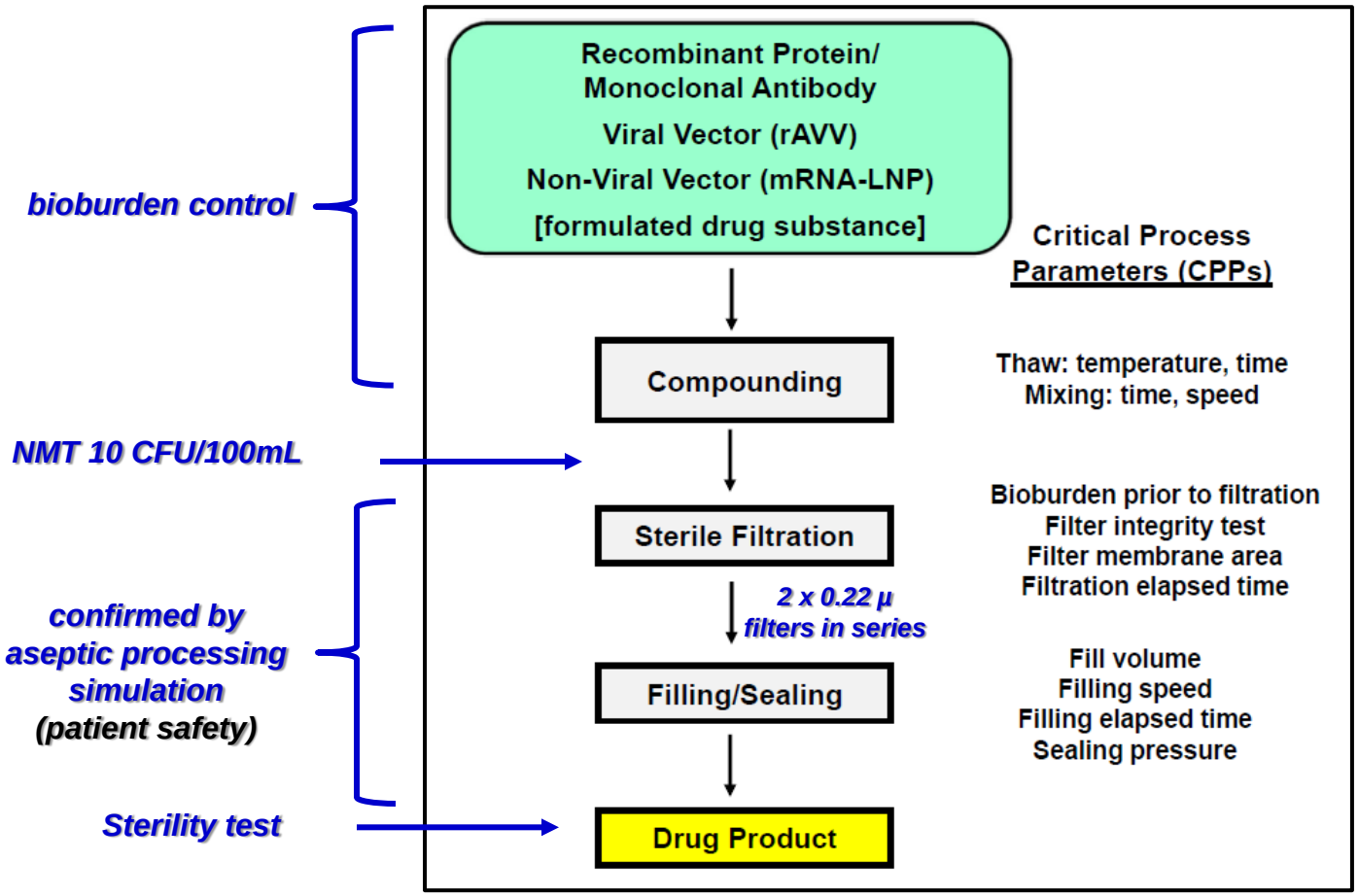
Pharmacovigilance, sometimes takes years, to pick up low-frequency adverse events (such as syncope) –

May 2008, 5 months later, Bayer reintroduces the original liquid Leukine formulation (without EDTA)

(A+ to Marketing)

Applied Risk-Management Across the Manufacturing Process





Aseptic Processing Simulation Mandatory

FIH and through all clinical development – proper training & confirmation

Because product sterility is a critical element of human subject safety, you should take special precautions for phase 1 investigational drugs that are intended to be sterile. You should give thorough consideration to implementing appropriate controls for aseptic processing to ensure a sterile phase 1 investigational drug. The guidance issued by FDA on aseptic processing is a good reference when using aseptic processing (Ref. 7). Particular manufacturing controls include:

- Conducting aseptic manipulation in an aseptic workstation (e.g., laminar air flow workbench, biosafety cabinets, or barrier isolator system) under laminar airflow conditions that meet Class A, ISO 5. You should perform all manipulations of sterile products and materials under aseptic conditions.

- Conducting a process simulation using bacterial growth media to demonstrate that the aseptic processing/controls and production environment are capable of producing a sterile drug

7 FDA "Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practices." **September 2004**

FDA U.S. FOOD & DRUG ADMINISTRATION

Guidance for Industry
CGMP for Phase 1 Investigational Drugs

Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
July 2008

Good reference on how to do Aseptic Process Simulation

PDA Parenteral Drug Association

PDA Points to Consider for Aseptic Processing **2016**

Aseptic process simulation – essential for patient safety

483 Case Example

Eli Lilly
Commercial Biologic DP Facility GMPs

FDA inspection of commercial biologic drug product manufacturing facility resulted in major concerns about cGMP control of mAb processes

The following discrepancies were noted during the review of media fills and batch records which were executed on the B103 vial filling line. Products aseptically filled on this line include but are not limited to Ramucirumab, Glucagon, (b) (4) , Olaratumab, (b) (4) , (b) (4) , Bamlanivimab, and Etesevimab. Specifically,

US FDA Inspection February-March 2021

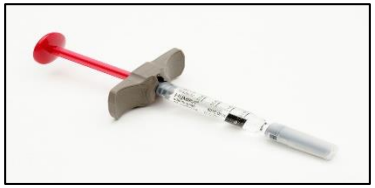
A. *Media Fills*

1. *Interventions performed during media fills do not reflect routine production. The firm normalizes the number of inherent interventions obtained for the entire year to determine the number of interventions performed per (b) (4) vials. They do not trend the frequency/type of interventions occurring per batch. For (b) (4) media fills performed annually on the vial filling line, the firm only performs the (b) (4) inherent interventions.*

2. *Adequate justification was not provided to support of how the conditions simulated during your Fill Duration Challenge – NLT (b) (4) in Media fill MF0116 – MF0271, D291263 is reflective of routing manufacturing.*

3. *Fatigue is not adequately challenged. Filling Operator Extended Personnel Shift was listed as being challenged for 14 hours, 9 minutes (Protocol Required Challenge NLT (b) (4)) during MF0273, Batch D256292 per APS Summary report, effective July 6, 2020. An aseptic operator's shift is (b) (4) . The media fill D256292 did not support the operator working on the aseptic line for 14 hours, 9 minutes. Management*

Container Closure Systems for Market-Approved Biopharmaceutical Drug Products	
BIOPHARMACEUTICAL	**CONTAINER CLOSURE SYSTEM**
Recombinant Protein Monoclonal Antibody	*type I glass vial with a chlorobutyl rubber stopper* *single-use prefilled syringe (PFS) comprised of a glass syringe barrel with a staked needle and a rigid needle shield, a plunger stopper, a plunger rod*
Viral Vector (rAAV)	*cyclic olefin polymer vial with a chlorobutyl rubber stopper*
Genetically Modified Patient Cells	*ethylene vinyl acetate (EVA) cryostorage bags designed for storage of blood*



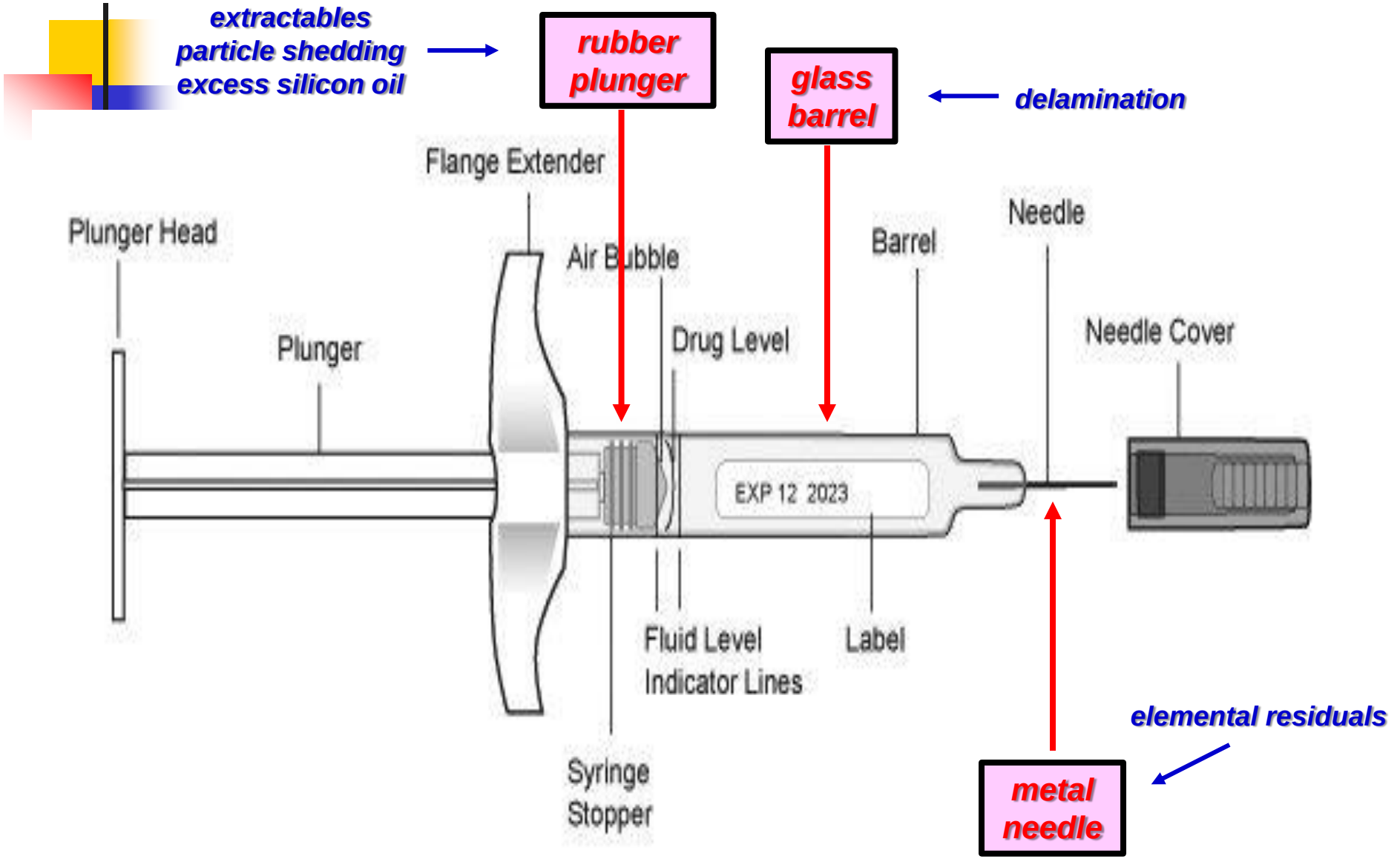
Device Requirements

Design Input/User Needs	*Design Output*
Required minimum/maximum delivery dose for drug	Drawing/specification for syringe minimum/maximum volume
Drug viscosity and desired/required delivery rate	Drawing/specification for needle bore, glide force, for example
Expected use condition (e.g., expected user experience/education level)	Content, reading level, for example, for the prefilled syringe's labeling
Maximum allowable temperature of drug	Packaging/labeling specifications for the prefilled syringe
No degradation of drug or syringe over the expected shelf-life as a result of contact with one another	Specifications for drug-contacting syringe materials
Expected shipping method and appropriate storage conditions	Design drawings/specifications for primary and secondary packaging
Drug delivery method (e.g., needle or needleless delivery)	Drawing/specification for needle and/or other associated syringe components

Glass vials are not 'devices', but prefilled syringes are!

'COMBINATION PRODUCTS'

Potential interaction between biopharmaceutical and product-contact surfaces

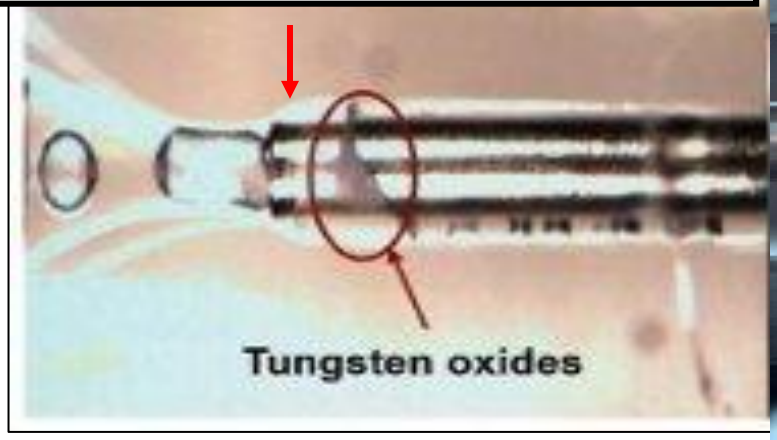


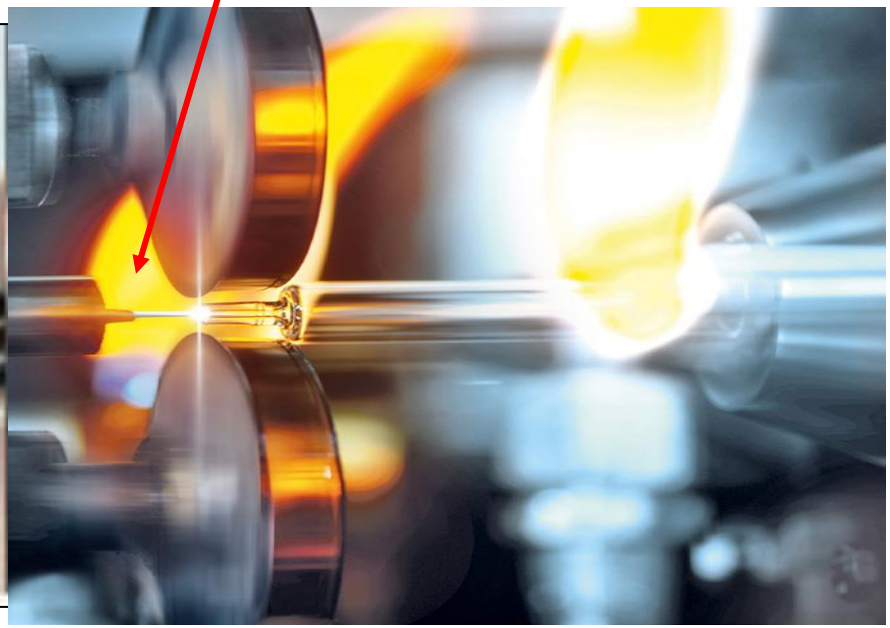
Impact of container closure on biopharmaceutical!

Prefilled Syringes – discovery of tungsten oxide residuals causing protein oxidation

During glass syringe manufacture, while the glass barrel is being formed at high temperature (~1200°C), a tungsten pin is used to shape and maintain the hole where the stainless steel needle will be glued in

<u>During pin removal</u>, residual tungsten oxides can remain, and accelerate protein aggregation, oxidation, and precipitation





PDA J Pharm Sci and Tech **2013**, *67* 670-679
Access the most recent version at doi:10.5731/pdajpst.2013.00941

Department of Drug Product Development, Amgen Inc.,

- ***Improved syringe washing processes at the vendors***
- ***Incoming batch check for residual tungsten (ICP/MS)***
- ***Test protein product for sensitivity to tungsten oxide***

Impact of biopharmaceutical formulation on container closure!

Glass Vials – discovery of protein solutions causing glass delamination

Using Micro-flow imaging (MFI) glass shards observed in solution in 2010

Amgen: delamination present in potentially every glass vial of Epogen manufactured since 1982!

Patient safety concern
glass shards could cut capillaries

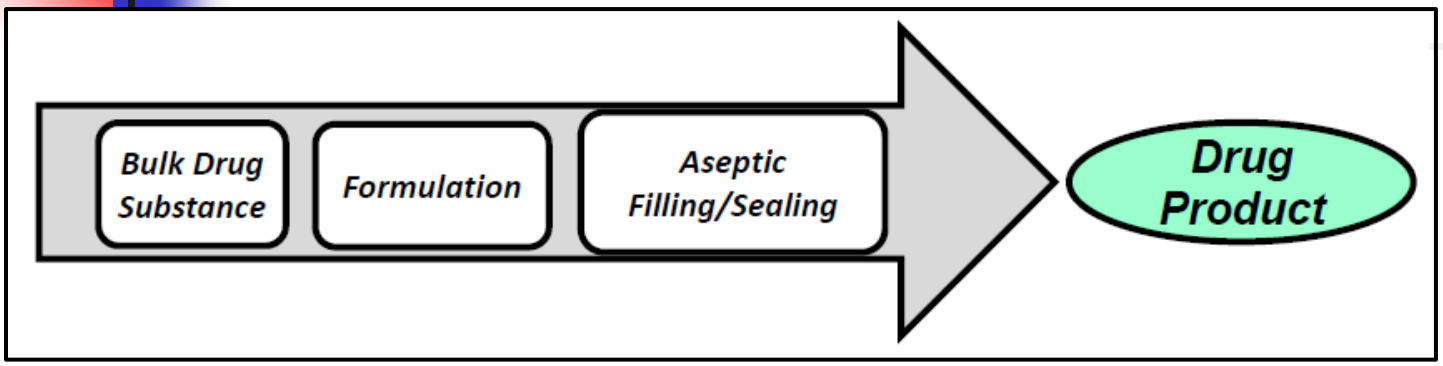
September 2, 2010

RECALLING FIRM/MANUFACTURER	RECALLING FIRM/MANUFACTURER
Recalling Firm: Amgen Inc., Thousand Oaks, CA	Recalling Firm: Centocor Ortho Biotech, Inc., Horsham, PA
VOLUME OF PRODUCT IN COMMERCE	VOLUME OF PRODUCT IN COMMERCE
78,074,450 vials	16,759,926 vials

2011 Advisory to Drug Manufacturers

- ***Glass vials manufactured by a tubing process (and thus manufactured under higher heat) are less resistant than molded glass vials***
- ***Biologic solutions formulated at high pH (alkaline) and with certain buffers (e.g., citrate) are more susceptible***
- ***Biologics stored at room temperature have a greater chance of glass lamellae formation than do products stored at colder temperatures***

***Applied* Risk-Management Across the Manufacturing Process**



CQA Category

Appearance
Identity
Quantity
Safety
General

Purity/impurities
Potency

Drug substance CQAs typically include those properties or characteristics that affect identity, purity, biological activity and stability. When physical properties are important with respect to drug product manufacture or performance, these can be designated as CQAs. In the case of biotechnological/biological products, most of the CQAs of the drug product are associated with the drug substance and thus are a direct result of the design of the drug substance or its manufacturing process.

Case Example

DS + DP

DEVELOPMENT AND MANUFACTURE OF DRUG SUBSTANCES
(CHEMICAL ENTITIES AND BIOTECHNOLOGICAL/BIOLOGICAL ENTITIES)

ICH Q11 2012

Drug Substance Specification

Table S.4.1-1 Drug Substance Release Specification

CQA	Analytical Procedure	Acceptance Criterion
Color (Ph. Eur. Color Scale)		
Clarity/Opalescence (Ph. Eur. Opalescent Value) (NTU)		
pH		
Osmolality (mOsm/kg[b])		
Identity of Faricimab by Lys-C Peptide Mapping		
Purity by SE-UHPLC		
Main Peak (area%)	*molecular volume variants*	
Sum of HMW Forms (area%)	*molecular volume variants*	
Purity by NR-CE-SDS[a]		
Main Peak (%CPA)	*molecular size variants*	
Sum of LMW Forms (%CPA)	*molecular size variants*	
Purity by IE-HPLC		
Main Peak (area%)	*molecular charge variants*	
Acidic Region (area%)	*molecular charge variants*	
Acidic Peak 2 (area%)	*molecular charge variants*	
Basic Region (area%)	*molecular charge variants*	
Content of Protein by UV (mg/mL)		
Potency by Bioassay		
Anti-VEGF by VEGF-Reporter Gene Assay (% relative potency)		
Anti–Ang-2 by Tie-2 Phosphorylation Assay (% relative potency)		
Bioburden (CFU/10 mL)		
Bacterial Endotoxins (EU/mL)		
Content *Polysorbate 20* by HPLC (mg/mL)		

[a] NR-CE-SDS is also referred to as non-reduced CE-SDS in other parts of the dossier.

[b] mOsmol/kg and mOsm/kg are considered equivalent terms and are both used in the dossier.

USA only could be Visual Appearance

Other tests can be used for identity, but …

ICH Q6B: must be 'highly specific and based on unique aspects of molecular structure or properties'

N-Glycan %'s, Sialic Acid Content ??

Impurity Profile: HCP, HCDNA, Protein A??

BLA Summary Review for Market Approval – Vabysmo (bispecific, faricimab) – Genentech – 2021

Table P.5.1-1 Drug Product Specification

CQA / Analytical Procedure	Release Acceptance Criterion	Stability Testing Acceptance Criterion
Physical State	Liquid	—
Color (Ph. Eur. Color Scale)	(b) (4)	
Clarity/Opalescence (Ph. Eur. Opalescent Value) (NTU)		
Extractable Volume (Ph. Eur./USP/JP) (mL/vial)		
Visible Particles	Practically free from particles[a]	Practically free from particles[a]
Subvisible Particles	(b) (4)	
Particles ≥ 10 µm per mL		
Particles ≥ 25 µm per mL		
Particles ≥ 50 µm per mL		
Subvisible Particles (b) (4)[b]		
Particles ≥ 10 µm per mL		
Particles ≥ 25 µm per mL		
Particles ≥ 50 µm per mL		
pH		
Osmolality (mOsm/kg[c])		
Identity of Faricimab by Lys-C Peptide Mapping	Positive identity	—

Aside from the dose form tests, the product-related tests are similar to drug substance

Table P.5.1-1 Drug Product Specification (cont.)

Analytical Procedure	Release Acceptance Criterion	Stability Testing Acceptance Criterion
Purity by SE-UHPLC	(b) (4)	
Main Peak (area%)		
Sum of HMW Forms (area%)		
Purity by NR-CE-SDS[d]		
Main Peak (%CPA)		
Sum of LMW Forms (%CPA)		
Content of Polysorbate 20 by HPLC (mg/mL)		
Purity by IE-HPLC		
Main Peak (area%)		
Acidic Region (area%)		
Acidic Peak 2 (area%)		
Basic Region (area%)		
Content of Protein by UV (mg/mL)		
Potency by Bioassay		
Anti-VEGF by VEGF-Reporter Gene Assay (% rel. potency)		
Anti–Ang-2 by Tie-2 Phosphorylation Assay (% rel. potency)		
Sterility, Final Container (Ph. Eur./USP/JP)		
Bacterial Endotoxins (EU/mL)		
Container Closure Integrity by Helium Leak Test		

[a] Visible particles release testing is based on AQL testing. Refer to Section P.3.4 *Controls of Critical Steps and Intermediates*. The result will be reported as practically free from particles if the AQL acceptance criteria are met.

[b] Subvisible Particles testing (b) (4) (b) (4)

[c] mOsmol/kg and mOsm/kg are considered equivalent terms and are both used in the dossier.

[d] NR-CE-SDS is also referred to as non-reduced CE-SDS in other parts of the dossier.

Two (2) specific DP process-related impurities that must be examined today

applicable when seeking market approval (even for biopharmaceuticals)

CASE EXAMPLE

The potential presence of elemental impurities in the active substance and finished product has been assessed on a risk-based approach in line with the ICH Q3D guideline for elemental impurities. Four finished product lots were screened by inductively coupled plasma mass spectrometry (ICP-MS). No elemental impurities were detected above 30% of the permitted daily exposure. The risk of carryover of elemental impurities from reagents and materials used for manufacture is considered negligible and no additional control is required.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/Applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report - Procedure under Article 5(3) of Regulation EC (No) 726/2004 - Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or finished product. Therefore, no additional control measures are deemed necessary.

Bimzelx	bimekizumab	UCB Pharma	EPAR	24 June 2021 EMA/393532/2021

Illustration of how to carry out a Nitrosamine Risk Assessment Approach

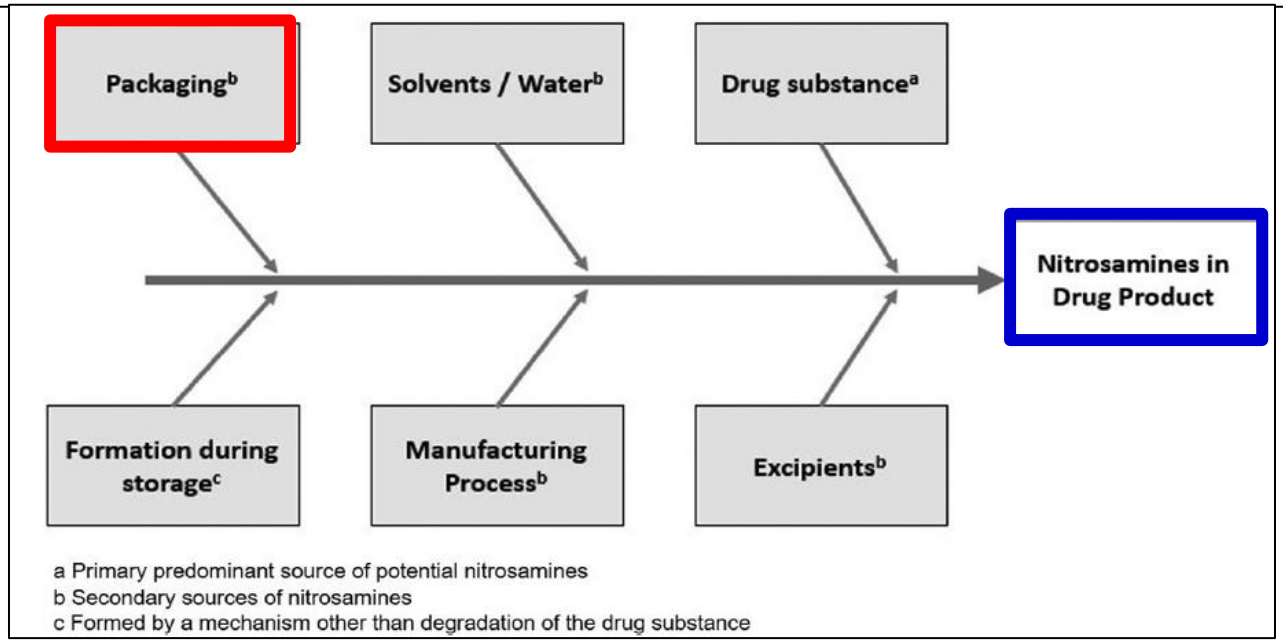
Evaluating Nitrosamines from Elastomers in Pharmaceutical Primary Packaging

PDA Journal of Pharmaceutical Science and Technology
Vol. 76, No. 2, March–April 2022

BETTINE BOLTRES*

Principal Scientific Affairs, Packaging & Delivery Systems, Scientific Affairs, West Pharmaceutical Services Deutschland GmbH & Co KG, Stolberger Str. 21 – 41, 52249 Eschweiler, Germany.

ABSTRACT: Nitrosamines have gained unexpected attention again, triggered by their discovery at significant concentrations in some active pharmaceutical ingredients and pharmaceutical products. Regulatory agencies not only expect the marketing authorization holders to include a nitrosamine risk assessment in their drug development process but to also apply it retrospectively to the marketed drug product. As part of this risk assessment, all possible sources of nitrosamines need to be evaluated. This review provides the chemical background of nitrosamines and elastomeric formulations, the current regulatory status in the pharmaceutical and other industries, and discusses analytical challenges of nitrosamine measurement. This evaluation of elastomeric components as a potential nitrosamine source proposes how this information can be used in a drug product risk assessment.



A few comments on stability testing during clinical development

Study Condition	Value of Study
LONG TERM *(fixed temp, at planned product storage condition)* *[typically on study for years]*	*'Primary data to support a requested storage period for either drug substance or drug product should be based on long-term, real-time, real-condition stability studies.'*
ACCELERATED *(fixed temps, above label claim temp storage)* *[typically on study for months]*	*'Studies under accelerated conditions may provide useful support data for establishing the expiration date, provide product stability information for future product development (e.g., preliminary assessment of proposed manufacturing changes such as change in formulation, scale-up), assist in validation of analytical methods for the stability program, or generate information which may help elucidate the degradation profile of the drug substance or drug product.'*
FORCED DEGRADATION *[typically on study for days]*	*'Studies under stress conditions may be useful in determining whether accidental exposures to conditions other than those proposed (e.g., during transportation) are deleterious to the product and also for evaluating which specific test parameters may be the best indicators of product stability.* *Studies of the exposure of the drug substance or drug product to extreme conditions may help to reveal patterns of degradation*

similarities/differences between chemical drugs and biopharmaceuticals seeking market approval

Parameter	Regulatory Requirement
LONG TERM	**For 'Label Claim'** **'Product expiration dating will be based upon the actual data submitted in support of the application.'** **Chemical Drug: min 12 months Biopharm: min 6 months**
ACCELERATED	**'Support' of product stability** **Test method validation – ability to detect change** **Chemical Drug: min 6 months Biopharm: _____**

CASE EXAMPLE

Vyvgart

efgartigimod alfa

human recombinant immunoglobulin 1(IgG1) derived Fc fragment

23 June 2022
EMA/641081/2022
EPAR

DS

DP

Drug Substance

The applicant proposed a shelf-life of 36 months for the active substance manufactured at the Lonza Slough and Lonza Tuas sites, based on stability studies performed in accordance with the ICH Q5C.The analytical methods and acceptance criteria applied during stability studies are identical to the active substance release specifications, except for the identity, safety and some process-related impurities. The stability studies included primary batches (PPQ batches) and supportive batches (clinical batches produced by previous process versions) manufactured at both sites. Batches were placed on long-term storage, accelerated storage and stressed storage conditions. Additional stability data were provided. Available long-term stability data from primary batches showed a stable active substance over 18 months for the representative PPQ batches and 24 months for the supportive and 36 months for the clinical batches (former processes) using the tested stability-indicating methods.

Based on the available data for representative batches, a stability shelf-life of 18 months is acceptable for the active substance.

The stability of the active substance was, moreover, evaluated upon freeze/thaw (F/T) cycles using two representative batches from either of the manufacturing sites. Given that no changes were found in the critical quality attributes after several F/T cycles at the long-term storage condition, it was concluded that the active substance quality was not compromised by this amount of F/T cycles.

Adequate post-approval stability protocol information is presented and acceptable handling of any confirmed out-of-specification (OOS) is proposed.

In conclusion, the stability results indicate that the active substance is sufficiently stable over the acceptable shelf-life of 18 months, in the proposed container.

Drug Product

The applicant proposed a shelf-life of 36 months at +5°C ± 3°C for the finished product. The stability studies were performed on primary and supportive batches stored at +5°C ± 3°C (long-term storage condition), +25°C ± 2°C/60 ± 5% relative humidity (accelerated storage condition), and +40°C ± 2°C/75 ± 5% relative humidity (stressed storage condition), in accordance with the ICH Q5C.

The primary batches included PPQ batches based on active substance sourced from Lonza Slough, together with PPQ and clinical batches based on active substance sourced from Lonza Tuas. The supportive stability batches included clinical batches produced by previous process versions at the commercial or clinical manufacturing site with active substance from either the Tuas or Slough site. Available long-term stability data from primary batches showed that the tested critical quality attributes of the finished product were stable and within the shelf-life acceptance criteria. This was supported by 18-36 months of stability data from supportive batches, which demonstrated a comparable and stable profile of the finished product.

The degradation pattern of the finished product was observed from stability studies using primary and supportive batches stored under accelerated and stressed conditions. The primary degradation pathways were identified for all the tested batches. The extrapolation of the stability data from finished product batches manufactured with active substance coming from former processes to the commercial finished product batches is not endorsed.

During the assessment, additional long-term stability data was provided for 18 months at 2°C-8°C for finished product batches representative of the commercial process. In addition, long-term stability data at 24 months at 2°C-8°C was provided for the initial finished product batches which is not considered representative of the commercial process. Furthermore, long-term stability data at 12 months at 2°C-8°C was provided for the primary batches. Based on the additional stability data provided for finished product batches representative of the commercial process, only a finished product shelf-life of 18 months at 2°C-8°C is acceptable.

similarities/DIFFERENCES between chemical drugs and biopharmaceuticals seeking market approval

Parameter	Regulatory Requirement
LONG TERM	For 'Label Claim' 'Product expiration dating will be based upon the actual data submitted in support of the application.' Chemical Drug: min 12 months Biopharm: min 6 months
ACCELERATED	'Support' of product stability Test method validation – ability to detect change Chemical Drug: min 6 months Biopharm: _____
FORCED DEGRADATION	"While the tripartite guideline on stability [ICH Q1A(R2)] describes the conditions of the accelerated and stress study, the applicant should note that those conditions may not be appropriate for biotechnological/biological products. Conditions should be carefully selected on a case-by-case basis.'" ICH Q5C

Typical forced degradation study conditions for biopharmaceuticals

CASE EXAMPLE

Table 3.2.P.8.1/ 11: Testing Protocol –Comparative Forced Degradation Study

Degradation Factor	Condition	Time-points	% HMWP by SE-HPLC	% Total impurities and any individual impurity by RP-HPLC	Assay by RP-HPLC
pH stress	pH 2	0, 1, 3, 8 days	√	√	√
	pH 10	0, 1, 3 and 6 hours	√	√	√
Chemical Treatment	Oxidation (3% H_2O_2)	0, 1, 6 and 12 hours	√	√	√
Photo Treatment	Photo exposure	0, 0.6, 1.2 Million lux hours	√	√	√
Mechanical Stress	Agitation at 250 RPM at 25°C	0, 1, 3, 7,15 days	√	√	√
Temp. Stress	60°C	0, 1, 3, 7,15 days	√	√	√
	2-8°C (Control)	0, 1, 3, 8,15 days	√	√	√
Initial time point (control)	Control (initial time-point)	0 hours	√	√	√

BLA Number: 761201
Office of Pharmaceutical Quality
Application Team Lead Assessment Number: 2
Assessment Date: April 15, 2021

Semglee (insulin glargine-yfgn)
Mylan Pharmaceuticals

Temperature stress forced degradation studies for EXTRAPOLATION of assigned market-approved product shelf life!

Q1E Evaluation of Stability Data

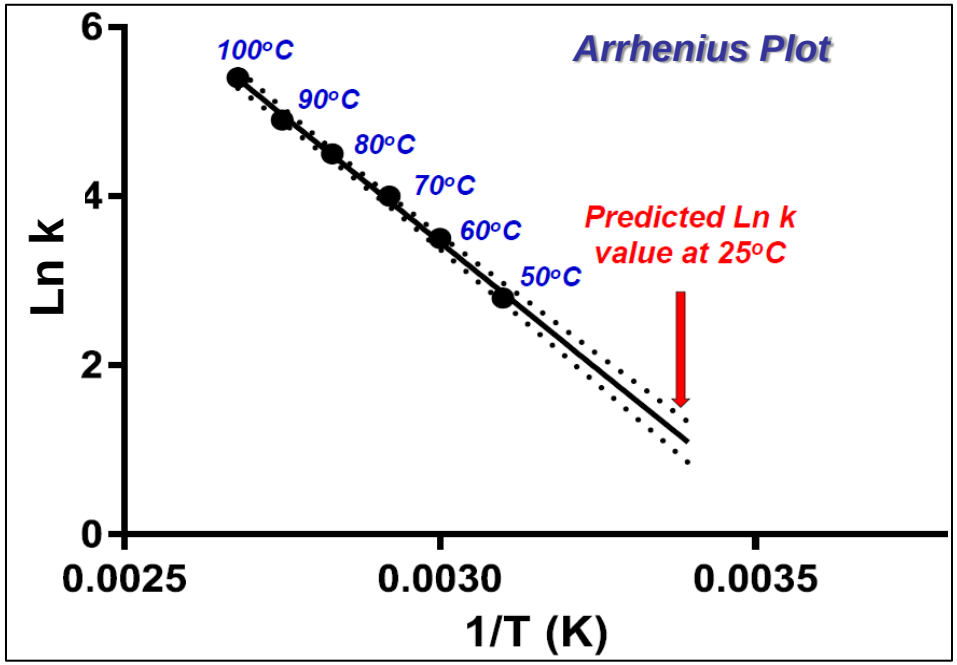
Chemical Drugs

Extrapolation is the practice of using a known data set to infer information about future data. Extrapolation to extend the retest period or shelf life beyond the period covered by long-term data can be proposed in the application, particularly if no significant change is observed at the accelerated condition.

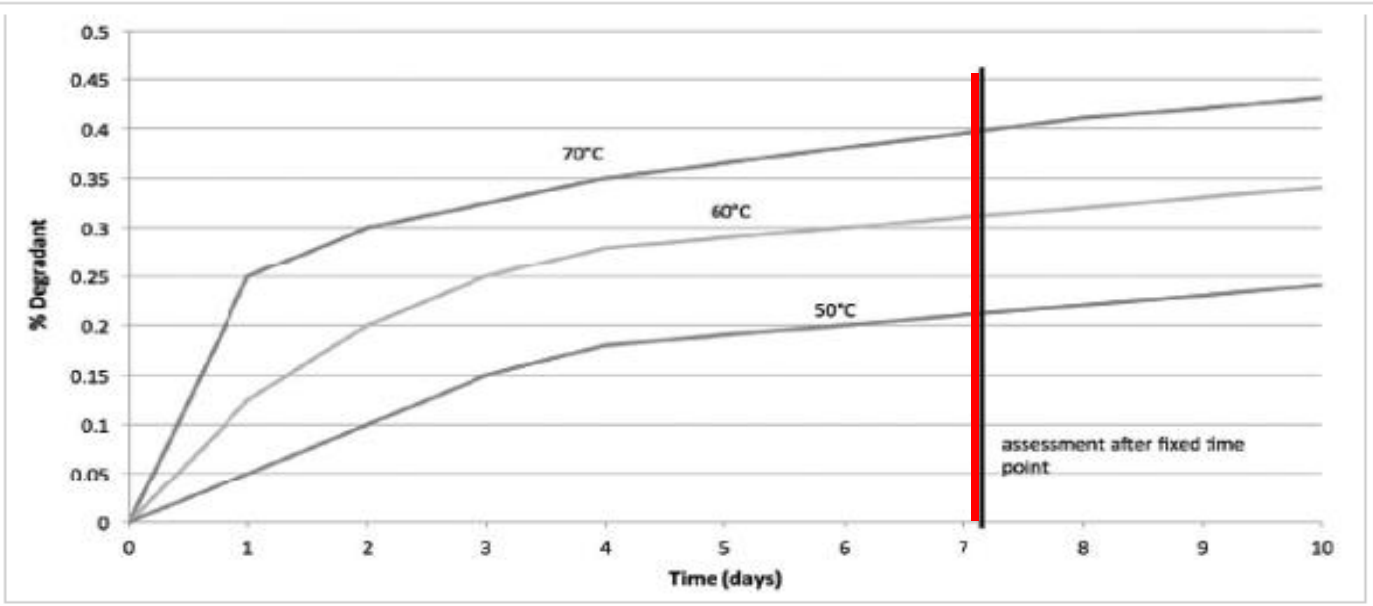
$$Rate = \frac{dC}{dt} = kC^n$$

$$k = Ae^{\left[-\frac{E_a}{RT}\right]}$$

C	Reactant Concentration
k	Rate constant
n	Reaction order
A	Pre-exponential factor
E_a	Activation energy
R	Gas constant
T	Temperature (K)



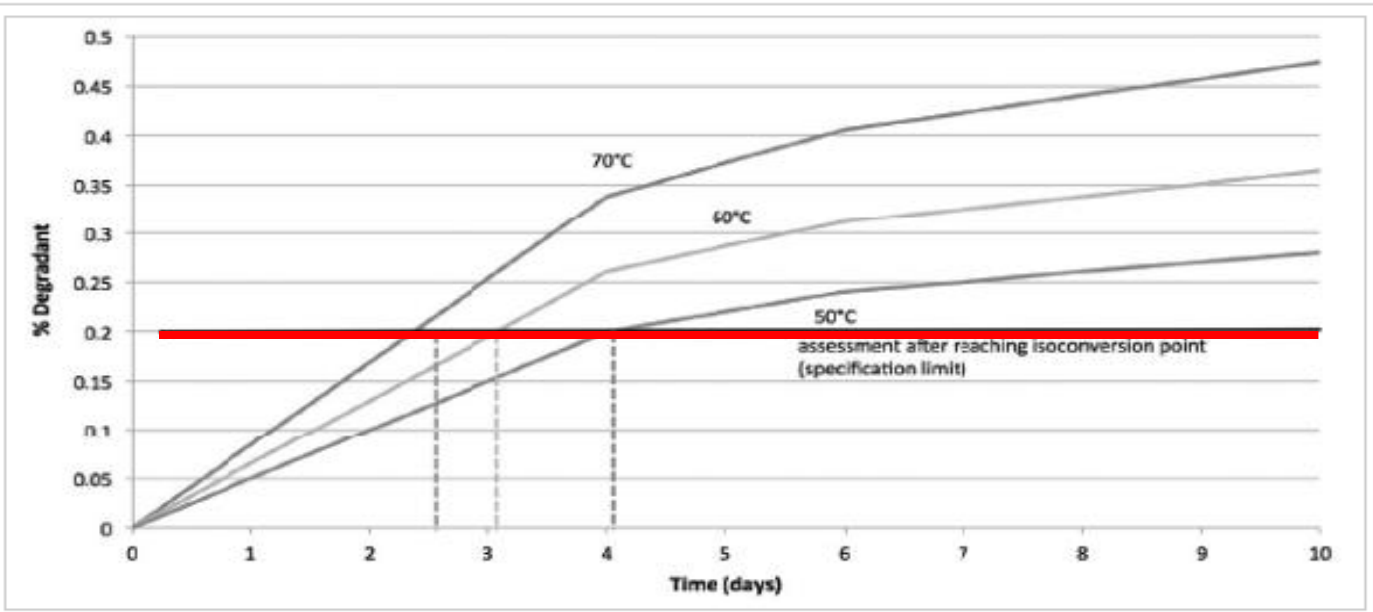
By studying the degradation rate at multiple high temperatures, the plot of these data leads to a degradation rate prediction at a lower temperature



Graph 1. Conventional accelerated stability testing[7]

Arrhenius study

(Arrhenius equation)



Graph 2. Accelerated Stability Assessment Program[7]

temp 50-80oC; relative humidity 10-75%

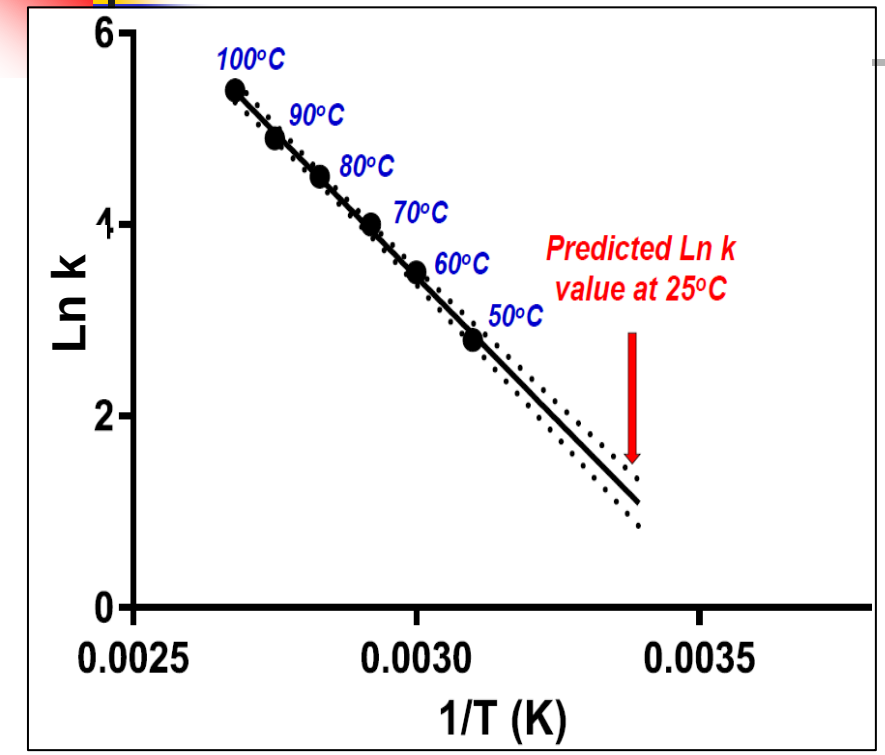
ASAP study

(humidity-corrected Arrhenius equation)

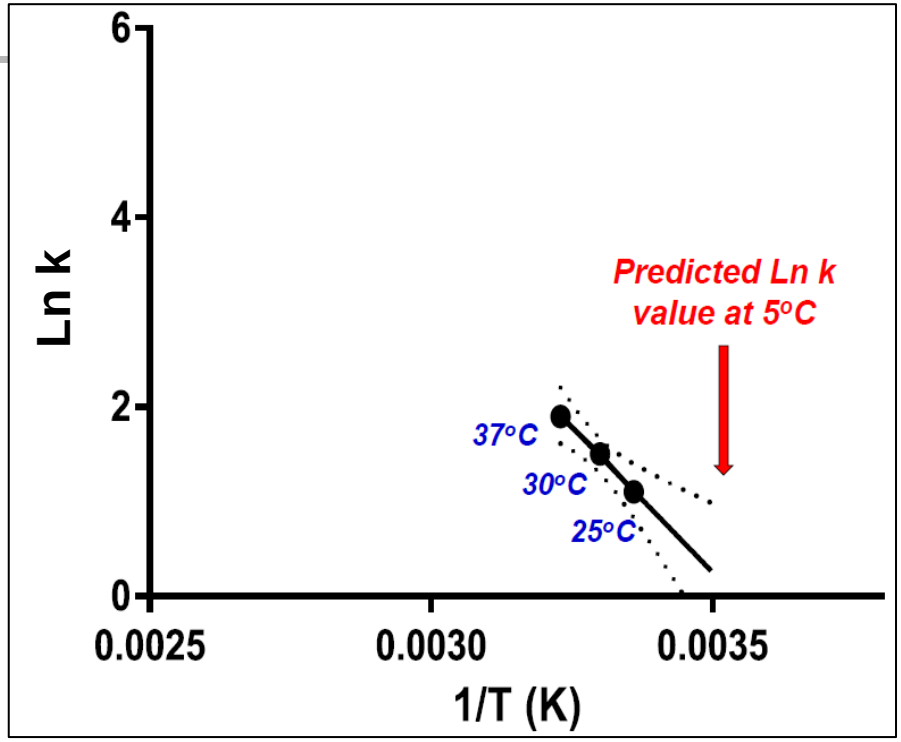
highly predictive for chemical drug tablets

But, for BIOPHARMACEUTICALS,
Arrhenius Plots may not be reliable to predict shelf life

Chemical Drugs



Biopharmaceuticals



limited test temperature range results in higher unpredictability (i.e., wider confidence limits) for true rate of instability

Biopharmaceuticals require real-time, real-condition data from the labeled claim stability to justify the shelf life of the drug product

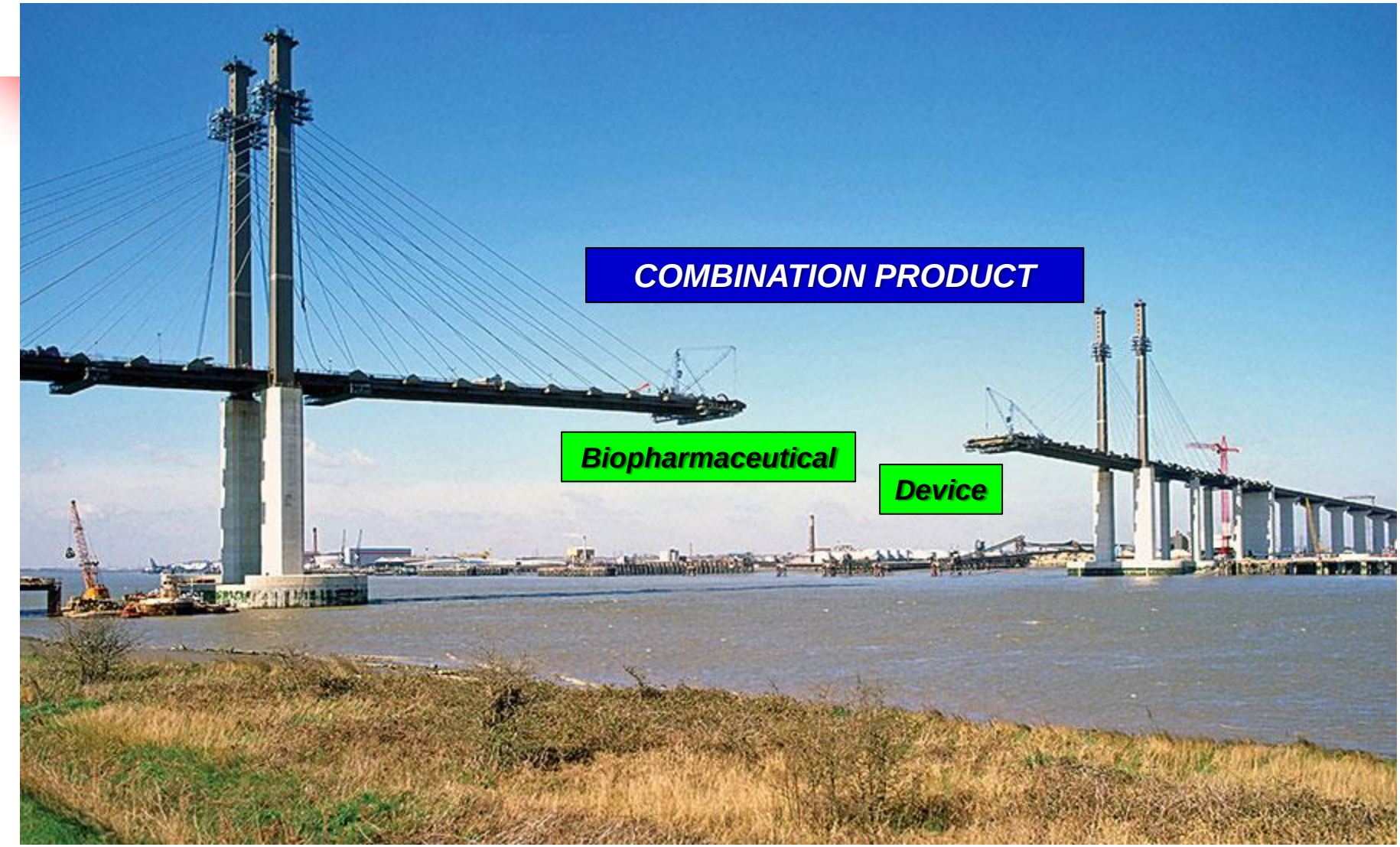
Insights from the evaluation of an IgG1 mAb product portfolio by an Arrhenius-based model

Commercial shelf-life based on real time data

Predicted shelf-life based on Arrhenius Plot

X: mAb would have failed shelf life specification if set on 'predicted rate'

mAb	Shelf-life	Shelf-Life (PI)	Difference	
1	24m	33m	38%	X
2	24m	25m	4%	
3	36m	36m	0	
4	30m	36m	20%	X
5	24m	37m	54%	X


COMBINATION PRODUCT
Biopharmaceutical
Device

Biologic

Definition of 'Drug' – Section 201(g) of the FD&C Act (21 USC 321(g))

articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man …

21 CFR 211

Definition of 'Device' – Section 201(h) of the FD&C Act (21 USC 321(h))

an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, … intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man, or intended to affect the structure or any function of the body of man, and which does not achieve its primary intended purposes through chemical action within or on the body of man and which is not dependent upon being metabolized for the achievement of its primary intended purposes

21 CFR 820

Definition of 'Combination Product'

a product comprised of two or more regulated components …

(which together achieves the intended use, indication or effect) (PMOA – primary mode of action – determines which FDA Center drives the review)

21 CFR 3.2(e)

A container closure system that only holds a biopharmaceutical is not a device – therefore, not a combination product

Glass vial

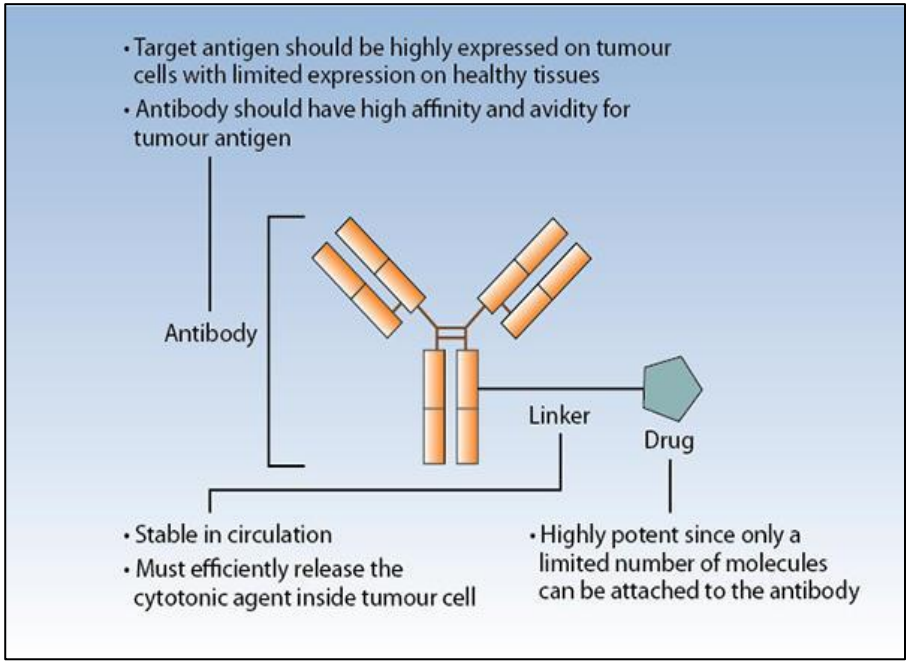
Rubber septum

Antibody-Drug Conjugates (ADCs) are combination products

Q.II.3. ***What type of marketing application should be submitted for a proposed antibody-drug conjugate?***
[Final December 2018]

A.II.3. A BLA should be submitted for a proposed monoclonal antibody that is linked to a drug (antibody-drug conjugate). FDA considers an antibody-drug conjugate to be a combination product composed of a biological product constituent part and a drug constituent part (see 21 CFR 3.2(e)(1); 70 FR 49848, 49857–49858 (August 25, 2005)).

CDER is the FDA center assigned to regulate antibody-drug conjugates, irrespective of whether the biological product constituent part or the drug constituent part is determined to have the primary mode of action. For more



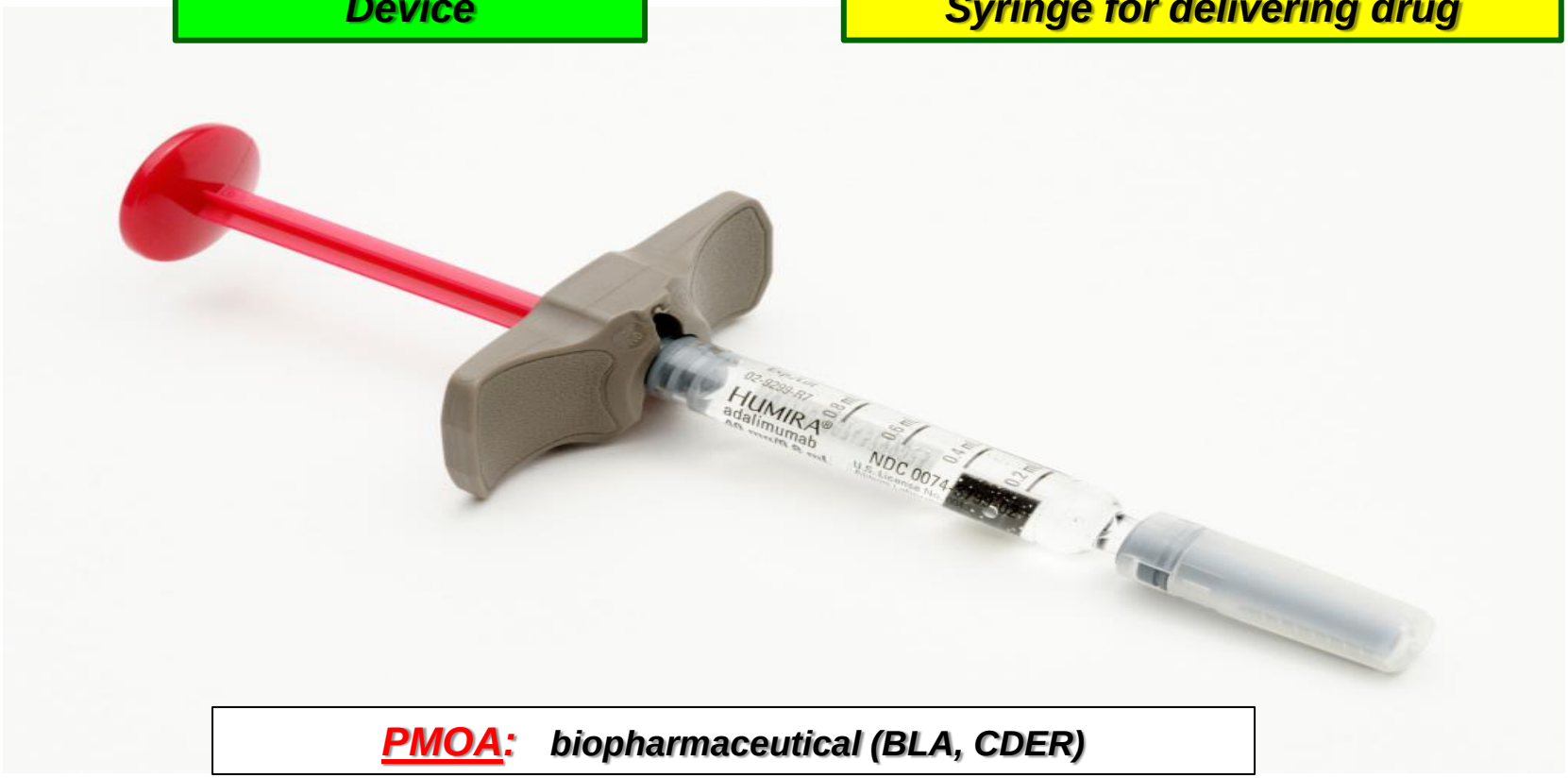
Questions and Answers on Biosimilar Development and the BPCI Act

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

September 2021

Biopharmaceutical Solution in a Prefilled Syringe

Biopharmaceutical	**mAb treats Crohn's disease**
Device	**Syringe for delivering drug**



PMOA: biopharmaceutical (BLA, CDER)

Current Good Manufacturing Practice Requirements for Combination Products

January 2017

"Streamlined" cGMPs for a Combination Product

Streamlined approach: Either of the two approaches permitted under 21 CFR part 4, which allows combination product manufacturers to demonstrate compliance with both the drug CGMPs and device QS regulation by designing and implementing a CGMP operating system that demonstrates compliance with part 211 or part 820 in its entirety plus specified provisions of the other set of regulations.

Biopharmaceutical in a prefilled syringe

must meet full cGMPs for the biopharmaceutical

+ must meet streamlined cGMPs for the device

Drug CGMP-based streamlined approach: A CGMP operating system that is intended to demonstrate compliance with all of the provisions from the drug CGMPs and the following provisions from the device QS regulation in accordance with 21 CFR 4.4(b)(1):

(i) 21 CFR 820.20	Management responsibility
(ii) 21 CFR 820.30	Design controls
(iii) 21 CFR 820.50	Purchasing controls
(iv) 21 CFR 820.100	Corrective and preventive action
(v) 21 CFR 820.170	Installation
(vi) 21 CFR 820.200	Servicing

Streamlined cGMPs for the device

The device has to be approved at the same time as the biopharmaceutical!

Meeting Type:	Type B	***ADBRY***
Meeting Category:	Pre-BLA	
Meeting Date and Time:	May 1, 2019; 9:00 – 10:00 AM ET	
Meeting Location:	FDA, White Oak Building 22	
Application Number:	IND 123797	
Product Name:	tralokinumab injection	

LEO Pharma A/S

Question 6:
Does the Agency agree on the submission strategy for the accessorized prefilled syringe functional performance information and human factors studies?

FDA Warning: 'As the owner of the combination product it is expected that you maintain the quality control strategy, including design controls, for the device constituent parts of your product.'

FDA's meeting minutes listed the specific streamlined cGMPs for the prefilled syringe

BUT… BLA filed April 2020 → Complete Response Letter April 2021

While the testing provided evidence for performance of the 510(k) cleared needle safety device component, the testing did not include testing of your final finished combination product or testing after the requested representative preconditioning (aging of the device, dropping of the device, and simulated shipping).

BLA resubmitted to address device GMPS, and approved December 2021 (6 month delay)

EMA guidance for handling biopharmaceuticals with integral devices

(prefilled syringes, etc.)

assessment of performance of the device

As a general principle for medicinal products falling within the scope of this guideline, the assessment of the suitability of a device (part) for its intended purpose should take into account the relevant quality aspects of the device (part) in the context of its use with the medicinal product. The complexity of the device (part), relevant patient characteristics and user requirements, as well as the clinical setting or use environment, are also important aspects of the assessment process. The medicinal product dossier should include a discussion of the impact of the device (part) on the Quality Target Product Profile (QTPP), Critical Quality Attributes (CQA) and overall control strategy of the medicinal product.

assessment of impact on the product

EUROPEAN MEDICINES AGENCY

Guideline on quality documentation for medicinal products when used with a medical device

22 July 2021
EMA/CHMP/QWP/BWP/259165/2019

Critical Importance of Human Factor Studies with Devices

If someone can do something dumb with your combination product, they will!

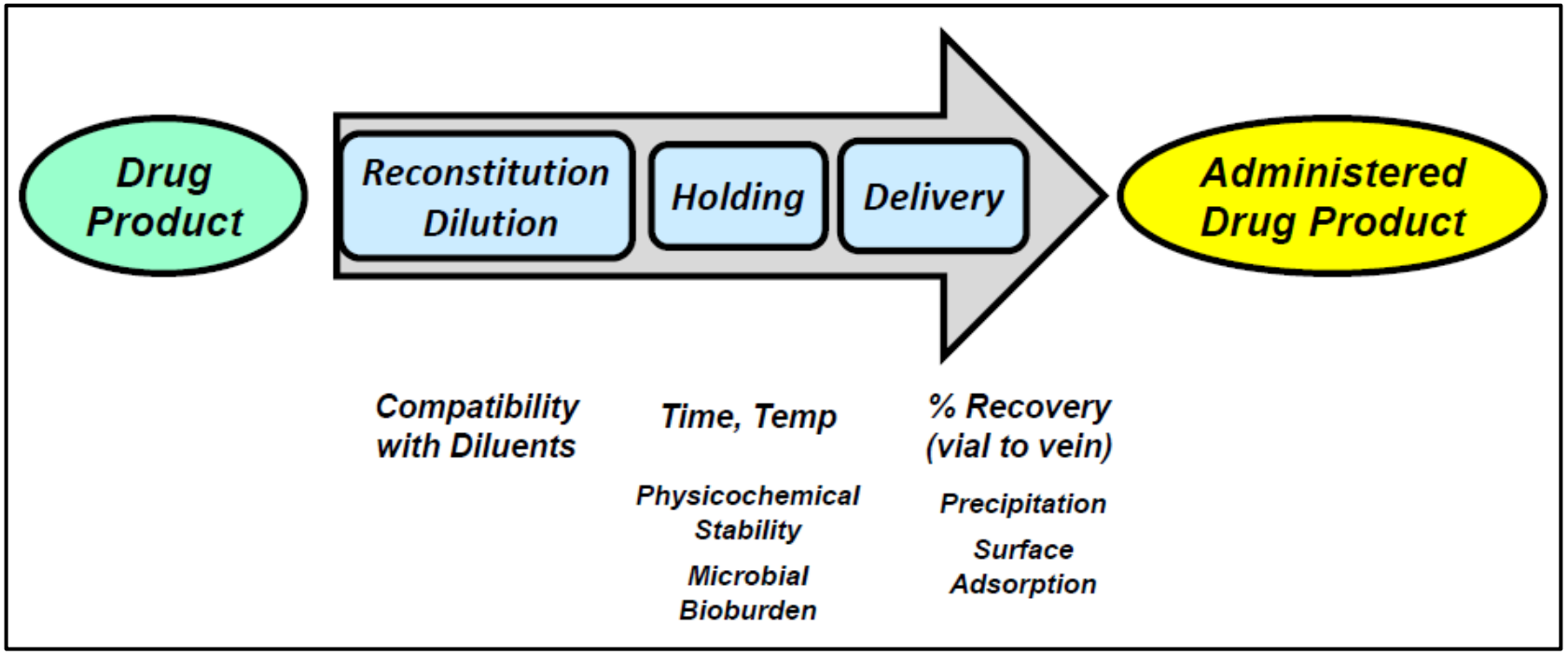
You are in an emergency room and a patient rushes in with a life threatening event. Do you know how to inject the life-saving drug?

Insulin for diabetic hyperglycemia coma

Epinephrine for anaphylactic shock

What do these two combination products have in common that is a potential human factor concern?

Applied Risk-Management Across the Manufacturing Process



CMC team needs to be aware of how the biopharmaceutical drug product is handled in the clinic, and kept up-to-date, if changes are made at a later date!

MINIMUM CMC Regulatory Compliance CONTINUUM

stability, handling of biopharmaceutical drug product in clinic setting

during clinical development

In-use stability data should be presented for preparations intended for use after reconstitution, dilution, mixing or for multidose presentations. These studies are not required if the preparation is to be used immediately after opening or reconstitution.

EUROPEAN MEDICINES AGENCY

Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials

27 January 2022
EMA/CHMP/BWP/534898/2008 Rev. 2

seeking market approval

Microbiological studies in support of the post-reconstitution and/or post-dilution storage conditions. Describe the test methods and results that employ a minimum countable inoculum (10-100 CFU) to simulate potential microbial contamination that may occur during dilution. The test should be run at the label's recommended storage conditions, be conducted for twice the recommended storage period, bracket the drug product concentrations that would be administered to patients, and use the label-recommended reconstitution solutions and diluents. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> *Antimicrobial Effectiveness Testing*, plus typical skin flora or species associated with hospital-borne infections. *In lieu* of this data, the product labeling should recommend that the post-reconstitution and/or post-dilution storage period is not more than 4 hours.

FDA Drug Databases: Drugs@FDA – FDA Approved Drug Products – Nexviazyme (Avalglucosidase alfa-ngpt) – Administrative and Correspondence Documents – Pre-BLA Meeting Minutes (June 30, 2020)

In-Use Stability

CASE EXAMPLE

Uplizna

Inebilizumab-cdon is a CD19-directed humanized afucosylated IgG1 monoclonal antibody

EMA EPAR

11 November 2021
EMA/266309/2022

In-use stability results, performed as part of the compatibility studies (described in P.2), support the maximum intended hold times of 4h at 25ºC and 24h at 2-8ºC of FP diluted into 0.9% (w/v) saline solution. The results demonstrate that there was no change (only change within method variability) in appearance, purity, charge isoforms, and potency, or any undesired changes in protein concentration when FP was diluted into 0.9% (w/v) saline, or upon subsequent agitation and hold, with all administration components tested. There was no sub-visible particle formation upon dilution, or upon subsequent agitation and hold at the final timepoint compared to the initial timepoint. Also, any sub-visible/visible particles observed for samples obtained through the injection port (pre-in-line filter) are removed after passing through the in-line filter (post-in-line filter).

CASE EXAMPLE

BLINCYTO (blinatumomab) for injection, for intravenous use
Initial U.S. Approval: 2014

bispecific antibody

FDA package insert

Table 1. Storage Time for Reconstituted BLINCYTO and IV Solution Stabilizer

Maximum Storage Time of Reconstituted BLINCYTO Vial*		Maximum Storage Time of Prepared IV Bag Containing BLINCYTO Solution for Infusion	
Room Temperature 23°C to 27°C (73°F to 81°F)	Refrigerated 2°C to 8°C (36°F to 46°F)	Room Temperature 23°C to 27°C (73°F to 81°F)	Refrigerated 2°C to 8°C (36°F to 46°F)
4 hours	24 hours	48 hours†	8 days

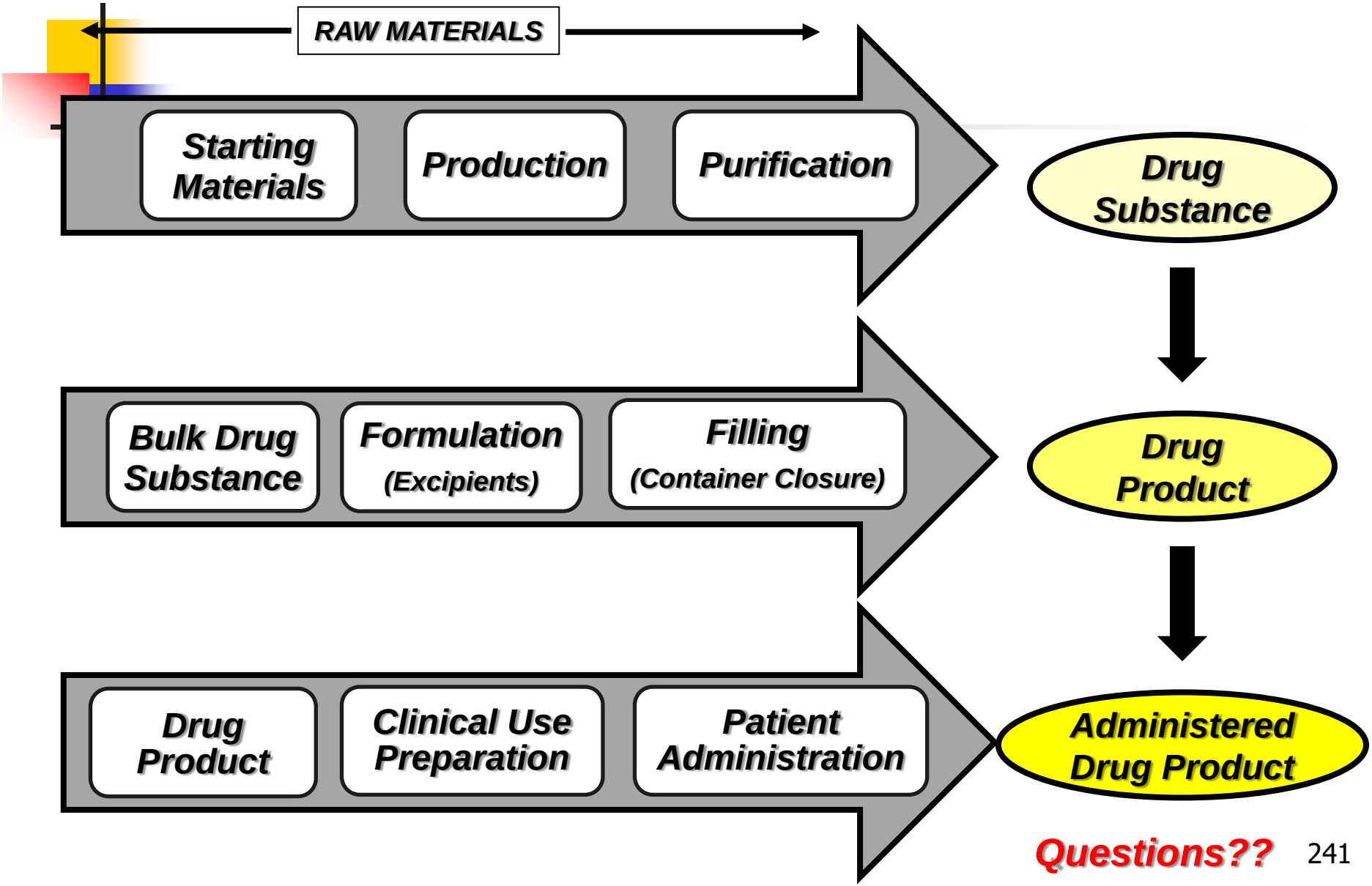
* While stored, protect BLINCYTO and IV Solution Stabilizer vials from light.
† Storage time includes infusion time. If IV bag containing BLINCYTO solution for infusion is not administered within the time frames and temperatures indicated, it must be discarded; it should not be refrigerated again.

2.4.2 Aseptic Preparation

Aseptic technique must be strictly observed when preparing the solution for infusion since BLINCYTO vials do not contain antimicrobial preservatives. To prevent accidental contamination, prepare BLINCYTO according to aseptic standards, including but not limited to:

- Preparation must be done in a USP <797> compliant facility.
- Preparation must be done in an ISO Class 5 laminar flow hood or better.
- The admixing area should have appropriate environmental specifications, confirmed by periodic monitoring.
- Personnel should be appropriately trained in aseptic manipulations and admixing of oncology drugs.
- Personnel should wear appropriate protective clothing and gloves.
- Gloves and surfaces should be disinfected.

Summary: Applied Risk-Management Across the Manufacturing Process



Questions??

Course Outline

4. Challenges of Demonstrating Protein-Based Biopharmaceutical Comparability After Manufacturing Process Changes

- Three (3) risk-based concerns that must be addressed for all proposed changes
  - risk at the stage of clinical development
  - risk due to the nature of the planned process change
  - risk due to remaining residual uncertainty
- Opportunity for comparability 'contracts' (PACMPs) when seeking market approval

Always something about a biopharmaceutical manufacturing process that needs (or someone wants) to be changed!

1) ***Improving manufacturing process robustness and control***
   - **Replacing a chromatography resin type to improve process-related impurity removal**
   - **Manufacturing site change to enhance cGMP compliance**

2) ***Improving biopharmaceutical purity, quality, or safety***
   - **Addition of a new chromatography polishing step**
   - **Tightening of biopharmaceutical release and/or shelf-life specifications**

3) ***Increasing manufacturing capacity***
   - **Exchanging a recombinant cell line to one with higher biopharmaceutical productivity**
   - **Scale-up (or scale-out) to increase production capacity**

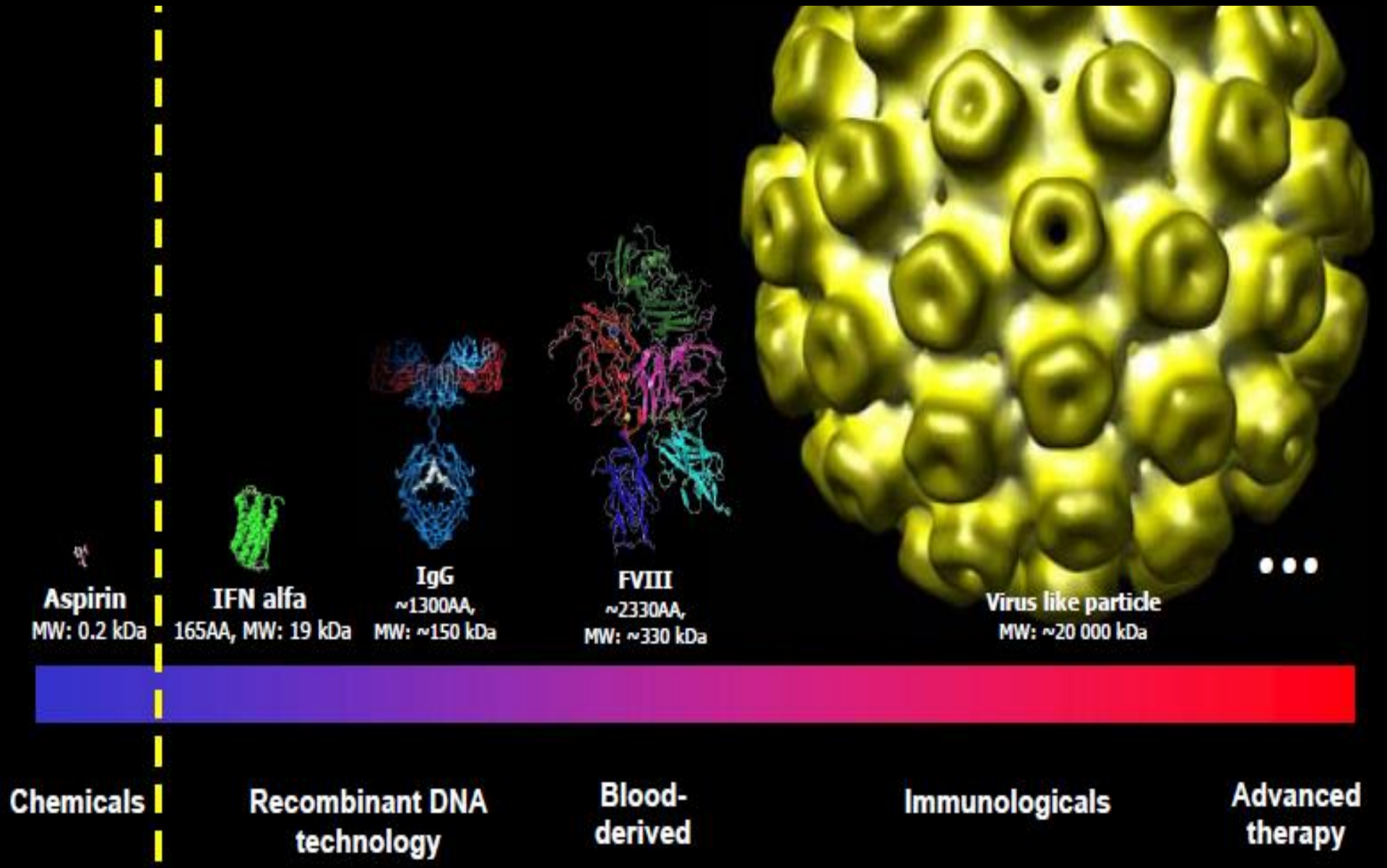
4) ***Business reasons***
   - **Reduction in cost of goods (COGs)**
   - **Acquisitions/mergers requiring manufacturing site changes**

But … every manufacturing process change should provide added value to offset the potential risk due to change!

STANDARD TO BE MET FOR CONFIRMING PRODUCT COMPARABILITY

equivalent ***'highly similar'***

→ ***increasing molecular complexity***



Challenge of ensuring that the biopharmaceutical remains "HIGHLY SIMILAR" after a manufacturing process change

But what is "HIGHLY SIMILAR"?

'not identical' 'not equivalent'

"any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product"

"minor differences in clinically inactive components"

"no clinically meaningful differences"

"HIGHLY SIMILAR" is subjective!

depends upon which attributes are compared
(primary structure, color, or all properties)

depends upon who is evaluating
(you, CMC team, Executive Mgmt, or FDA/EMA)

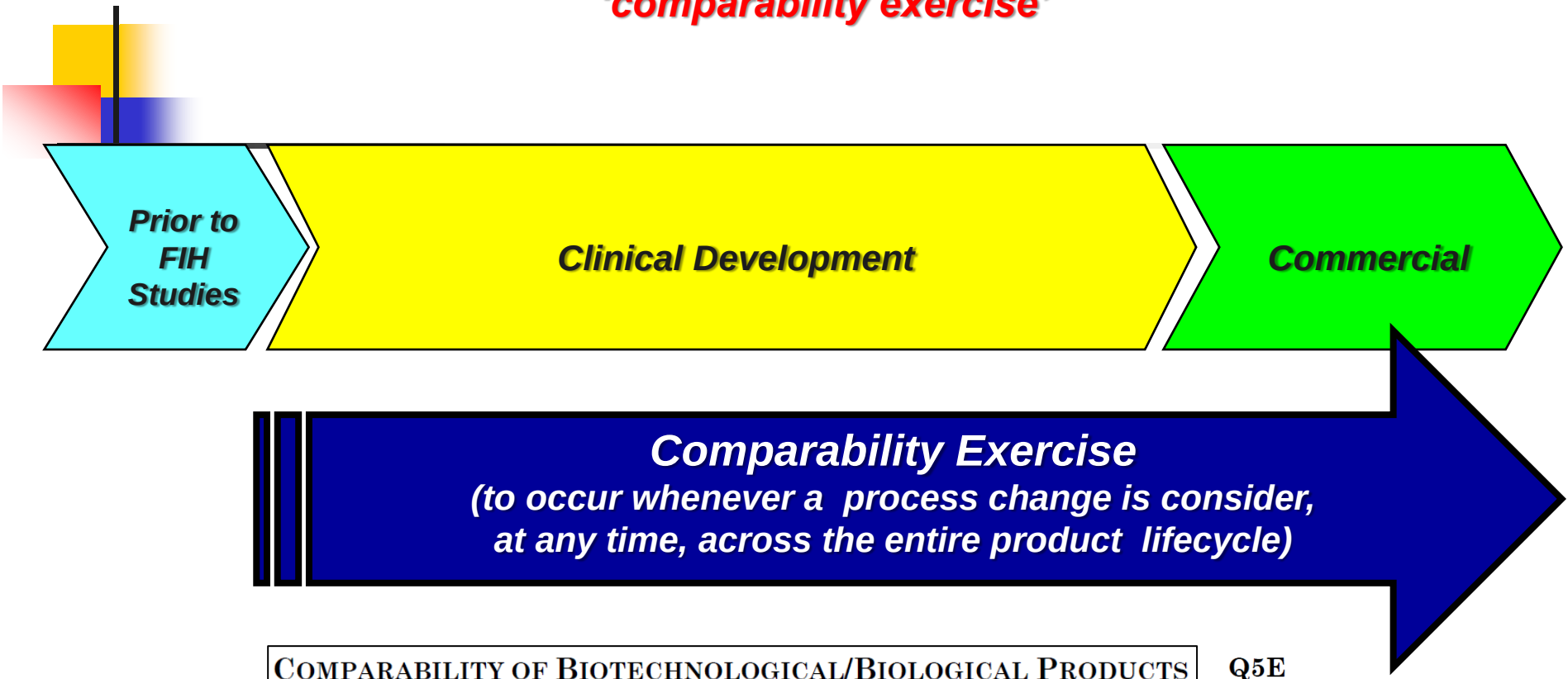
same standard applied

'Highly Similar' applies to innovator manufacturers

'Highly Similar' applies to biosimilar manufacturers

Risk/Benefit assessment due to a manufacturing process change

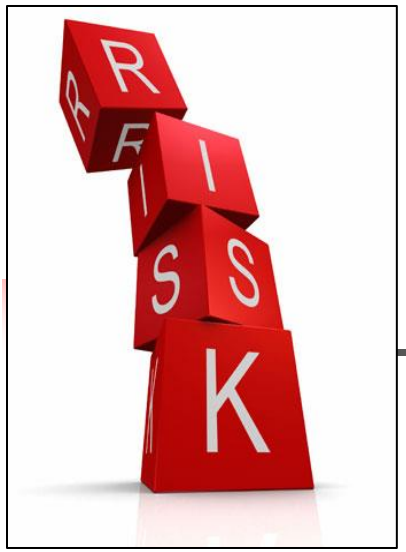
'comparability exercise'



COMPARABILITY OF BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS SUBJECT TO CHANGES IN THEIR MANUFACTURING PROCESS

Q5E
2004

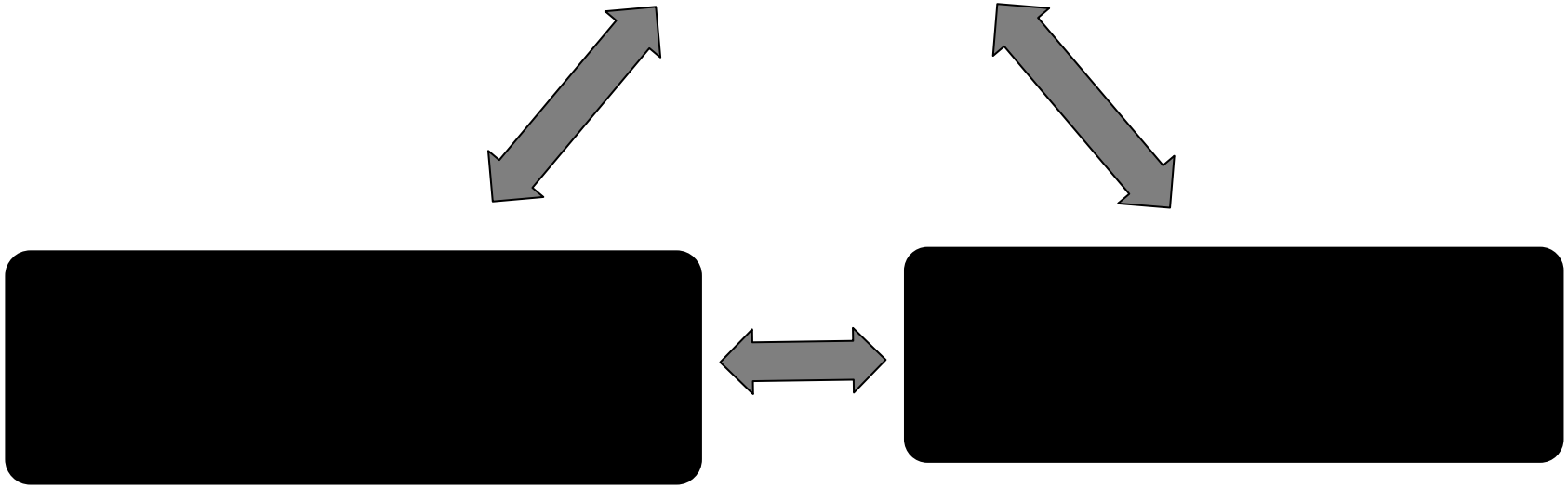
"The goal of the comparability exercise is to ascertain that pre- and post-change drug product is <u>comparable</u> in terms of quality, safety, and efficacy."



3 risk-based concerns addressed by an effective comparability study

Assess the level of risk due to the STAGE of clinical development when the change is planned

← 'minimum CMC regulatory compliance continuum'



Comparability exercise goal at different stages of clinical development

ICH Q5E

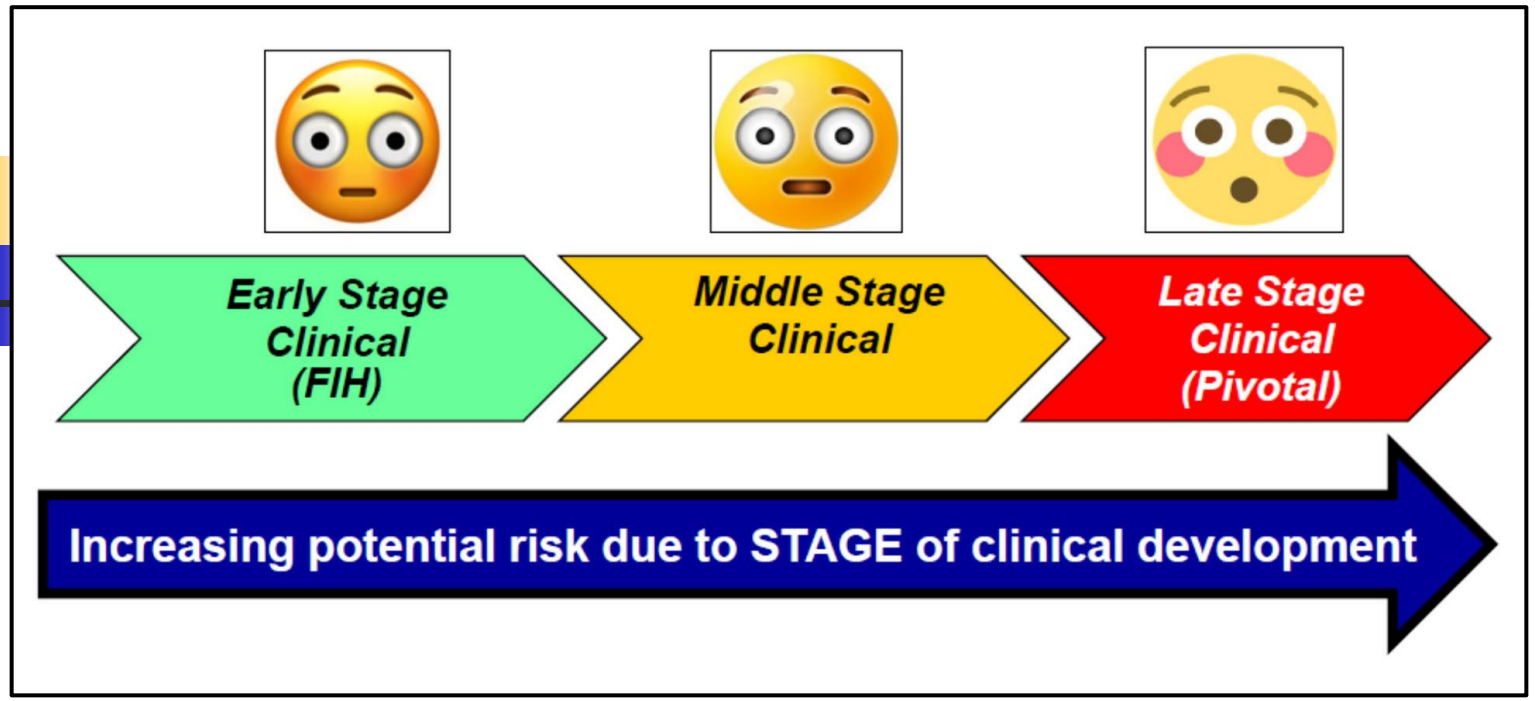
1 Where changes are introduced in development before nonclinical studies, the issue of assessing comparability is not generally raised because the manufacturer subsequently conducts nonclinical and clinical studies using the post-change product as part of the development process.

2 During early phases of nonclinical and clinical studies, comparability testing is generally not as extensive as for an approved product.

3 As knowledge and information accumulate, and the analytical tools develop, the comparability exercise should utilise available information and will generally become more comprehensive.

4 Where process changes are introduced in late stages of development and no additional clinical studies are planned to support the marketing authorisation, the comparability exercise should be as comprehensive and thorough as one conducted for an approved product. Some outcomes of the comparability studies on quality attributes can lead to additional nonclinical or clinical studies.

Risk-based concerns increase as the stage of clinical development advances



	ICH Q5E: Product Comparability Testing by Clinical Stage	
1	Prior to Clinical	not required
2	Early Clinical Stage	not as extensive
3	Mid Clinical Stage	becomes more comprehensive
4	Late Clinical Stage	comprehensive & thorough*
	Commercial	comprehensive & thorough*

* Change can impact statistical efficacy or safety

(illustrates the 'minimum CMC regulatory compliance continuum' strategy)

Case Example

FDA's heightened level of concern for manufacturing process changes immediately before a pivotal clinical study

Novartis at an EOP2 meeting sought FDA advice on changing (1) the MCB, (2) the manufacturing process and (3) the manufacturing site for a mAb

Suitability of bridging data package between Selexys and Novartis materials

Clinical and toxicological studies performed to date for crizanlizumab under IND 110,752 were conducted using Selexys material (i.e. SelG1 mAb) produced in [redacted] CHO [redacted] cells [redacted]. To ensure supply of future clinical studies as well as commercial demand, Novartis has optimized the production of crizanlizumab. The Novartis material (i.e. SEG101 mAb) is produced in the Novartis [redacted] cell line [redacted] and drug substance and drug product will be manufactured in Novartis sites. Novartis intends to demonstrate comparability between Selexys material (used in current Phase I and II studies) and Novartis material (to be used in future clinical/ toxicological studies and as commercial product) with a comparability package comprising analytical in-vitro-comparison in accordance with ICH Q5E, a study in the cynomolgus monkey and a study in human healthy subjects. [redacted]

[redacted] Does the Agency agree with this approach?

Selexys based in Oklahoma, USA → Novartis based in Switzerland

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: February 28, 2017, 11:00 AM – 12:00 PM ET

FDA Response to Question 7:

Based on the preliminary data provided in the meeting packages, the proposed commercial crizanlizumab product manufactured at Novartis differs from the Selexys material in [redacted] (b) (4) Your nonclinical study results with cynomolgus monkeys also indicated that these differences may potentially impact the PK of crizanlizumab. If such differences are confirmed through analyses of additional post-change lots, you will need to provide human PK/PD data to demonstrate that the differences have no impact on the safety and efficacy.

The Agency has concerns regarding your ability to demonstrate comparability of the pre- and post-change products based on the information provided. Given the above, your proposal to submit an application that relies on clinical data from studies which use the old product is risky. You should consider conducting a clinical trial using the new product to demonstrate safety and efficacy.

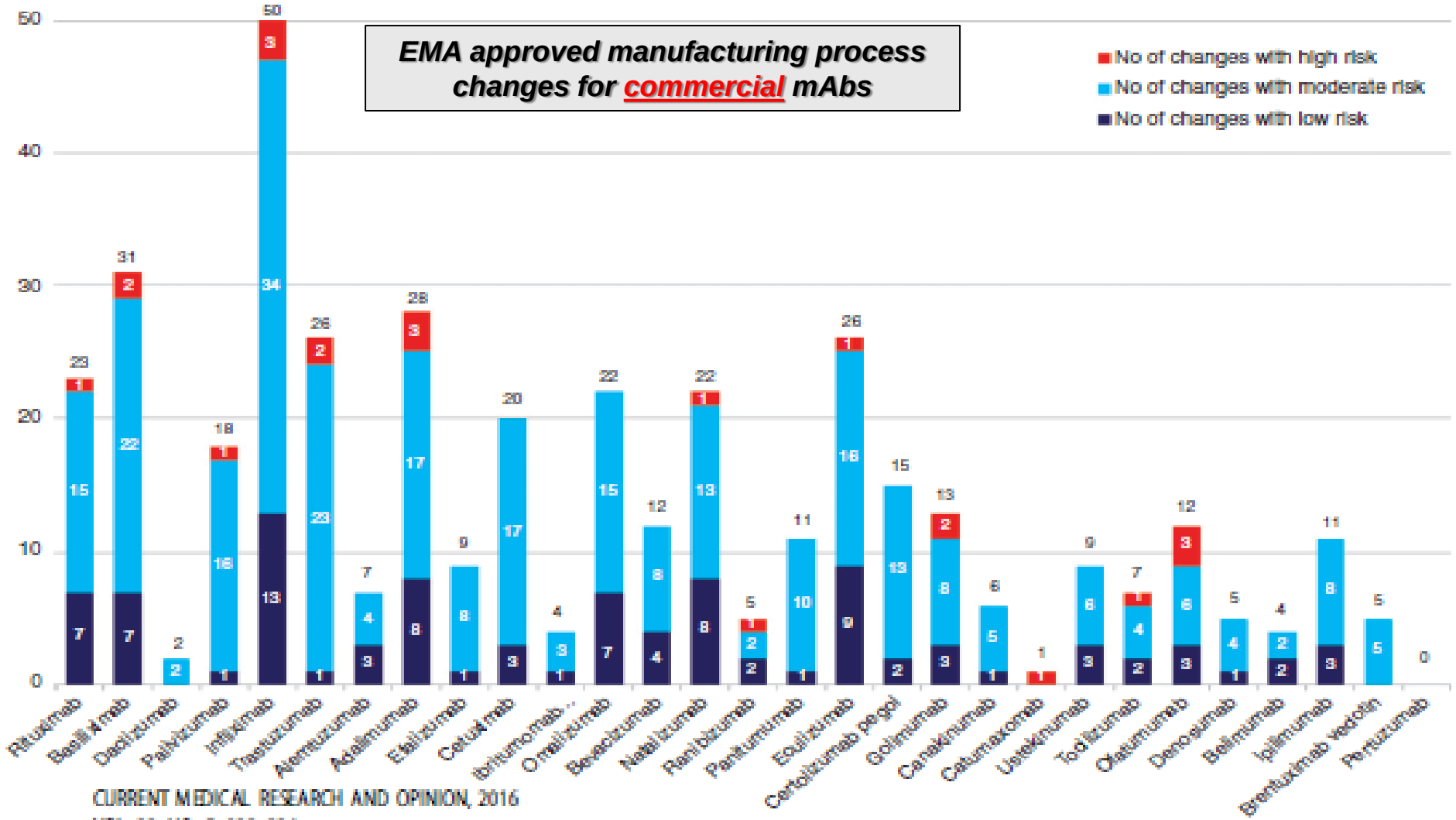
Translation: stronger Phase 3 clinical package needed

ADAKVEO® (crizanlizumab-tmca)

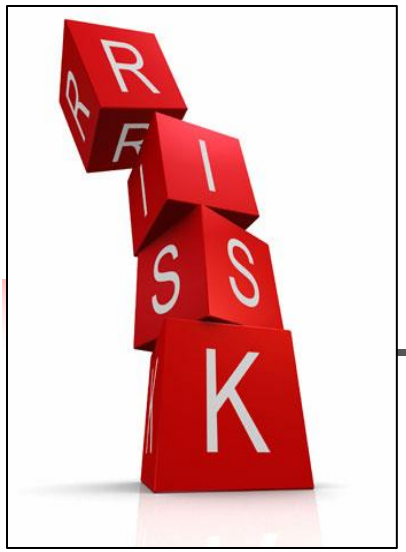
FDA market approved November 2019 – manufactured in Switzerland by Novartis

'sooner than later' is preferred for manufacturing process changes

But* that doesn't mean that changes cannot be successfully managed during late stage or even after commercial approval. *It's just a higher level of risk!



CURRENT MEDICAL RESEARCH AND OPINION, 2016
VOL. 32, NO. 5, 829–834



3 risk-based concerns addressed by an effective comparability study

Assess the level of risk due to the STAGE of clinical development when the change is planned

[redacted]

Assess the level of risk due to the NATURE (type, extent, process location) of the planned process change

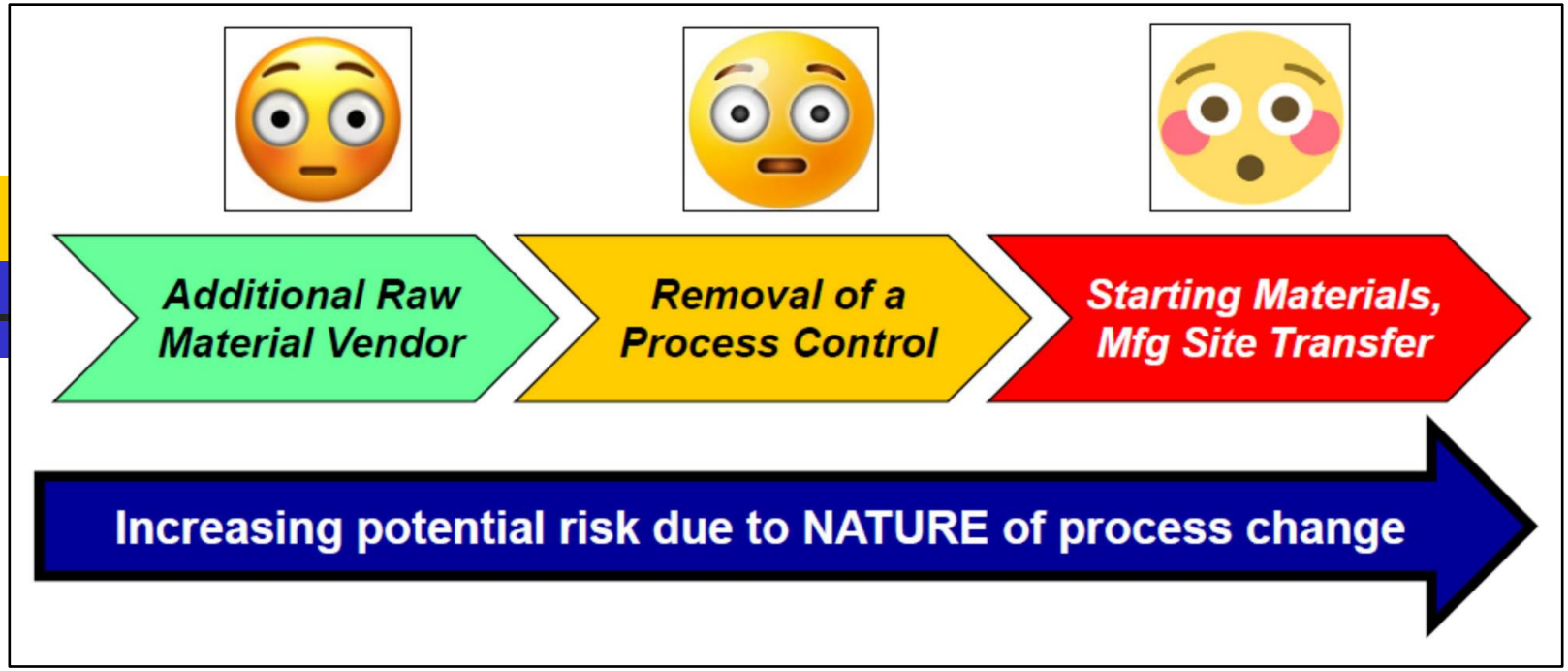
Assessment of level of risk due to the NATURE of the proposed change

ICH Q5E

The process assessment should consider such factors as the criticality of the process step and proposed change, the location of the change and potential for effects on other process steps, and the type and extent of change. Information that can aid this assessment is generally available from several sources. The sources can include knowledge from process development studies, small scale evaluation/validation studies, experience with earlier process changes, experience with equipment in similar operations, changes in similar manufacturing processes with similar products, and literature. Although information from external sources is useful to some extent, it is within the context of the specific manufacturing process and specific product that the change should be assessed.

Consider potential risk due to:

- ***Criticality of process step undergoing change***
- ***Location of change in overall manufacturing process***
- ***Downstream impacts***



Is there any Regulatory Authority guidance available on <u>correct</u> risk-level assignment due to the NATURE of process change?

During <u>clinical development</u>: YES (for type of proposed change)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials

27 January 2022
EMA/CHMP/BWP/534898/2008 Rev. 2

Changes to IMPD	Substantial Modification (SM)	Non-substantial Modification (NSM)
Manufacturing process of the active substance	Changes such as: • new expression cell line • new master cell bank • introduction of a working cell bank if prepared from an approved MCB • change of a raw material of biological origin • changes to the viral safety tests performed on cell banks or unprocessed bulk batches, • change in scale of the production bioreactor (upstream process), • changes to the cell culture conditions potentially impacting on quality attributes	• Addition or tightening of IPC if not due to safety reasons • Modification of the process parameters (same process, analogous raw materials) where no effect on product quality is demonstrated. • reprocessing if adequately described and accepted in the initial submission • minor changes in the manufacturing process which do not require a comparability exercise • changes to the controls of non-critical raw materials
Manufacturing process of the investigational medicinal product	• Significant changes to the manufacturing process and critical process controls (e.g. bioburden limit)	• Modifications of process parameters (same process) where no effect on product quality is demonstrated. • Scale-Up of filling process if supported by appropriate media fills.

Substantial modification means any change which is likely to have a substantial impact on the safety and rights of the subjects or on the reliability and robustness of the data generated in the clinical trial. Substantial modifications require regulatory approval to implement. Non-substantial modifications, documentation should not be proactively submitted.

Is there any Regulatory Authority guidance available on correct risk-level assignment due to the NATURE of process change?

Market approval and post: YES (for type of proposed change)

ICH Q12

3.2.1 ECs Definition ***Established Condition***

ECs are legally binding information considered necessary to assure product quality. As a consequence, any change to ECs necessitates a submission to the regulatory authority.

EMA Risk-Level for Process Change		
Major Risk	***Moderate Risk***	***Minor Risk***
Type II Variation (formal approval)	***Type IB Variation (30 day wait)***	***Type IA Variation (Annual Reporting)***

Variation Guidelines 2013/C 223/01

https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-2/c_2013_2008/c_2013_2008_pdf/c_2013_2804_en.pdf

FDA Risk-Level for Process Change		
Major Risk	***Moderate Risk***	***Minor Risk***
Prior Approval Supplement (PAS)	***Change Being Effective (CBE-30)***	***Annual Report***

21 CFR 601.12

caution

CAUTION

FDA has issued numerous guidances on level of risk for post-market approval manufacturing process type changes – BUT they have limitations by product type

Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products	Food and Drug Administration Center for Biologics Evaluation and Research Center for Drug Evaluation and Research **1997**	***Inclusion*** ***BLAs recombinant proteins, mAbs, biosimilars***
CMC Postapproval Manufacturing Changes for Specified Biological Products To Be Documented in Annual Reports Guidance for Industry	Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) **2021**	***Inclusion*** ***BLAs recombinant proteins, mAbs, biosimilars***
Postapproval Changes to Drug Substances Guidance for Industry	Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) **2018**	***Inclusion*** ***NDAs ANDAs Chemical Drugs***
Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products	Food and Drug Administration Center for Biologics Evaluation and Research Center for Drug Evaluation and Research **2021**	***Inclusion*** ***Specific BLAs only: Advanced Therapy Vaccines***

PAS

Process changes including, but not limited to,

- extension of culture growth time leading to significant increase in number of cell doublings beyond validated parameters;
- new or revised recovery procedures;
- new or revised purification process, including a change in a column;
- a change in the chemistry or formulation of solutions used in processing;
- a change in the sequence of processing steps or addition, deletion, or substitution of a process step; or

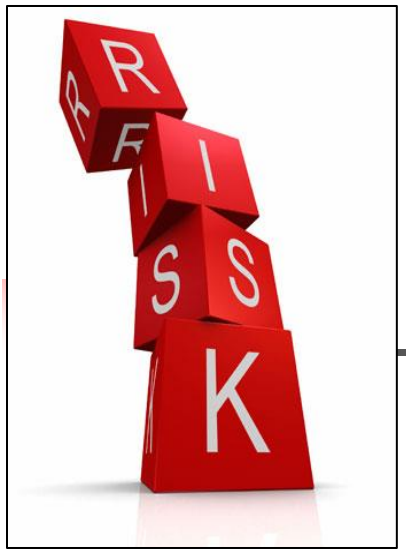
CBE

1. Addition of duplicated process chain or unit process, such as a fermentation process or duplicated purification columns, with no change in process parameters.
2. Addition or reduction in number of pieces of equipment (e.g., centrifuges, filtration devices, blending vessels, columns, etc.) to achieve a change in purification scale not associated with a process change.

AR

3.1. Manufacturing batch size or scale change caused by minor changes in the size of pooled or separated batches to perform the next step in the manufacturing process if all batches meet the approved in-process control limits and the critical process parameter ranges for the next step remain unaffected.

3.2. Changes to batch sizes that do not involve use of different equipment (e.g., minor changes in roller bottle number, fermenter volume, or load volumes for chromatography columns).



3 risk-based concerns addressed by an effective comparability study

Assess the level of risk due to the STAGE of clinical development when the change is planned

Address the level of risk due to RESIDUAL UNCERTAINTY STILL REMAINING after all required testing is completed

Assess the level of risk due to the NATURE (type, extent, process location) of the planned process change

ICH Q5E: 'Determinations of product comparability can be based solely on quality considerations, if the manufacturer can provide assurance of comparability through analytical studies."

Step 1

QUALITY (Analytical/Functional Studies)

ICH Q5E

Composed of 3 main studies

a) Consistency batches (spec comparison before and after change; including a historical data analysis for 'drift' in CQA values)

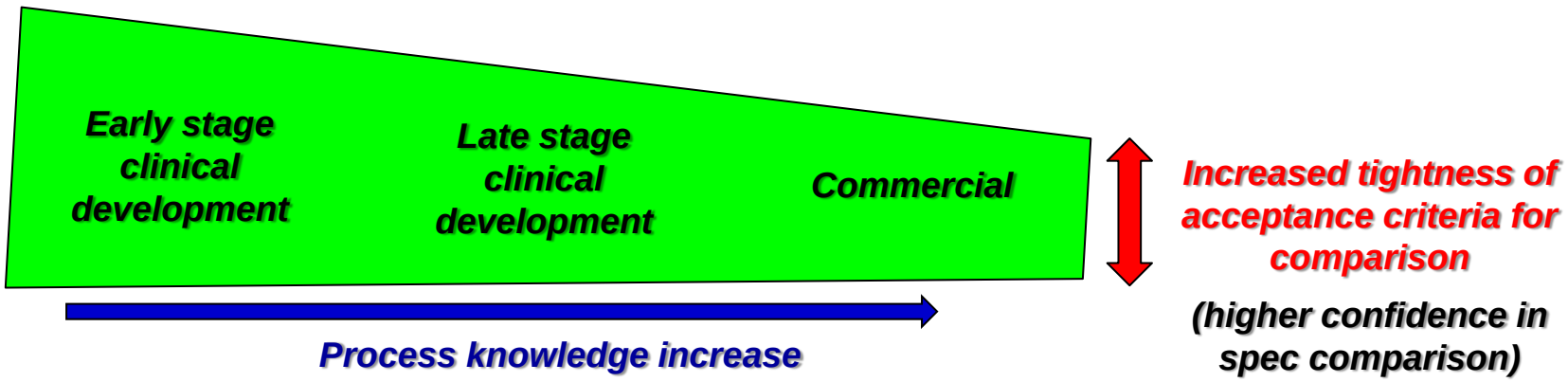
b) Relevant, comprehensive physicochemical, biological and functional assay characterization (head-to-head testing preferred)

c) Accelerated and Stress stability slope comparison (differences in rate of molecular variant formation)

(Regulatory Authority expectation for predefined acceptance criteria needed for defining 'highly similar')

#1a Consistency batches (spec comparison before and after change)

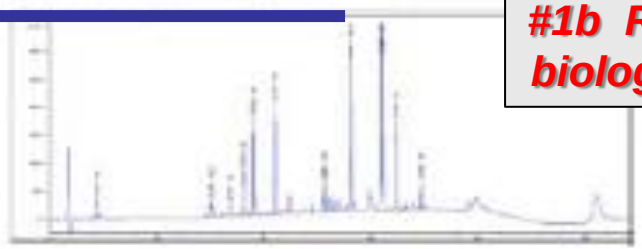
- ***Acceptance criteria should be established and justified based on data obtained from lots used in preclinical and/or clinical studies, data from lots used for demonstration of manufacturing consistency and data from stability studies, and relevant development data*** ***ICH Q6B***
- ***Specifications … should be based on risk to clinical performance, not what can be achieved by process*** ***Janet Woodcock (former CDER Director)***



Fingerprinting

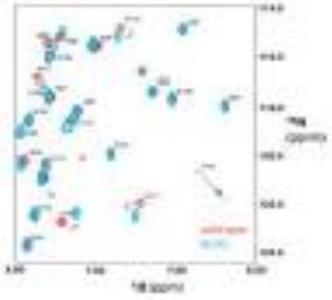
U.S. Food and Drug Administration
Protecting and Promoting Public Health

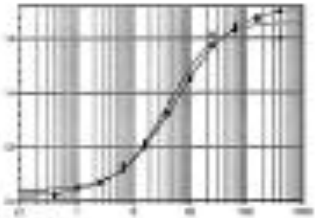
#1b Relevant, comprehensive physicochemical, biological and functional assay characterization



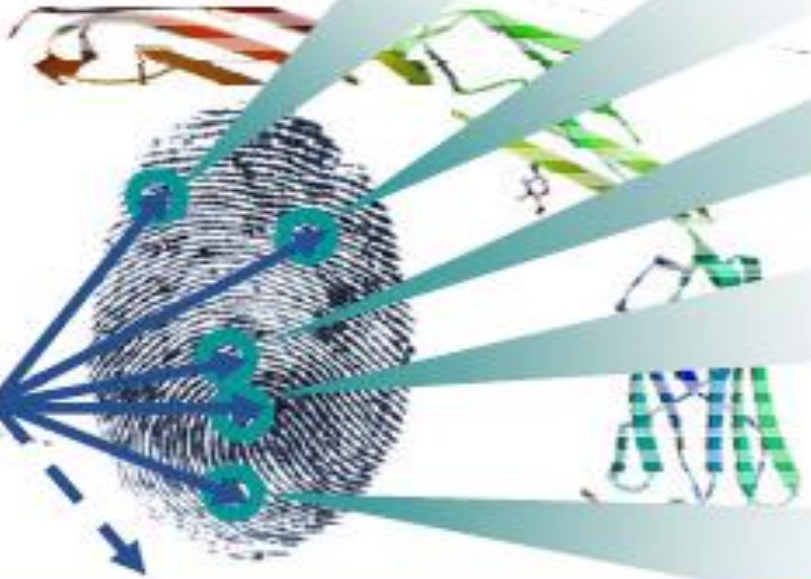
Sequence & Modifications

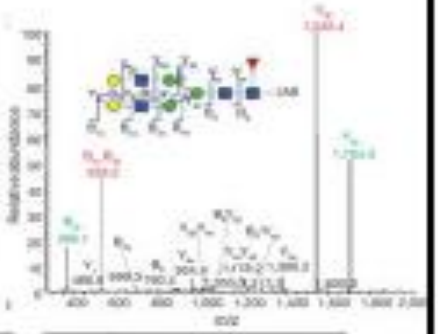
Higher Order Structure





Bioactivity





Glycoforms

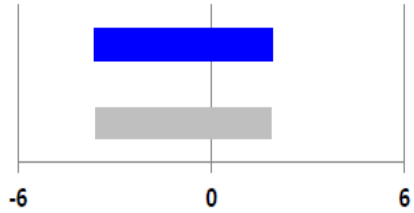
Impurity Profile

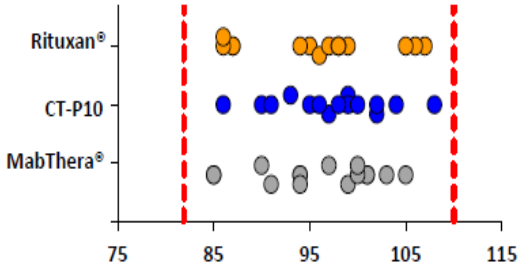
30

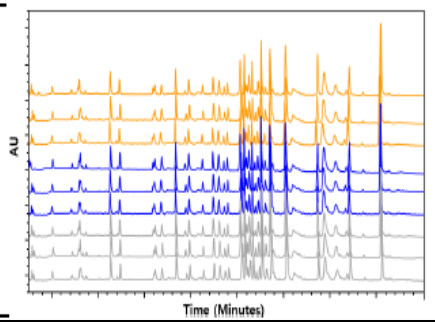
Illustration of <u>comprehensive</u> physicochemical characterization comparability
LC/MS for a biosimilar mAb →

Statistical Analysis for Similarity

	Quality Attribute	Test[1,2]	Limits
Tier 1	Very high criticality	Equivalence test: 90% CI of mean difference	$\pm 1.5\sigma_R$
Tier 2	High to moderate criticality	≥ 90% lots within quality range	± 2SD or ± 3SD
Tier 3	Low criticality or qualitative test	Presentation of raw/graphical data	Visual







FDA U.S. FOOD & DRUG ADMINISTRATION

September 2017

Statistical Approaches to Evaluate Analytical Similarity

(withdrawn in 2018, but …)

Tier 1: Protein Content, Bioassay
Tier 2: Size Variants, Charge Variants
Tier 3: Peptide Map, Secondary Structure

Statistical considerations for Step 1 analytical/functional comparability

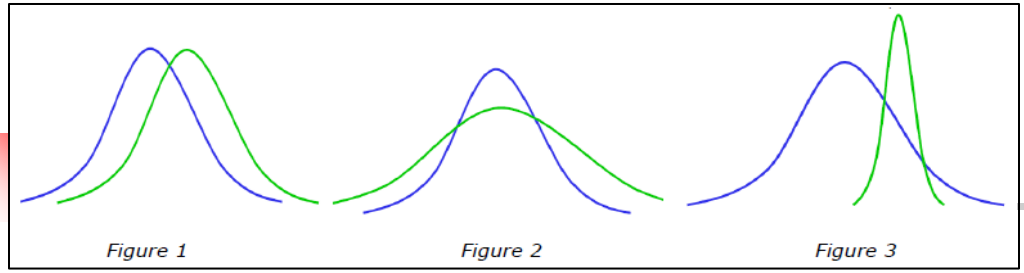


Figure 1 Figure 2 Figure 3

"Similarity Condition"

'Distributions can be different regarding location (Figure 1), spread (Figure 2) or combinations thereof (Figure 3). As 'similarity' is context-dependent, no universally applicable/agreeable similarity condition exists.'

- ***Similarity in 'distributions' – Figure 1***
- ***Similarity in 'means' – Figure 2***
- ***Similarity in 'overlap of distribution' – Figure 3***

Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development

26 July 2021
EMA/CHMP/138502/2017

BIOSIMILARS

Considering the inherent heterogeneity present in protein products and the expected lot-to-lot variability stemming from manufacturing processes, the Agency recommends that a sponsor include at least 10 reference product lots (acquired over a time frame that spans expiration dates of several years), in the analytical assessment to ensure that the variability of the reference product is captured adequately… The Agency recommends that a sponsor include at least 6 to 10 lots of the proposed product in the comparative analytical assessment ….

U.S. FOOD & DRUG ADMINISTRATION

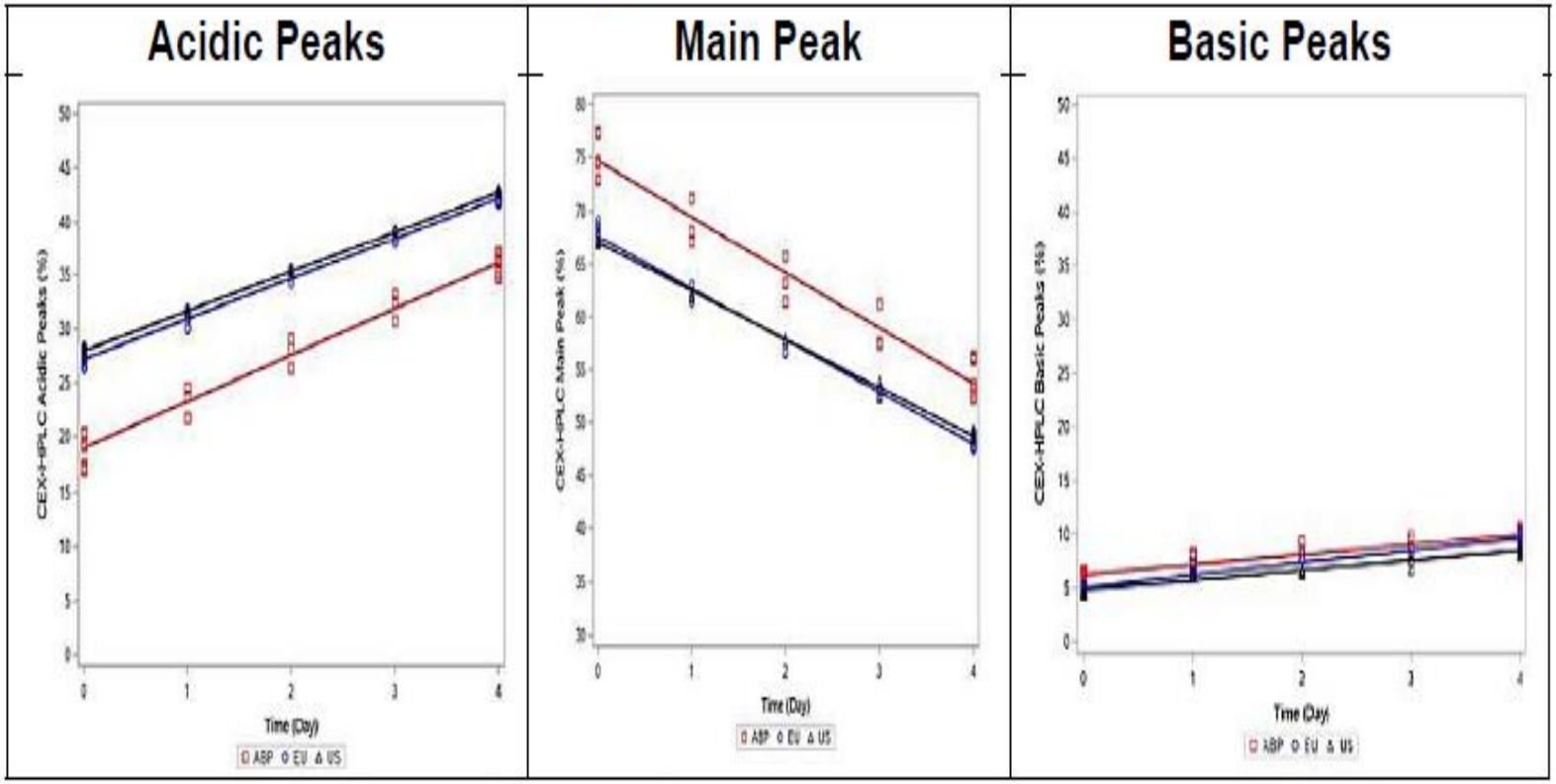
Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations

May 2019

(… reappeared but deleted 'tier')

#1c Stress stability rate of degradation slope comparison (rate of molecular variant change due to temp stress)

Figure 11 - CEX-HPLC acidic, main, and basic peak degradation rates for ABP215, US-licensed Avastin, and EU-approved bevacizumab at 50°C



Source: Figures excerpted from the Applicant's 351(k) BLA submission

CASE EXAMPLE

Regulators expect to see a full comparability exercise!

MAA filing: "mAb used for clinical trials not comparable to commercial mAb"

Justification based only on comparison of specifications (step 1a)

A major objection was raised regarding comparability between the clinical material and the commercial material. Additional data from extended characterisation, in-process controls, and short-term stressed stability studies (batch release data was submitted with the original application) was provided in response to the major objection and deemed satisfactory.

but … full Step 1 added (#1b and #1c) during MAA review

The comparability studies were performed according to ICH Q5E, and batches were compared based on routine in-process data, release testing, characterization testing, and short term stressed stability data with prospectively defined acceptance criteria.

1a *1b* *1c*

In conclusion, based on the submitted data, comparability has been considered demonstrated for the process changes.

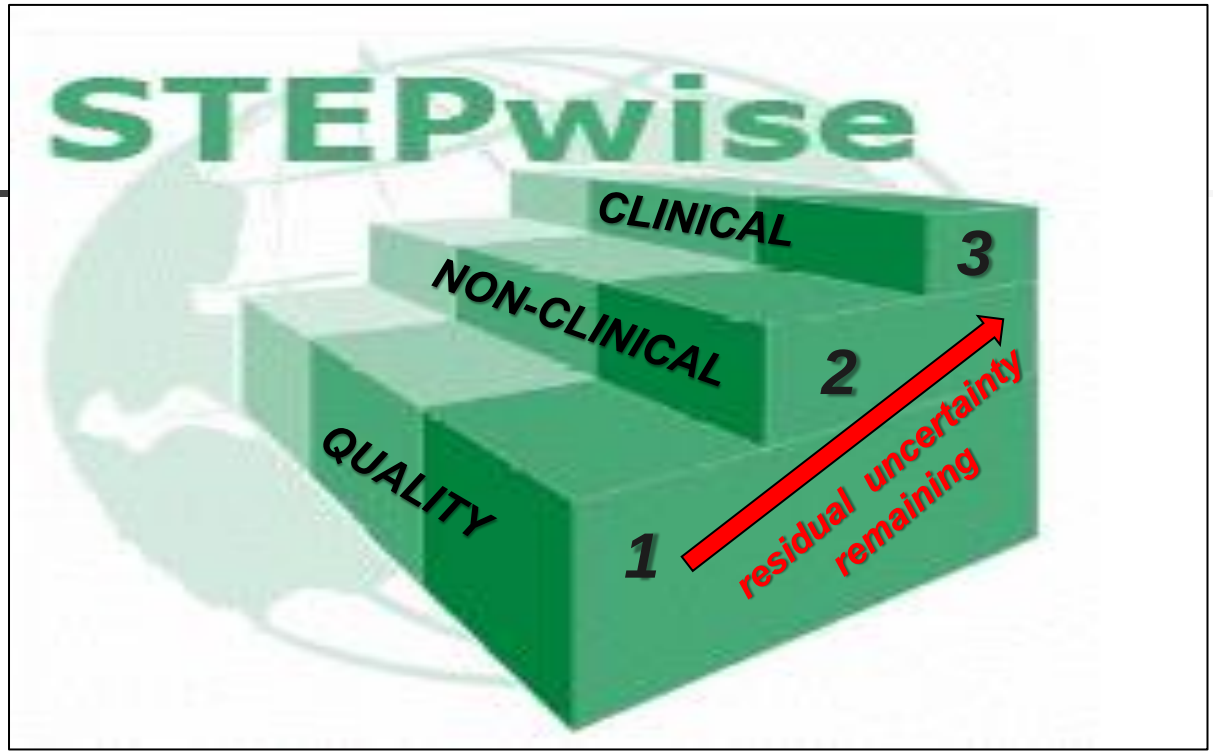
Takhzyro (lanadelumab)

CHO-based

18 October 2018
EMA/794314/2018

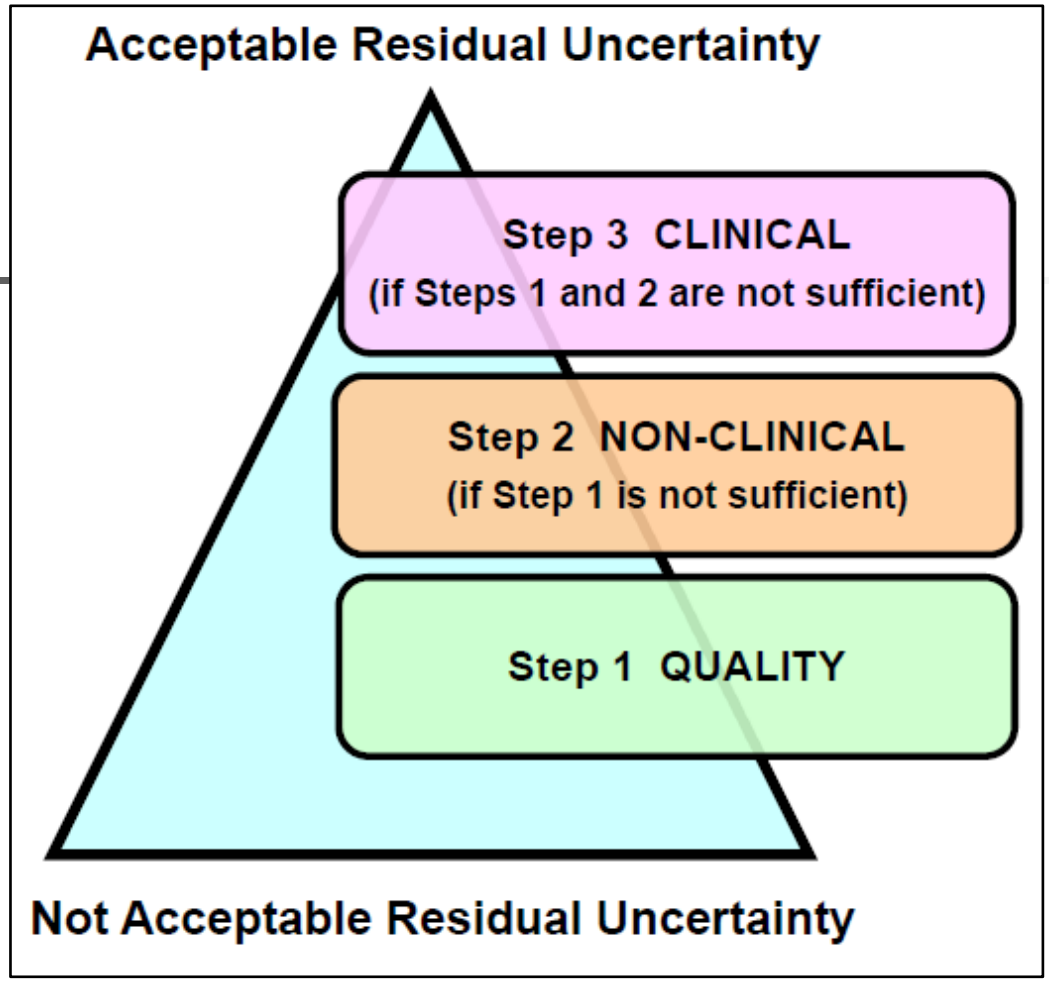
Shire

Goal: reduce RESIDUAL UNCERTAINTY



Determinations of product comparability can be based solely on quality considerations (see section 2.2) if the manufacturer can provide assurance of comparability through analytical studies as suggested in this document. Additional evidence from nonclinical or clinical studies is considered appropriate when quality data are insufficient to establish comparability. The extent and nature of nonclinical and clinical studies will be determined on a case-by-case basis in consideration of various factors, which include among others:

ICH Q5E



Innovator Biopharmaceutical — ***<u>Optional</u>, only if necessary to reduce residual uncertainty***

Biosimilar — ***<u>Mandatory</u> (does not have in-depth CMC knowledge of innovator's manufacturing process)***

CASE EXAMPLE

Innovator Biopharmaceutical

addressing residual uncertainty across two major manufacturing process changes

Step 1 for drug substance/product + Step 3 (Human pK) for drug product

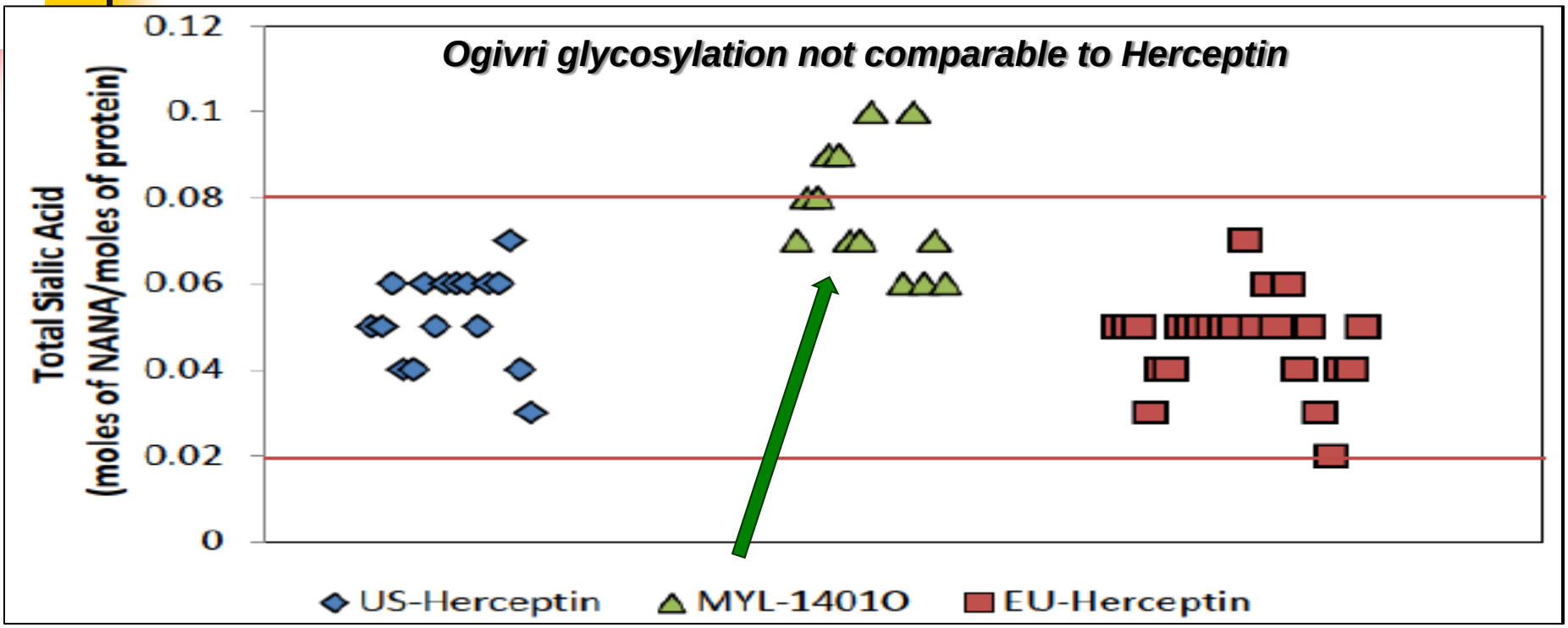
Three versions of the active substance manufacturing process have been used during the clinical development: Process 1 (C1), Process 2 (C2) (Clinical) and Process 2 (C2) (Commercial). The active substance manufacturing history has been described in sufficient detail.

To support comparability between the different manufacturing processes two formal ICHQ5E compliant comparability evaluations were performed. An initial comparability assessed early (C1) to late phase (C2) processes and a commercial comparability, which assessed late phase (C2) to commercial phase process (C2). Furthermore, a Phase 1 clinical comparative pharmacokinetic study was also performed as part of the overall assessment of the comparability of the commercial finished product to the clinical finished product.

Lundbeck A/S **Vyepti** eptinezumab Assessment report 11 November 2021 EMA/9446/2022

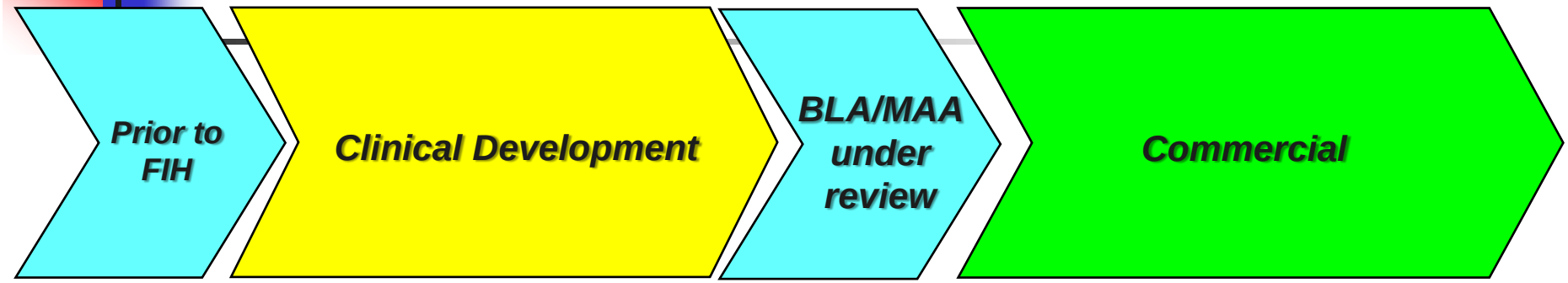
Biosimilar vs Innovator

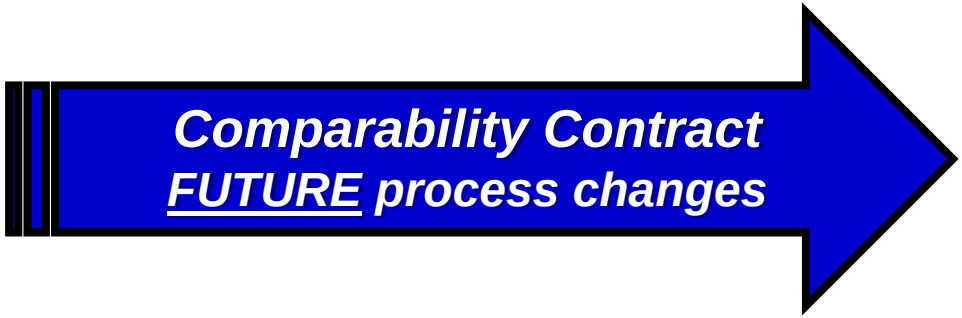
Step 1 showed glycosylation differences; residual uncertainty addressed by Step 3 (human pK)



mol/mol). MYL-1401O lots with minor differences in glycosylation with respect to the US-Herceptin lots were included among those used in clinical studies. Residual uncertainty about biosimilarity that resulted from the differences in high mannose and sialylated glycans is adequately addressed by data that showed no impact of these differences on PK. These

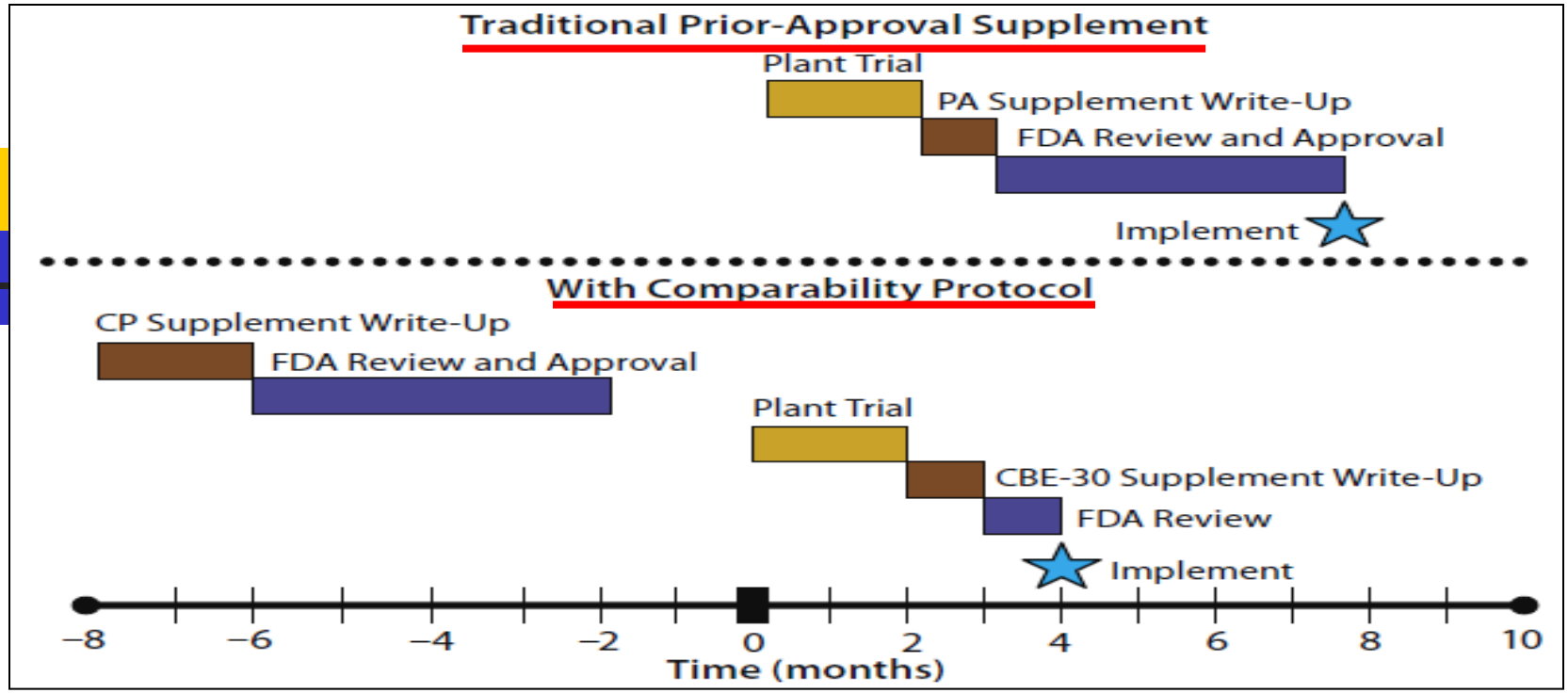
Preparing for FUTURE manufacturing process changes with a regulatory authority signed 'contract'





EMA, ICH: post approval change management protocol (PACMP)

FDA: comparability protocol (CP) = PACMP



Note, <u>total elapsed time sometimes is longer</u> with the contract route, but time to implement a process change after completion is shorter!

<u>Benefits of a regulatory authority contract</u>

(1) Uncertainty risk reduction – regulatory authority has reviewed and approved of what you are doing – should be no surprises when work and report is finished

(2) Downgrade of regulatory review requirements (PAS → CBE-30 → AR; Type II → Type 1B) – quicker final release of biologic batches into inventory

3) Higher certainty of maintaining commercial inventory supply

Critical basics for obtaining these contracts!

ICH harmonisation for better health

TECHNICAL AND REGULATORY CONSIDERATIONS FOR PHARMACEUTICAL PRODUCT LIFECYCLE MANAGEMENT

Q12 November 2019

Step 1: Submission of a written protocol that describes the proposed change(s), its rationale(s), risk management activities, proposed studies and acceptance criteria to assess the impact of the change(s), other conditions to be met (e.g., confirmation that there is no change to the approved specification), the proposed reporting category for the change(s), and any other supportive information (see also below). The PACMP document can be located in CTD Module 3.2.R.[3] This protocol is reviewed and approved by the regulatory authority in advance of execution of the protocol.

Weakest Links

- ***Under-estimating amount of detail* to provide in request**
- ***Inadequate pre-defined acceptance criteria* for confirming 'highly similar'!**

***Typical* comparability contracts submitted in a BLA**

(these were all approved by FDA)

Drug Substance:

i. Protocols approved:

1. Qualification of new cell banks (Section 3.2.S.2.3)
2. At-scale chromatography resins/membrane lifetime study (Section 3.2.S.2.5)
3. Requalification of primary and working reference standards (Section 3.2.S.5)
4. Qualification of new primary and working reference standards (Section 3.2.S.5)
5. Ongoing stability studies and post-approval annual stability protocol (Section 3.2.P.8.2)

Fylnetra
(pegfilgrastim-pbbk)

Kashiv BioSciences, LLC

FDA BLA CMC Review
05/10/2022

Note, if it is not in writing from the regulatory authority, it is not an approved future manufacturing process change protocol!

CASE EXAMPLE

EMA review of a proposed PACMP

future additional manufacturing DP site for a mAb

Assessment report

25 February 2021
EMA/176464/2021

Jemperli
dostarlimab

GlaxoSmithKline

The post-approval change management protocol (PACMP) presented in the dossier outlines the comparability plan for the addition and implementation of an alternate commercial site for the production of Jemperli 50 mg/mL finished product. The alternate site will be added post-approval as an additional site of manufacture, primary packaging, inspection, secondary packaging and labelling, storage, and batch release testing of finished product to expand manufacturing capacity and mitigate supply continuity risk. The finished product may in future be sourced from both the finished product sites upon approval of the post-approval variation.

An ongoing process verification approach that integrates process development and process validation/qualification will be included into an overall program aimed at increasing the level of process knowledge and understanding, to ensure that the process is operated under a state of control. The potential differences between the manufacturing process as run at the current finished product site and the process at the alternate site are minimal.

The alternate site will execute batches at commercial scale, after technology transfer of the process to the site. Comparability studies will be performed. The product quality assessment will consist of the release testing results, higher order characterization analysis, and stability study data from the PPQ batches. Overall, the provided information on the PACMP presented is considered sufficient.

PACMP for a future additional DS manufacturing site would be most difficult

Don't underestimate the amount of work that may be needed to confirm product comparability for your manufacturing process changes!

Questions??

CMC Regulatory Compliance Strategy for Recombinant Proteins and Monoclonal Antibodies

Closing Thoughts

- Clinical strategy risk vs CMC strategy risk
- Reduce CMC risk by engaging with regulatory authorities
- Warnings – Impacts on CMC regulatory compliance strategy
- BLA/MAA market approval process
- Sources of CMC information on FDA/EMA websites

Perspective on Clinical Strategy vs CMC Strategy

CLINICAL strategy deficiencies cause TERMINATIONS

CMC strategy deficiencies cause DELAYS

REGENERON

"just a CMC delay"

(Fc fusion protein)

FDA Issues Complete Response Letter (CRL) for Aflibercept 8 mg Biologics License Application Solely Due to an Ongoing Review of Inspection Findings at a Third-party Filler *(Catalent)*

June 27, 2023

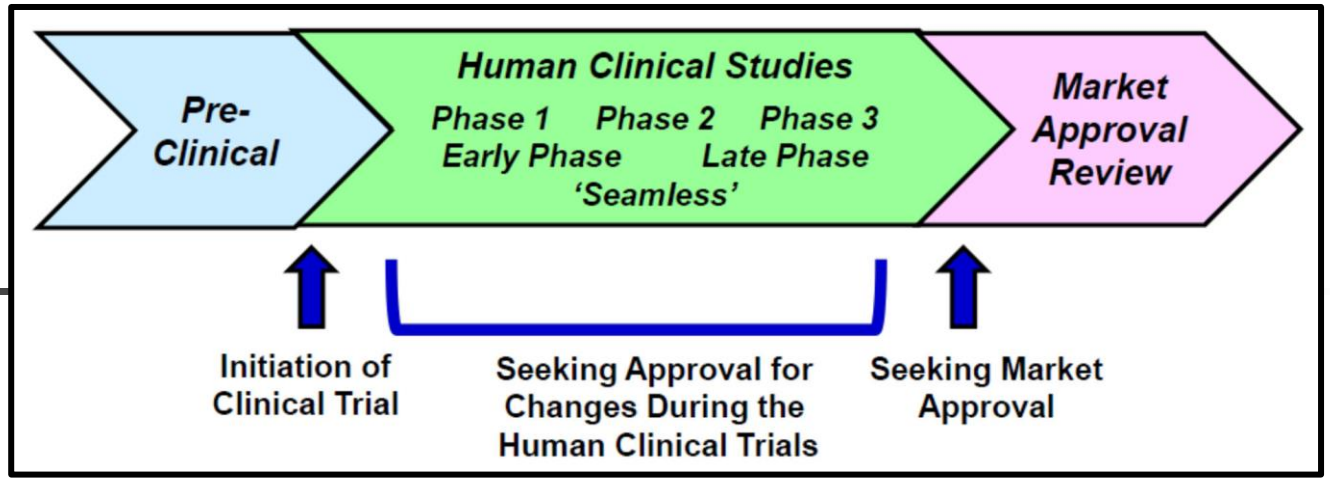
No issues with clinical efficacy or safety, trial design, labeling or drug substance manufacturing were identified in the CRL

No additional clinical data or trials have been requested

TARRYTOWN, N.Y., June 27, 2023 (GLOBE NEWSWIRE) -- Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) today announced that the U.S. Food and Drug Administration (FDA) has issued a Complete Response Letter (CRL) for the Biologics License Application (BLA) for aflibercept 8 mg for the treatment of patients with wet age-related macular degeneration (wAMD), diabetic macular edema (DME) and diabetic retinopathy (DR), solely due to an ongoing review of inspection findings at a third-party filler. The CRL did not identify any issues with the aflibercept 8 mg clinical efficacy or safety, trial design, labeling or drug substance manufacturing, and no additional clinical data or trials have been requested. Regeneron is committed to working closely with the FDA and the third-party filler to bring aflibercept 8 mg to patients with wAMD, DME and DR as quickly as possible.

CMC regulatory compliance strategy GOAL → to avoid the potholes and sink holes on the clinical development path toward market approval

To SUCCESSFULLY reduce the CMC risk → teamwork
internal (among the various company disciplines – Mfg, Dev, QU, RA) and external (the regulatory authorities)



2 Key Elements to Reducing the Risk of Potential CMC Regulatory Compliance Delay

1) FDA/EMA published guidances are INVALUABLE!

- ***pay attention to them (as discussed during the course)***

2) View Regulatory Authority reviewers AS YOUR PARTNER!

- ***teamwork required – you and they both share the job of protecting patients***
- ***you are the expert of your process/product – but you need to convince the regulatory authority that you are doing your part to protect the patients***

FDA encourages sponsors to communicate their CMC regulatory compliance strategy

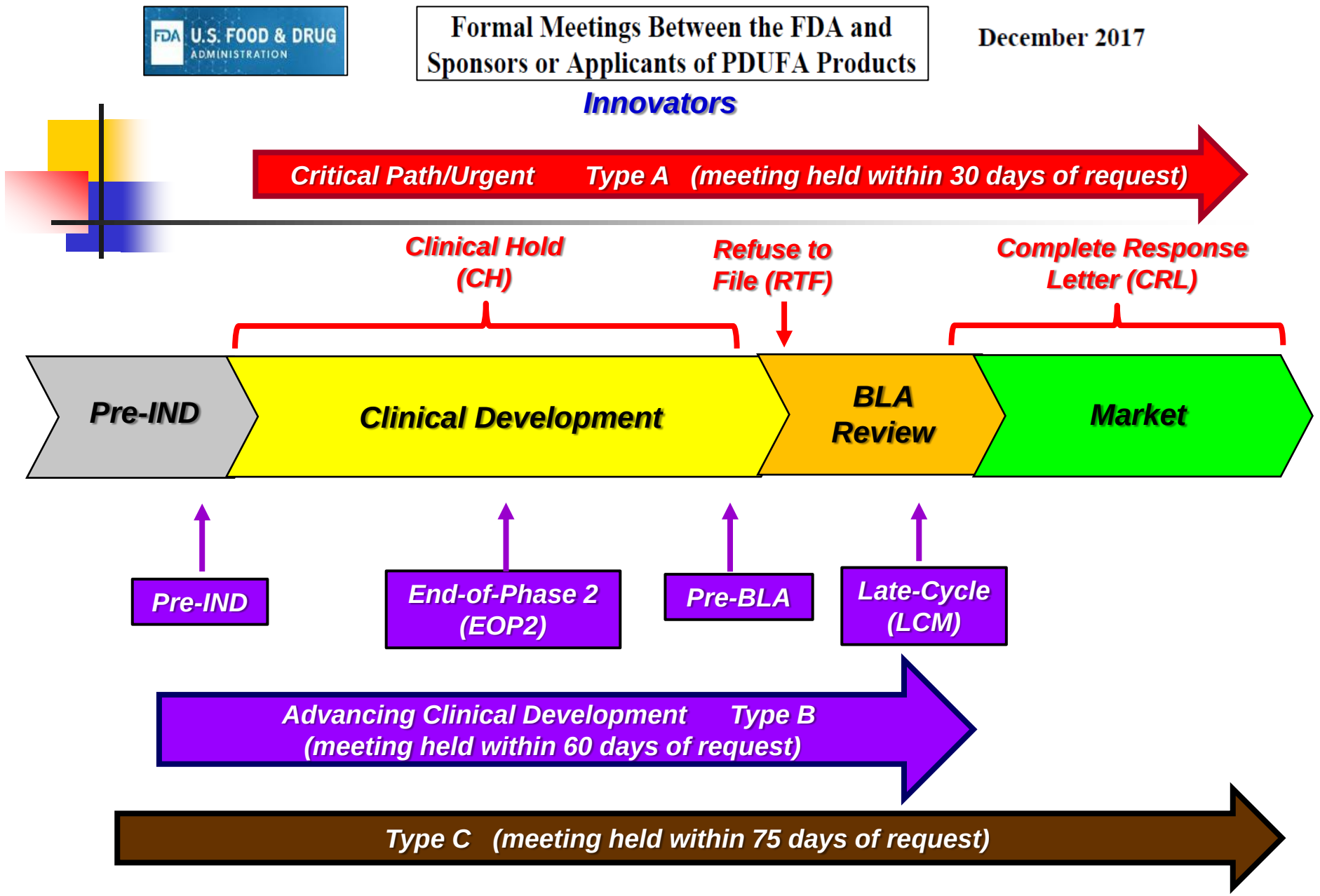
Best Practices for Communication Between IND Sponsors and FDA During Drug Development Guidance for Industry and Review Staff[1] **December 2017**

FDA believes that scientific and regulatory recommendations provided during drug development meetings with sponsors may result in more efficient and robust development programs. This philosophy is articulated in 21 CFR 312.47, 21 CFR 312.82, FDA's meetings guidances,[9] CDER's Manuals of Policies and Procedures (MAPPs), and CBER's Standard Operating Policy and Procedures (SOPPs). Sponsors can request meetings with FDA at any time during drug development, and FDA strongly encourages sponsors to request the critical milestone meetings, and BIA or BPD meetings identified in the references cited above. FDA's decision to grant or deny meeting requests is resource-dependent and is based on the maturity of the drug's development at the time of the meeting request, taking into consideration the potential utility of the meeting. The procedures for requesting and conducting effective meetings between sponsors and FDA are fully described in the meetings guidances.

EMA encourages sponsors to communicate their CMC regulatory compliance strategy

Scientific advice is one of the Agency's key instruments for supporting the development of high-quality, effective and safe medicines, for the benefit of patients. Early dialogue and scientific advice lead to better development plans, promote the collection of high-quality data and, most importantly, help to ensure that patients only take part in those clinical trials that are likely to be robust enough to generate data that are relevant to support the evaluation of a marketing authorisation application or extension of indication.

EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH
ANNUAL REPORT 2020

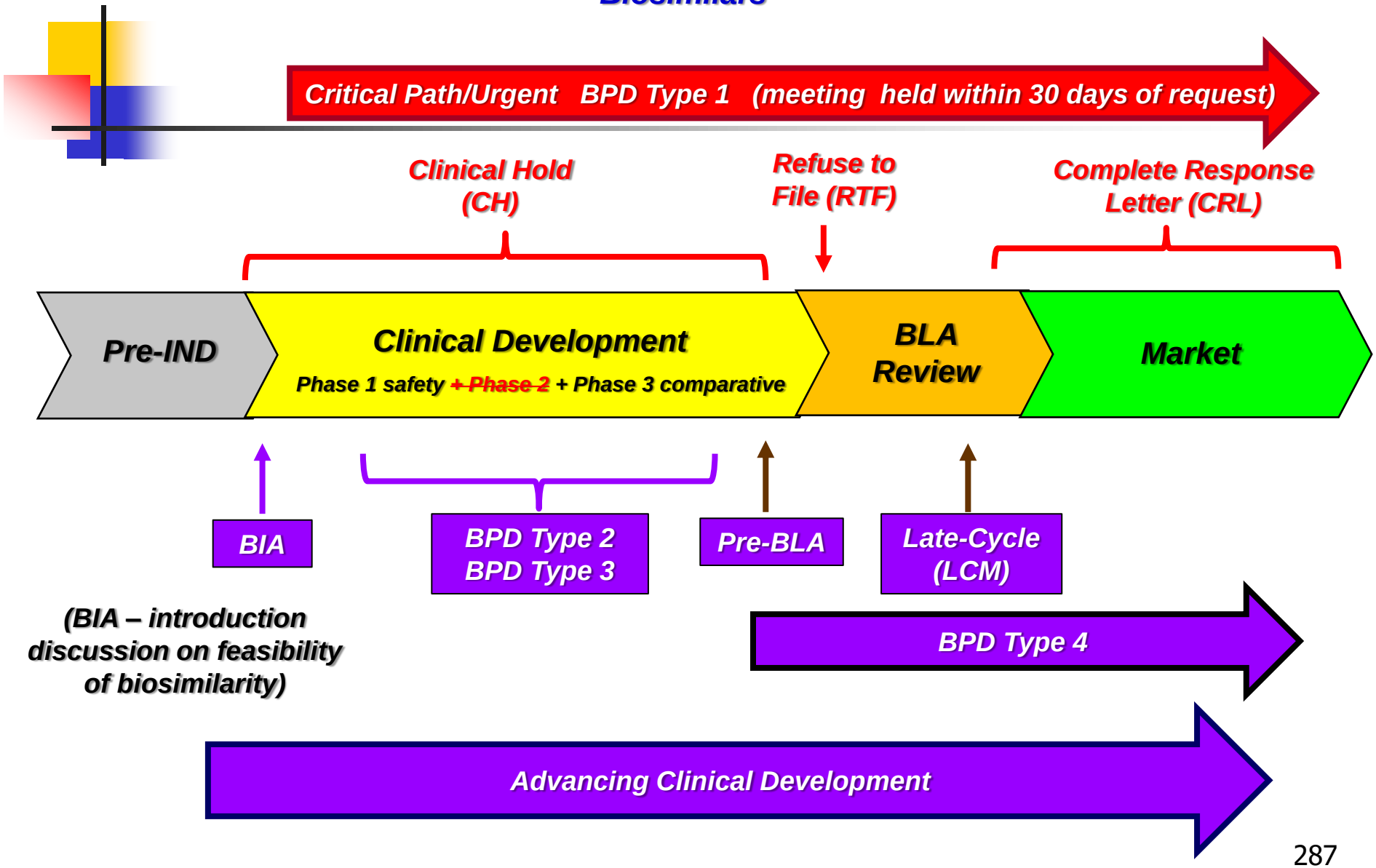

U.S. FOOD & DRUG ADMINISTRATION
Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products
December 2017
Innovators
Critical Path/Urgent Type A (meeting held within 30 days of request)
Clinical Hold (CH)
Refuse to File (RTF)
Complete Response Letter (CRL)
Pre-IND
Clinical Development
BLA Review
Market
Pre-IND
End-of-Phase 2 (EOP2)
Pre-BLA
Late-Cycle (LCM)
Advancing Clinical Development Type B (meeting held within 60 days of request)
Type C (meeting held within 75 days of request)

U.S. FOOD & DRUG ADMINISTRATION

Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products

June 2018

Biosimilars



287

One-size-fits-all meeting opportunities to discuss CMC regulatory compliance strategic issues!

EMA From Laboratory to Patient: The Journey of a Medicine Assessed by EMA (2019); www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/how-scientific-advice-works#why-scientific-advice-when-guidelines

STEP 01 A medicine developer who wishes to request scientific advice first needs to notify EMA and send a briefing document. A meeting can be organised, in particular for first users of scientific advice or for complex medicines.

STEP 02 The developer then sends a list of specific scientific questions and proposed responses. EMA determines whether the questions are valid or not for scientific advice.

STEP 03 For each scientific advice procedure (or 'protocol assistance' procedure for orphan medicines) validated, two members of the SAWP who have sound expertise to address the scientific questions are appointed as coordinators.

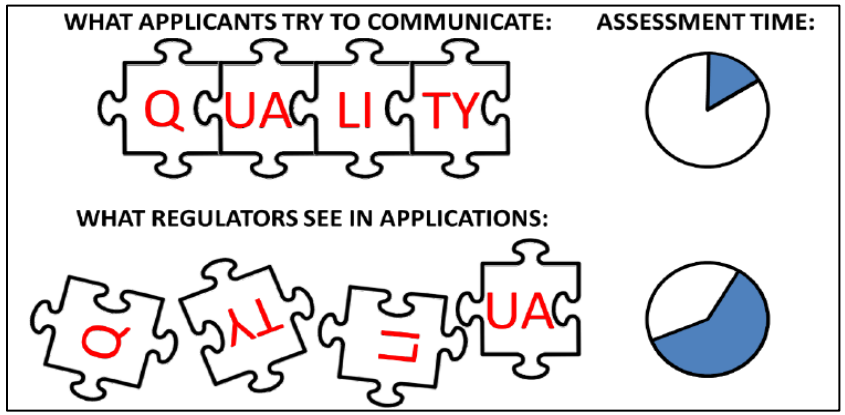
STEP 04 Each coordinator forms an assessment team calling on assessors from their national agency or other EU agencies. Each team prepares a report addressing the scientific questions; they draft a list of issues for discussion with all the other members of the SAWP and may ask the applicant for any additional documents or clarifications.

STEP 08 The SAWP consolidates a response to the scientific questions. Final advice is discussed and adopted by the CHMP and then sent to the medicine developer.

Two Warnings

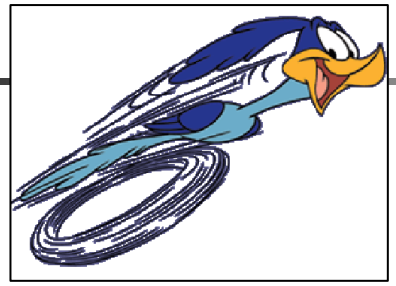
Impacts on the CMC Regulatory Compliance Strategy

Clinical expediting



Quality of the CMC submissions

#1 Impact of clinical expediting on the CMC regulatory compliance strategy much less time for the CMC team to get everything in place!



Exciting clinical speed opportunities to shorten the timelines …

… but stresses the CMC Team strategy!

FDA: Breakthrough Therapy, Fast Track, Accelerated Approval

FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014)

EMA: Conditional Marketing, Exceptional Circumstances

EMA European Medicines Agency website

EMA: PRImary MEdicine (PRIME)

EMA European Medicines Agency Guidance on Interactions in the Context of PRIME (May 2018)

CASE EXAMPLES

ALTUVIIIO [antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ehtl]

IND filed May 2017 → **BLA filed** August 2022 (5 yrs)

Fast Track Designation
Breakthrough Therapy Designation

Teclistamab-cqyv, a bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager, is a humanized immunoglobulin G4-proline, alanine, alanine (IgG4-PAA) antibody.

IND filed February 2017 → **BLA filed** December 2021 (4 yrs)

Breakthrough Therapy Designation

Biosimilars are not expedited since there is no unmet medical need

FDA is concerned about the capability of the CMC team if expedited clinical pathway is granted!

A. Manufacturing and Product Quality Considerations

The sponsor of a product that receives an expedited drug development designation may need to pursue a more rapid manufacturing development program to accommodate the accelerated pace of the clinical program. The sponsor's product quality and CMC teams should initiate early communication with FDA to ensure that the manufacturing development programs and timing of submissions meet the Agency's expectations for licensure or marketing approval.[40]

When sponsors receive an expedited drug development designation, they should be prepared to propose a commercial manufacturing program that will ensure availability of quality product at the time of approval. The proposal should consider estimated market demand and the commercial manufacturing development plan. The proposal should also consider manufacturing facilities and a lifecycle approach to process validation. Additionally, the proposal should include a timeline for development of the manufacturing capabilities with goals aligned with the clinical development program. After the initial discussion following designation, frequent communication during development will generally facilitate meeting manufacturing development goals and product quality goals.

Sponsors of such products should allow for an earlier submission of the CMC section (including product quality information) for timely review, and, critically, for inspection activities.[41] Coordination with the sponsor and contract manufacturers may be necessary to ensure that manufacturing facilities and equipment are ready for inspection during review of the clinical section of the application. A comprehensive meeting with FDA's product quality review groups in advance of submission may facilitate the quality assessment of products designated for expedited programs.

Although sponsors must ensure the availability of quality product at the time of approval, FDA may exercise some flexibility on the type and extent of manufacturing information that is expected at the time of submission and approval for certain components (e.g., stability updates, validation strategies, inspection planning, manufacturing scale-up). The level of flexibility will be determined on a case-by-case basis after consideration of factors such as the following: (1) product characteristics, (2) seriousness of the condition and medical need, (3) manufacturing processes, (4) the robustness of the sponsor's quality system, and (5) the strength of the sponsor's risk-based quality assessment. FDA's consideration of the sponsor's proposal for an integrated postmarketing plan will also take into account whether elements of the plan may be appropriately executed as a postmarketing commitment or requirement. For example, FDA will consider impacts on clinical performance, such as safety and immunogenicity. Sponsors should meet with the Agency to discuss their proposed plan as soon as possible and no later than the pre-NDA or pre-BLA meeting.

FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014)

When granted expedited clinical review, EMA recommends a number of areas where required CMC activities can have flexibility during the MAA filing

Experience to date has shown that applicants face challenges to complete quality and manufacturing development data requirements during development of products in early access approaches.

In order to address and overcome these challenges, EMA wishes to support applicants with guidance regarding their pharmaceutical development programme and flexibility on the provision and type of data packages in the context of a MAA taking into consideration the overall benefit-risk of the product. Specific guidance covers prior knowledge, risk assessment, process validation, specification setting, GMP compliance, stability testing, and comparability, as well as early identification of quality issues / attributes that are critical to the clinical use of the medicinal product.

EUROPEAN MEDICINES AGENCY

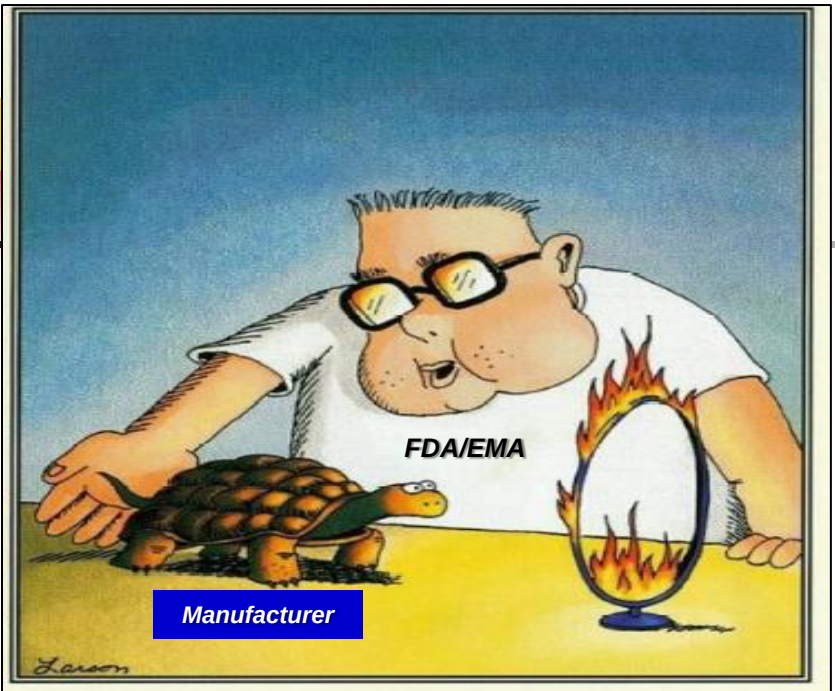
Toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME and certain marketing authorisation applications targeting an unmet medical need

22 April 2022
EMA/CHMP/BWP/QWP/IWG/694114/2019

Where EMA MIGHT BE willing to be flexible and accept higher CMC residual risk in MAA submissions

Module 3	POTENTIAL CMC Flexibility (when PRIME designated)
Process Validation	Process validation scheme (plan) in place of completed process validation Concurrent process validation in place of completed process validation Decoupling drug substance PPQ from drug product PPQ
Control Strategy	Filing with a more 'constrained' control strategy (augmented with additional testing or tighter controls)
GMP Compliance	Launching from an investigational manufacturing site Use of Starting Material of lower GMP level
Product Stability	Extrapolation of shelf life from similar biologic products
Product Comparability	Prior knowledge to tailor comparability studies Separate assessment of individual process changes

#2 Room for improvement in CMC regulatory compliance communication



From the perspective of the manufacturer

From the perspective of the regulatory authority reviewer

Manufacturer's Perspective	C O M P L E T E
Regulatory Reviewer's Perspective	C O ▢ P ⅂ Ǝ T E

Overall, Module 3 of your BLA is not well prepared. Frequently, you refer to information/data in numerous reports, but do not provide an informative summary with your conclusions based on the information. While reports are important to verify some specific information or evaluate raw data, your summaries with interpretations and conclusions form the basis for the Agency's review. Submitting a large number of reports with minimal data interpretation did not allow for an efficient review process. For example, reports related to process characterization and determination of in-process controls were difficult to interpret. Additionally, there are many inconsistencies, missing information, and typographical errors throughout your BLA. We expect that you will address these, and other such issues in any resubmission.

Coherus BioSciences

UDENYCA (pegfilgrastim-cbqv)

biosimilar

BLA Complete Response Letter (CRL)

06/09/2017

Seek Regulatory Authority Input – But Do It Correctly!

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B	**Tepezza**
Meeting Category:	End of Phase 2	teprotumumab
Meeting Date and Time:	August 19, 2016 from 9:30AM – 10:30AM (EST)	

CMC Questions

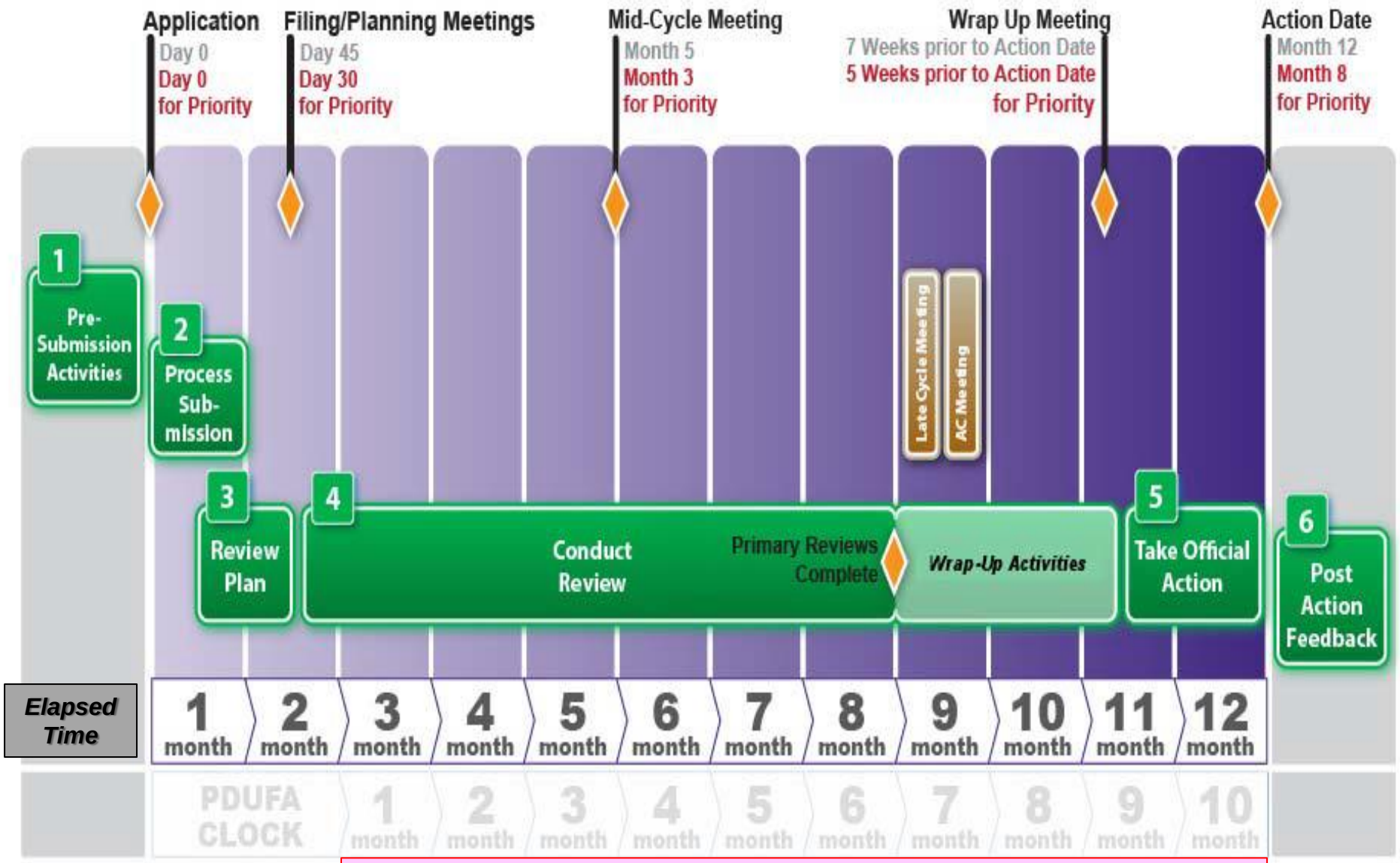
Given the breakthrough status recently granted to teprotumumab, we strongly encourage you to request a CMC only meeting to discuss product development, including product characterization, process development, analytical methods development, and stability studies. The current meeting package is incomplete and contains substantial errors, e.g., mislabeled, incomplete, and inaccurate figures and tables, an unclear description of the bioassay bridging strategy, etc. (see specific responses to your questions below). To enable effective meetings with meaningful discussions and efficient receipt of substantially informative advice, please ensure that subsequent meeting packages contain complete and accurate information (with appropriate data) to describe and support the questions posed.

9. The manufacturing of teprotumumab is being changed (site transfer and process adaptions) for both the drug substance and drug product. Does the Agency agree that the proposed program to demonstrate biological comparability is adequate and sufficient to support a BLA filing?

FDA Response: No; insufficient information was provided to support the proposed comparability program. A number of potential issues with the proposed program have been identified.

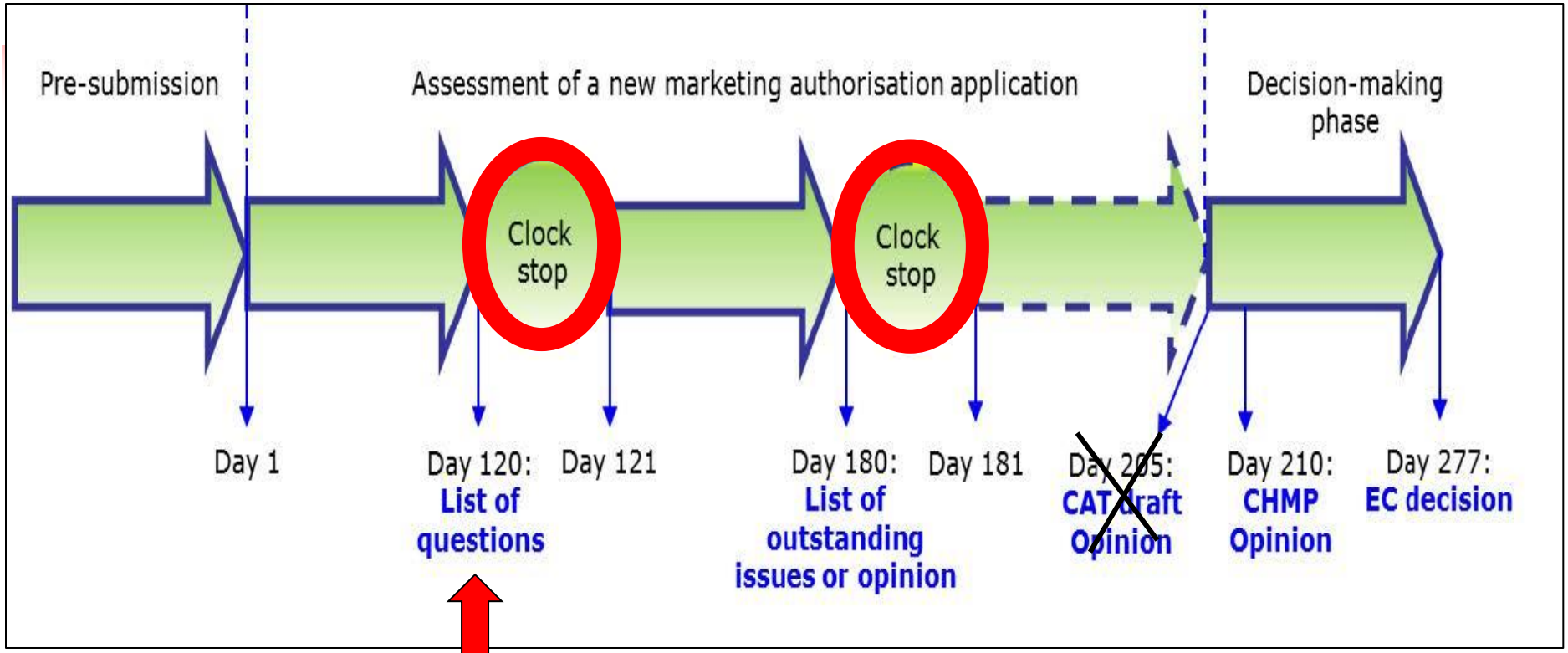
www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761143Orig1s000AdminCorres.pdf

BLA Review Activities – All Disciplines



Standard review 10 months Priority review 6 months

MAA Review Activities – All Disciplines

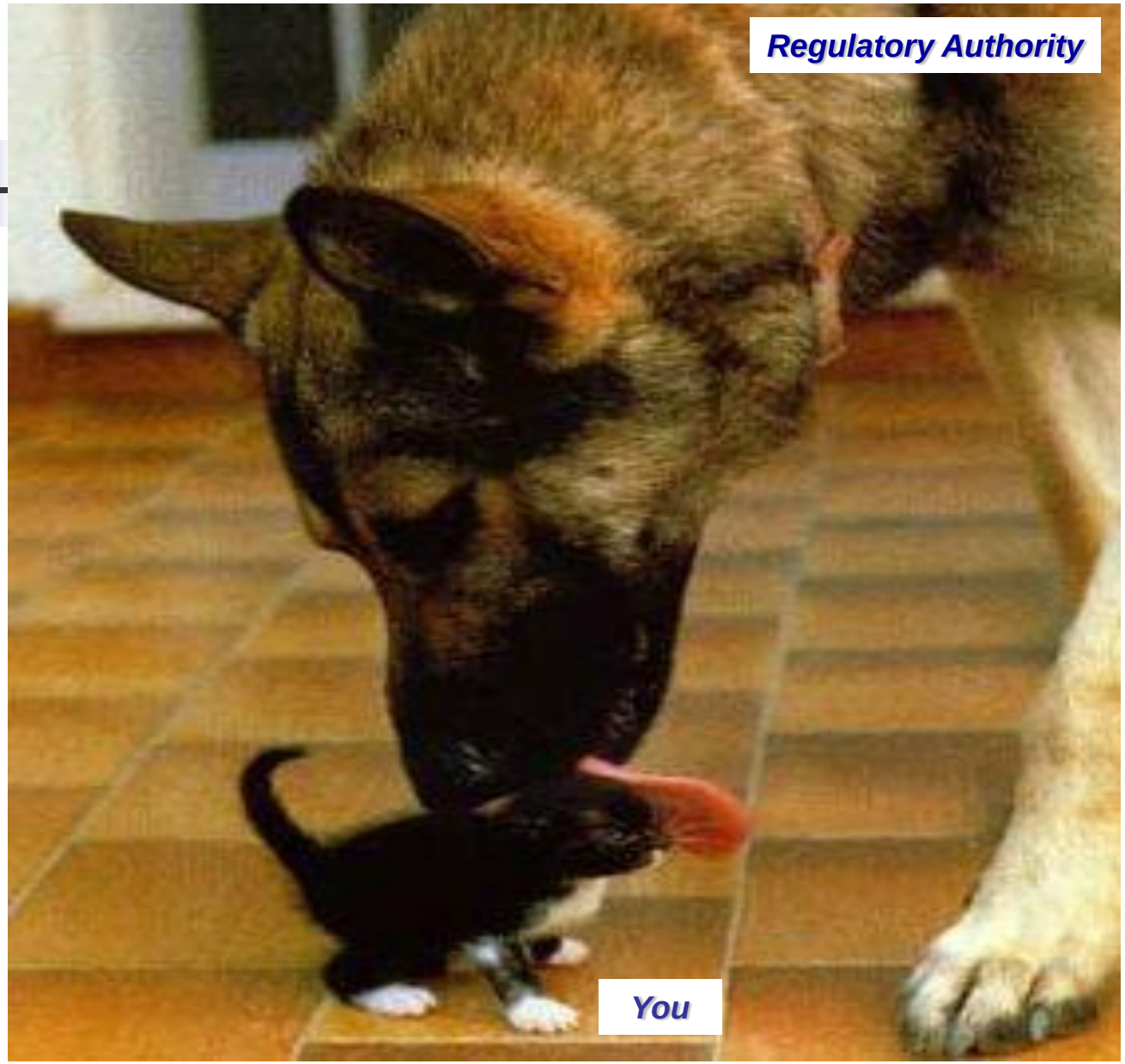


List of Questions (LoQ) sent to Sponsor

Decision time for Sponsor

Respond to all questions (within 6 months) or withdraw MAA

Regulatory authorities are your 'friend'!



QUESTIONS??

CMC Regulatory Compliance Strategy for Recombinant Proteins and Monoclonal Antibodies

Summary of Course

- ✓ **CMC Regulatory Compliance Strategy is Challenging for Biopharmaceuticals**

  Due to the increasing diversity of protein-based biopharmaceuticals, the regulatory authorities have control systems in place to regulate these evolving manufacturing processes and products

- ✓ **Risk-Based Approach to Managing the CMC Regulatory Compliance Strategy**

  Critically necessary to apply a risk-based, QbD/QRM approach to effectively manage the 'minimum CMC regulatory compliance continuum'

- ✓ **Applying the Risk-Managed CMC Regulatory Compliance Strategy**

  CMC strategy can be applied across the manufacturing process from raw materials → starting materials → production → purification → drug substance (bulk) → formulation → drug product → administered drug product

- ✓ **Challenges of Demonstrating Protein-Based Biopharmaceutical Comparability After Manufacturing Process Changes**

  Manageable, but tread carefully – implement sooner than later, when possible

While it is impossible to plan precisely for all CMC unknowns, steps can be taken to limit the impact!

Thank you

Where is all of this CMC information located on the regulatory authorities websites?

(will demonstrate this in class, if time)

Protein-Based Biopharmaceuticals approved by FDA CDER (www.FDA.gov/Drugs)

Drug Approvals and Databases

Drugs@FDA: FDA-Approved Drugs

Search by Drug Name, Active Ingredient, or Application Number

[Protein-Based Biopharmaceutical]

Approval Date(s) and History, Letters, Labels, Reviews

Illustrate with:

mAb	Saphnelo (anifrolumab-fnia)
ADC	Zynlonta (loncastuximab tesirine-lpyl)
rProtein	Skytrofa (lonapegsomatropin-tcgd)
biosimilar	Yusimry (adalimumab-aqvh)

Protein-based biopharmaceuticals approved by EMA (www.EMA.Europa.EU)

Medicines Search □ **Human** □ **EPAR**

Medicine Name

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[EPAR – Assessment Report]

Illustrate with:	***mAb***	Xevudy	sotrovimab
	ADC	**Trodelvy**	sacituzumab govitecan
	rProtein	**Besremi**	ropeginterferon alfa-2b
	biosimilar	**Yuflyma**	adalimumab