CMC Regulatory Compliance For Biopharmaceuticals

John Geigert, Ph.D., RAC, President

BioPharmaceutical Quality Solutions

3533 Corte Esperanza Carlsbad, CA 92009 USA

+1-760-525-5154 BPQS@aol.com

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CMC Regulatory Compliance Strategy for Biopharmaceuticals

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 Biopharmaceuticals

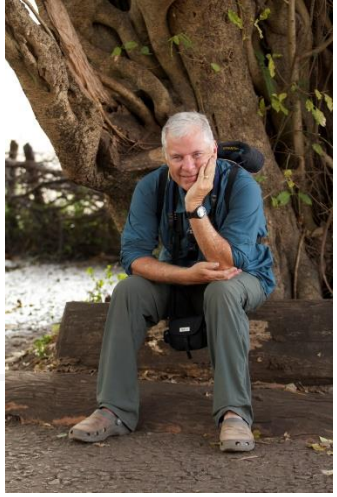
Course Outline

1. **CMC Regulatory Compliance is Challenging for Biopharmaceuticals**
   - Discussion of the increasing diversity of biopharmaceuticals and their regulation
   - Major CMC regulatory compliance differences biopharmaceuticals and chemical drugs
2. **Risk-Managed Biopharmaceutical CMC Regulatory Compliance Strategy**
   - 'Minimum CMC Regulatory Compliance Continuum'
   - Three (3) interactive components to protect patients
   - Regulatory authority recommended risk-based approach (QbD/QRM)
3. **Applied Risk-Managed CMC Regulatory Compliance Strategy**
   - Applied CMC strategy applied across the biopharmaceutical manufacturing process from raw materials → starting materials → protein production → protein purification → bulk drug substance (plus a few comments onto the drug product stage)
4. **Demonstrating Comparability After Manufacturing Process Changes**
   - Three (3) key design elements of an effective risk-managed comparability exercise
   - Comparability contracts (PACMPs) with regulatory authorities

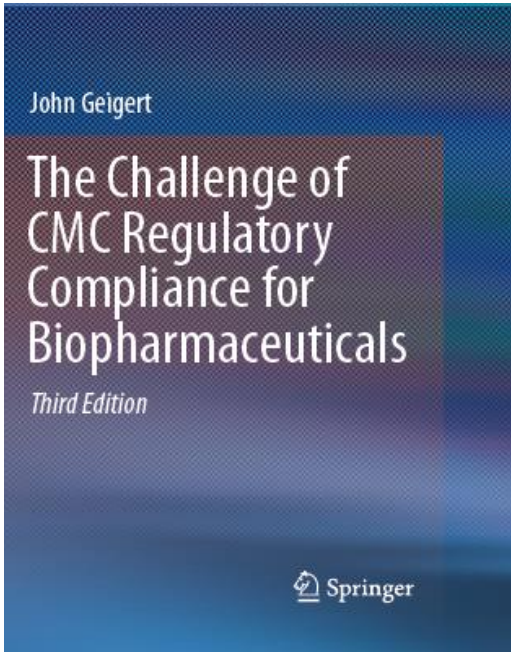
(Continuous presentation over the 2 days of instruction)

(Please ask your questions)

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



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

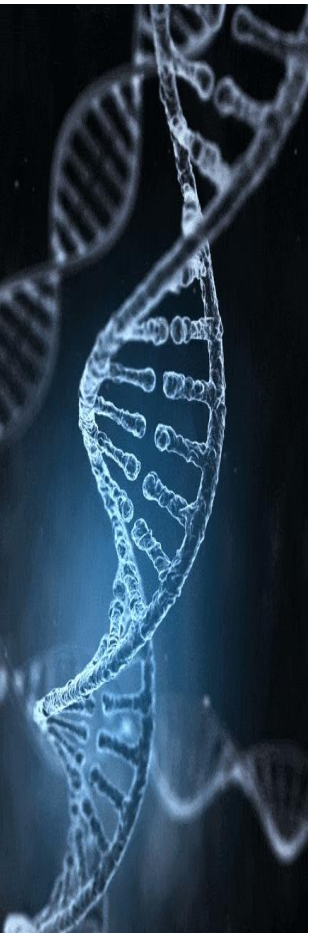


- ***45 years experience in Chemistry, Manufacturing & Control (CMC) strategies for the clinical development and commercialization of recombinant proteins, monoclonal antibodies; and now gene therapies and cellular therapies***
- ***Senior CMC Expert and Vice President Quality in the industry***
  (Cetus, 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 Biopharmaceuticals



Course Outline

1. **CMC Regulatory Compliance is Challenging for Biopharmaceuticals**

- *Discussion of the increasing diversity of biopharmaceuticals (both protein-based and gene-based)*
- *Introduction to the regulatory authority systems in place (FDA/EMA) for CMC regulation of these evolving manufacturing processes and products*
- *Major CMC regulatory compliance differences between biopharmaceuticals and chemical drugs*

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 'biological' is rather long and rambling, but includes the basic 3 components

Note: will discuss the "FDA legal definition" of a biological shortly

EMA's explanation of a 'biological' is straightforward

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Definition of biological medicinal product

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

***Biologic/Biological:* Consensus Definition**
(EMA, FDA, WHO, etc.)

***3* components**

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

Manufacture of Biological Medicines has occurred for <u>decades</u>

Extraction of porcine insulin protein from pig pancreases (since 1930's) Eli Lilly

2 tons of pig pancreases → ~200 g pig insulin

Since 1982, replaced by recombinant human insulin

50L bioreactor → > 200 g

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

***3* components**

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

"BIOPHARMACEUTICALS"

[Caution: term has been hijacked – now 'BioHealth']

FDA/EMA Guidances
(do not use the term 'biopharmaceutical') → **rDNA-derived, recombinant DNA-derived**

(In this course: I will use original definition when mentioning biopharmaceuticals!)

Biopharmaceutical medicine types have come in 5 ‘waves’!

Gene transduced/transfected into cell line

Gene (DNA) coding
for amino acid sequence

Recombinant Cell Line

Bacteria
Yeast
Insect
Mammalian
Human

BIOREACTOR

DNA

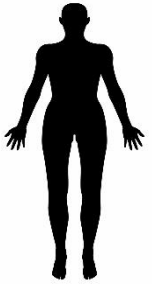
↓ *transcription*

mRNA

↓ *translation*

Recombinant Protein/
Monoclonal Antibody

Harvest → Purify

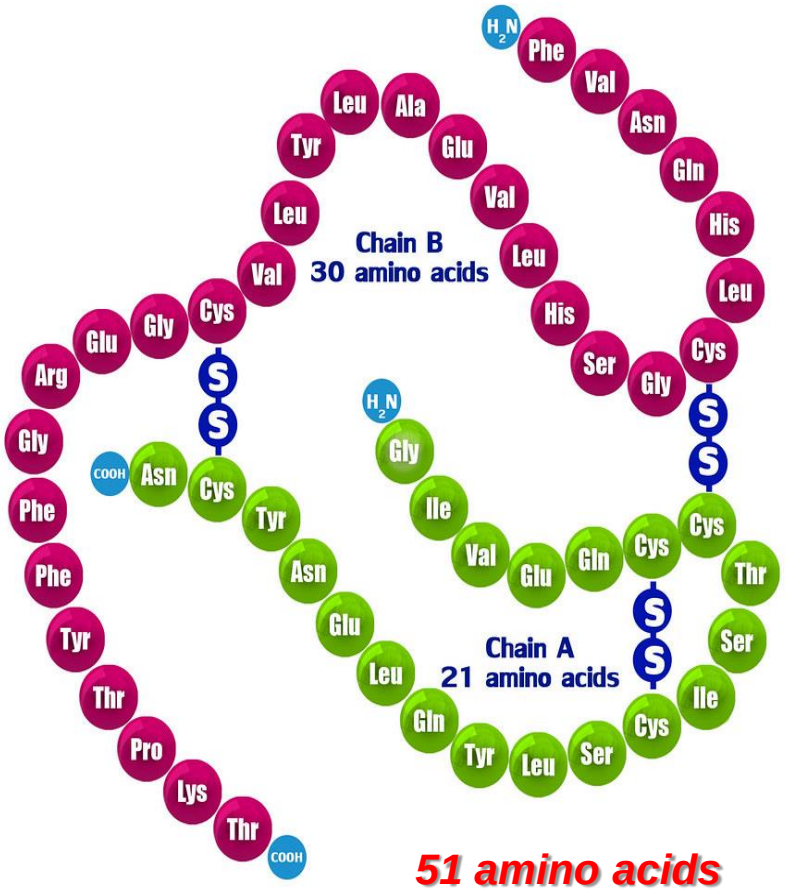


Recombinant protein/mAb
administered to patient

WAVES 1, 2, 3, 4 – all protein-based

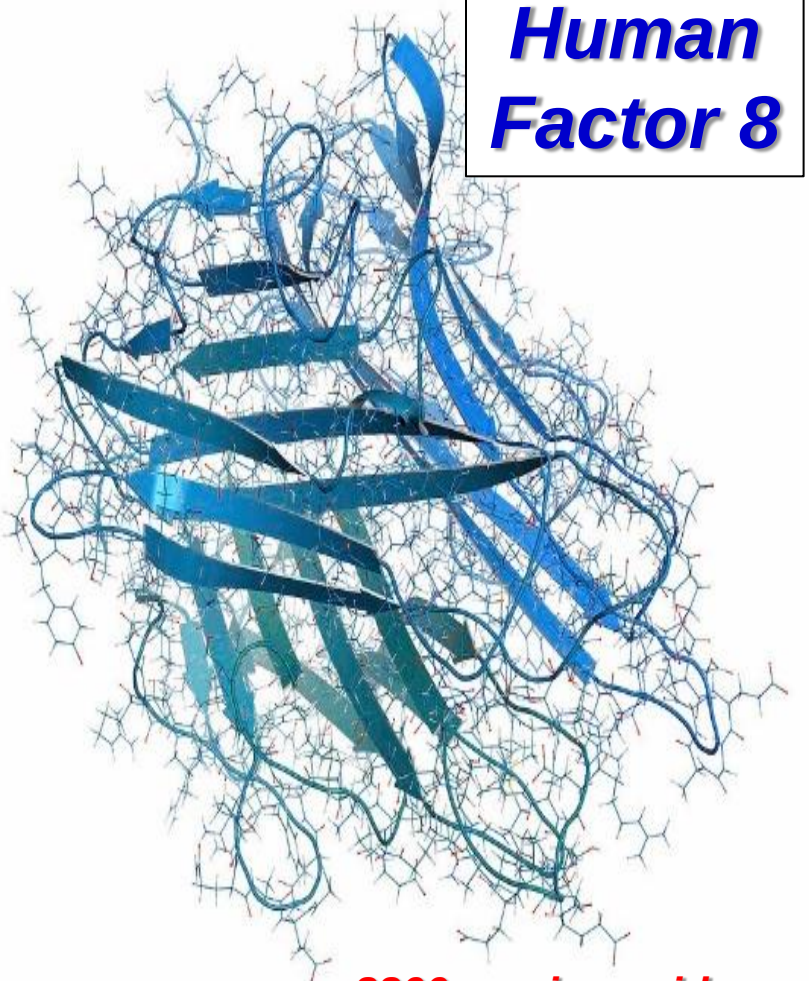
WAVE 1
Recombinant Proteins

Human Insulin



51 amino acids

Human Factor 8



2300+ amino acids

1982 1st recombinant protein

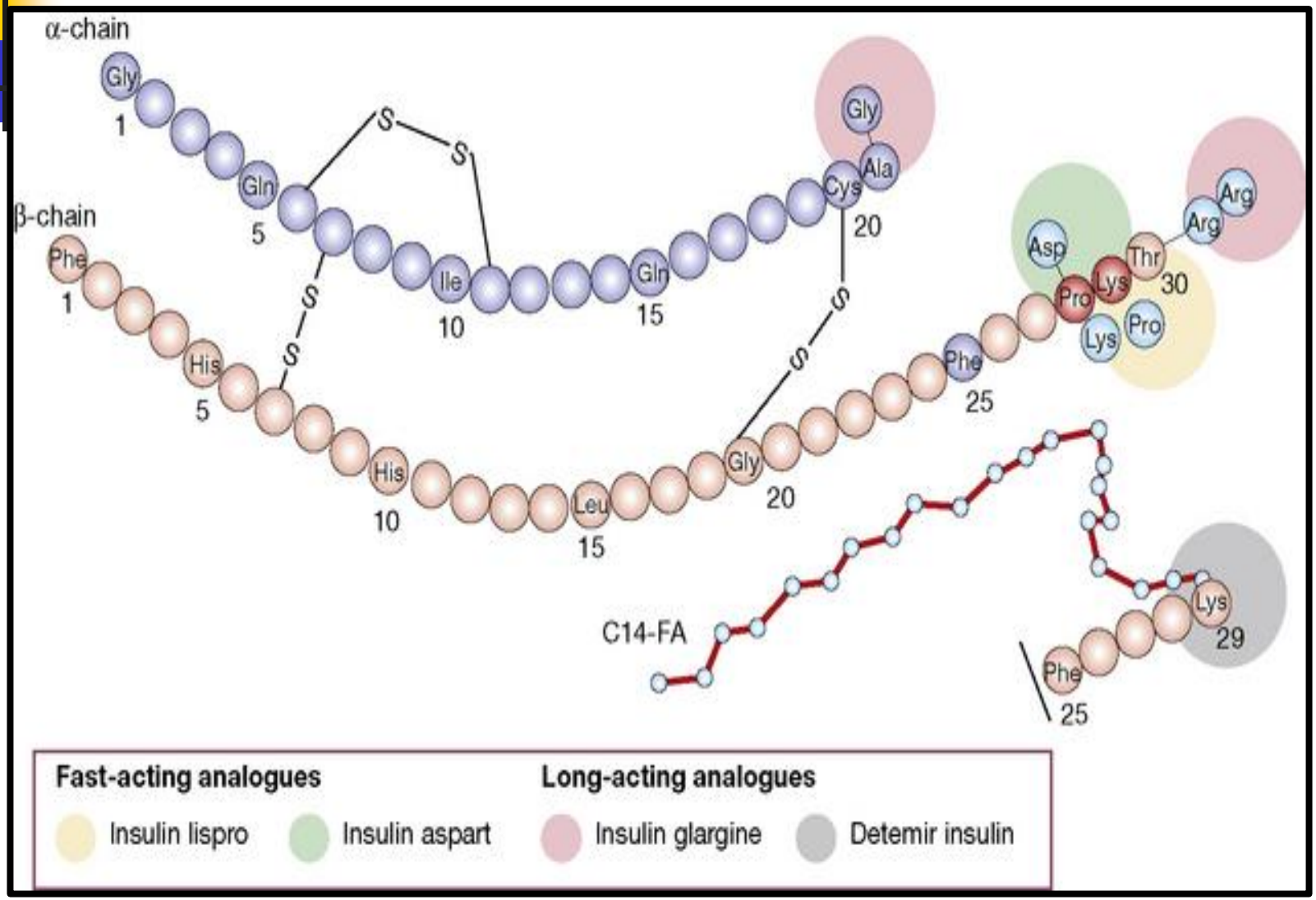
Global human insulin market: > $30 billion annually

TODAY

100+ recombinant protein medicines market approved by FDA/EMA

Gene changes have led to numerous site-specific codon (amino acid) changes

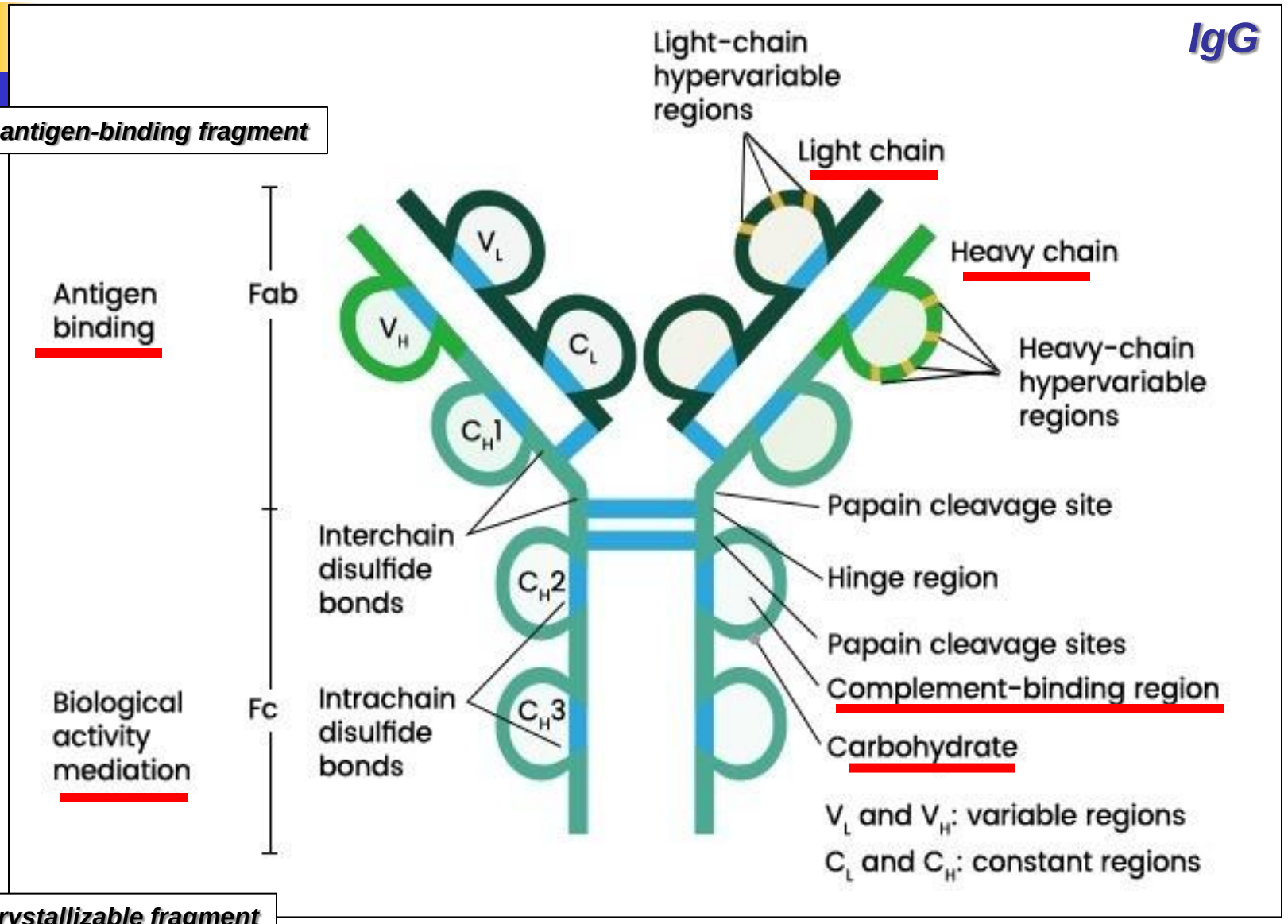
(illustrated by human insulin analogues)



WAVE 2
Monoclonal Antibodies

recombinant immunoglobulin protein – single specific antigen binding

Fab – antigen-binding fragment



Fc – crystallizable fragment

1986 1st mAb (murine)

1997 1st commercially successful monoclonal antibody (chimeric)

Murine
Chimeric
Humanized
Fully Human

TODAY

120+ monoclonal antibody medicines market approved by FDA/EMA

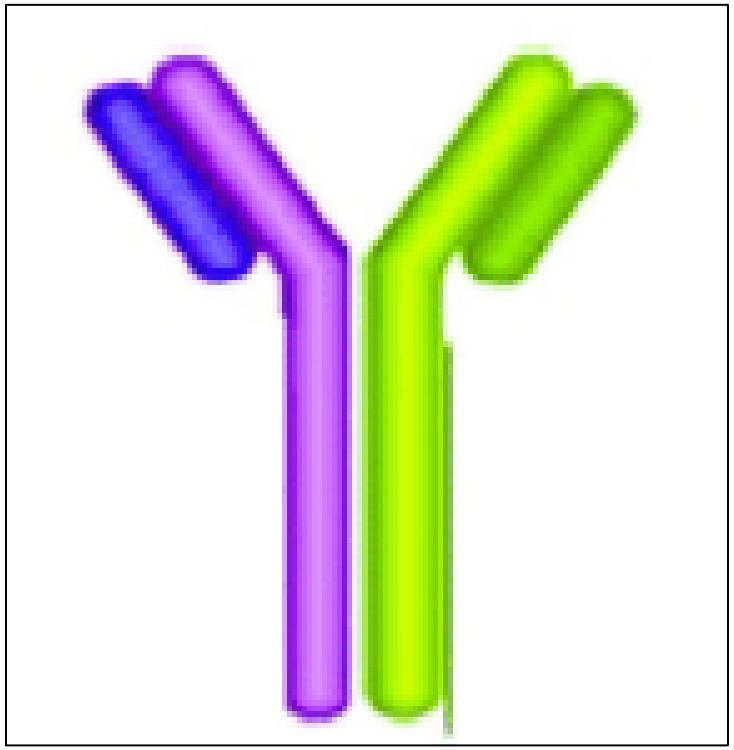
Humira (adalimumab) best selling medicine in the world: ~ $21 billion annually

WAVE 3
Re-Engineered Antibodies

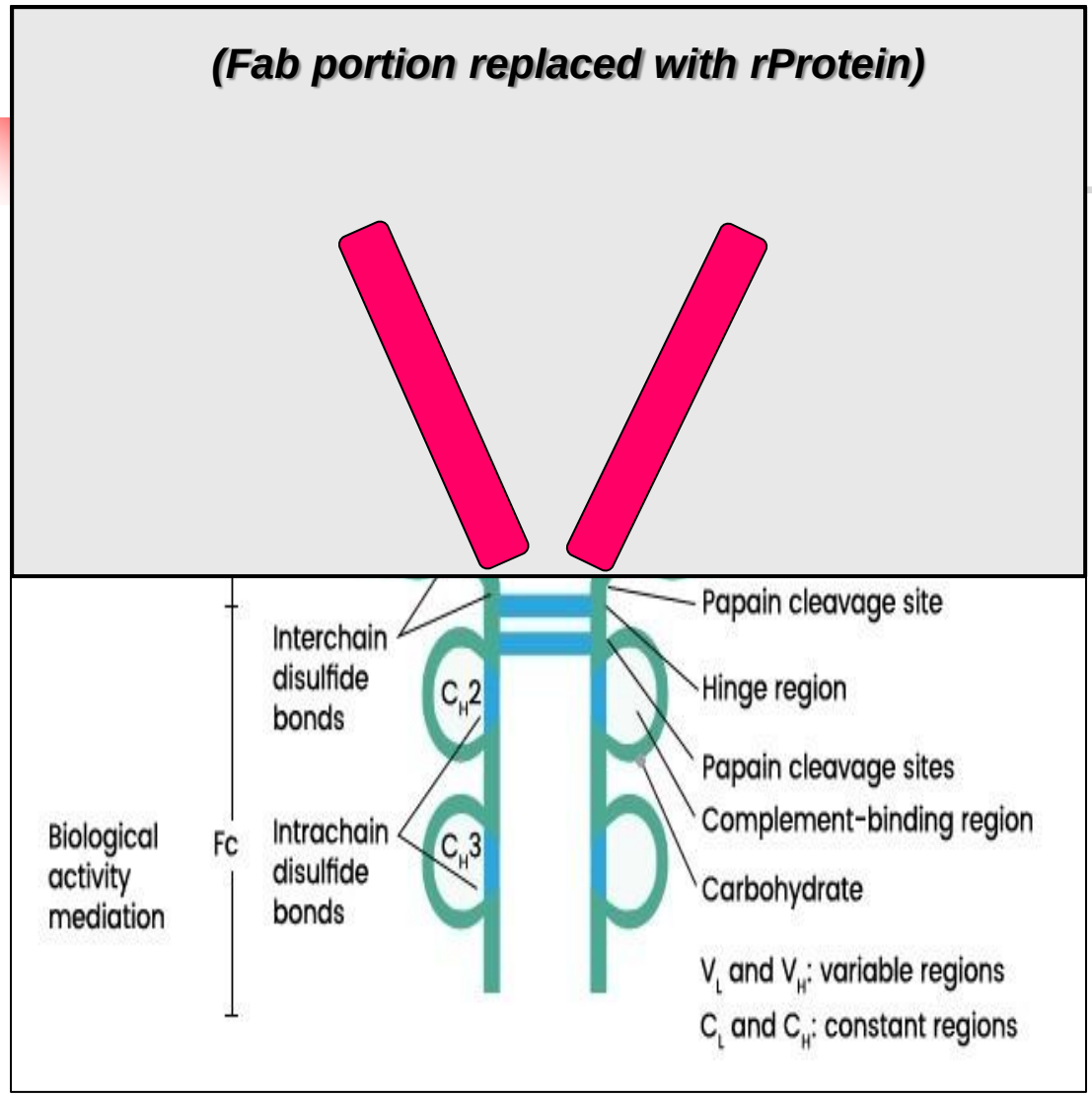
Bispecific Antibody

2 specific antigen bindings

Hemlibra	Factor IX	Factor X
Rybrevant	EGF	c-MET
Vabysmo	VEGF-A	Ang2



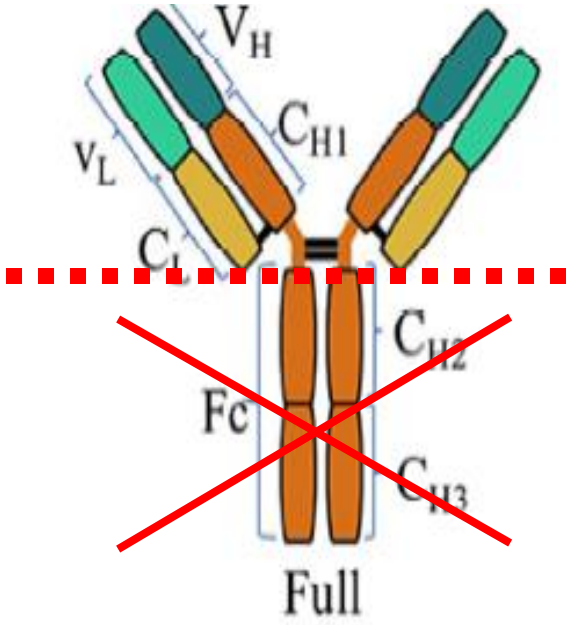
Fc-Fusion Protein



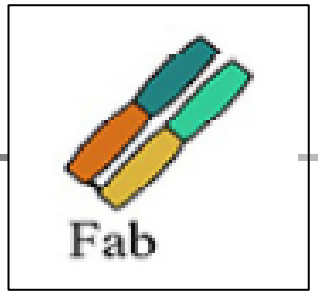
Enbrel	***TNFR-Fc domain***
Eylea	***VEGF-Fc domain***
Nulojix	***CTLA-4-Fc domain***
Trulicity	***GLP-1-Fc domain***

Fab Fragment

155 kDa

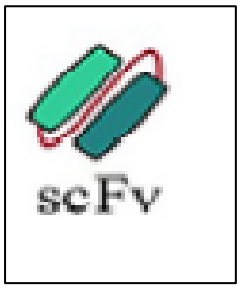


(Fc portion removed)



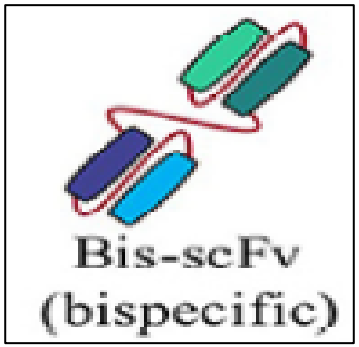
Fab Fragment

Lucentis VEGF-A 48 kDa



Single Chain Fragment Variable

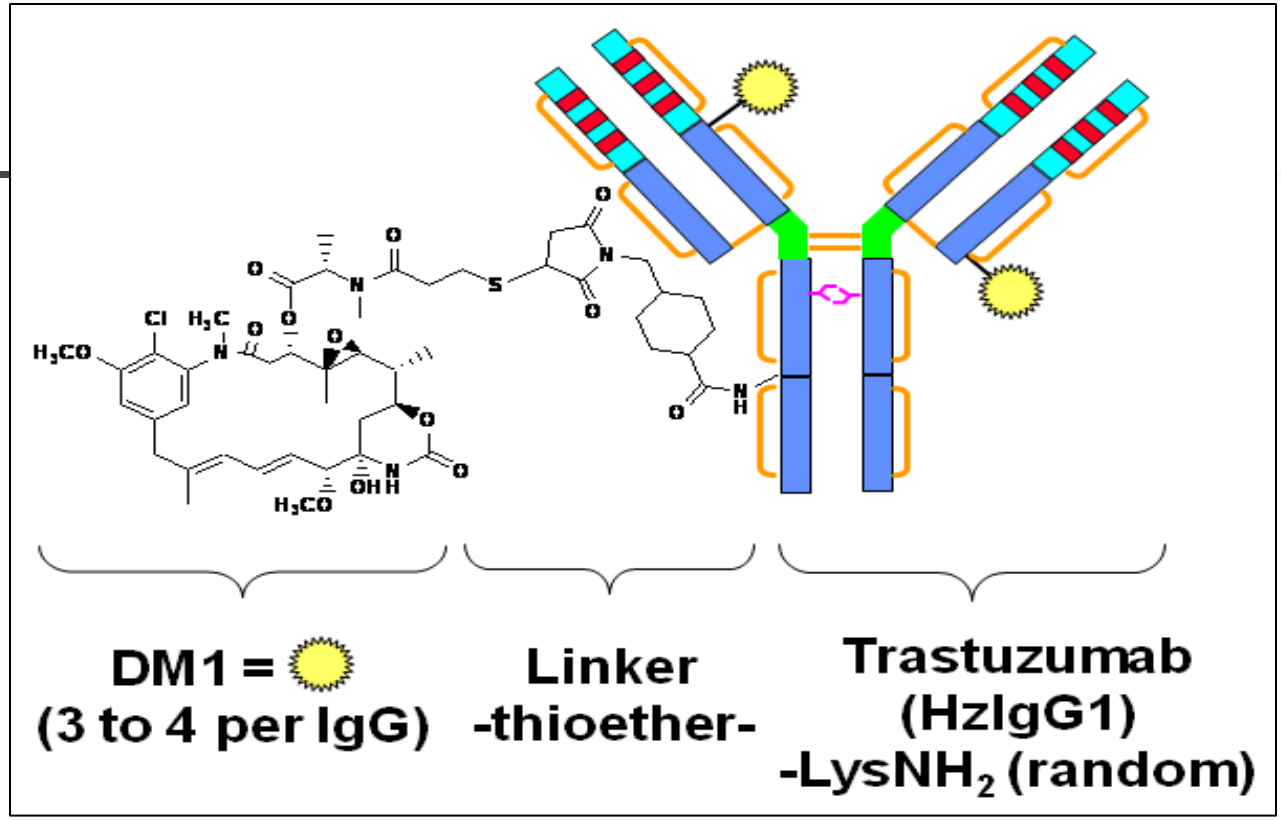
Beovu VEGF-A 26 kDa



Bispecific scFV

Blincyto CD3/CD19 54 kDa

Antibody-Drug Conjugate (ADC)



Chemical drug (toxin) linked to the monoclonal antibody

will discuss later

Zynlonta	*PBD alkylating agent*	*DAR 2*
Kadcycla	*maytansine*	*DAR 4*
Besponsa	*calicheamicin*	*DAR 6*
Enhertu	*topoisomerase inhib*	*DAR 8*

DAR – Drug Antibody Ratio

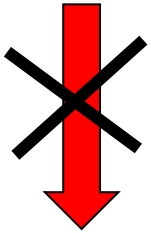
WAVE 4
Biosimilars

INNOVATOR Manufacturer

Must prove
STATISTICAL
safety & efficacy

must prove
'medical benefit'

commercial biopharmaceutical (rproteins/mAbs)



biosimilar blocked from market entry UNTIL innovator's marketing exclusivity and patent coverage ends

BIOSIMILAR Manufacturer

Must prove
COMPARATIVE
safety & efficacy

must prove
'no clinically
meaningful differences'

commercial biosimilar (rproteins/mAbs)

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

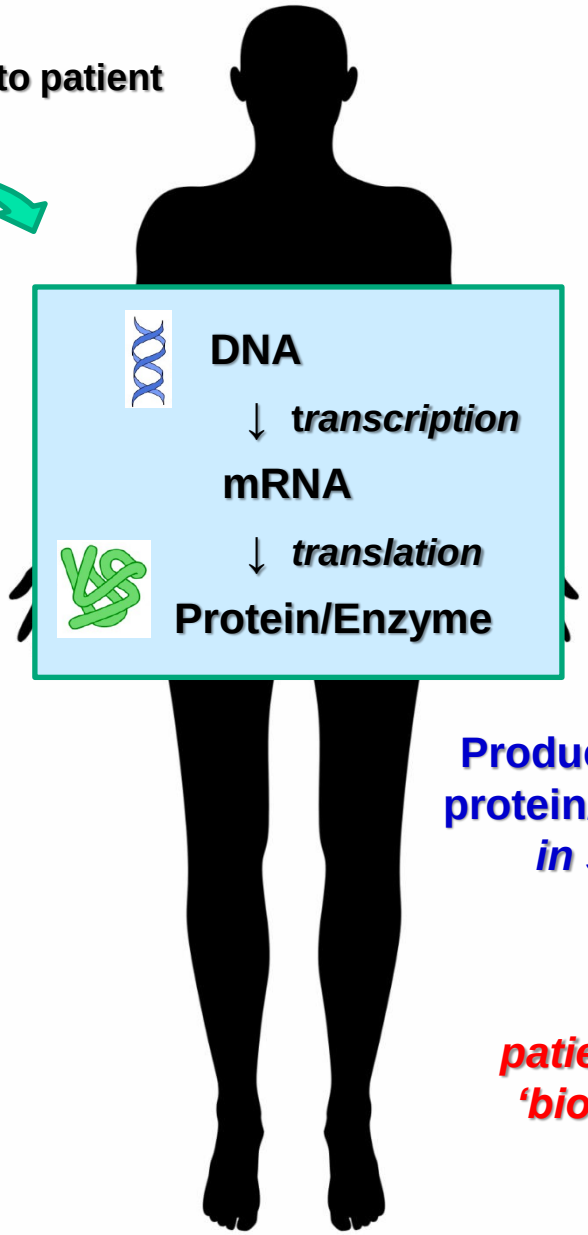
Biopharmaceutical Type	*Reference Product [innovator manufacturer]*	*Biosimilars [biosimilar manufacturer]*	
recombinant protein	*Neulasta (pegfilgrastim) [Amgen]*	*Fulphia [Mylan]*	*Nyvepria [Pfizer]*
monoclonal antibody	*Herceptin (trastuzumab) [Genentech/Roche]*	*Kanjinti [Amgen]*	*Ontruzant [Sandoz]*
Fc fusion protein	*Enbrel (etanercept) [Amgen]*	*Erelzi [Sandoz]*	*Eticovo/Benepali [Samsung]*
Fab fragment	*Lucentis (ranibizumab) [Genentech/Roche]*	*Byvooiz [Samsung]*	

70+ biosimilars market approved by FDA/EMA

Gene transduced/transfected into patient

in vivo *ex vivo*

Gene (DNA/RNA) coding for amino acid sequence



Production of protein/enzyme *in situ*

NEXT INCOMING WAVE

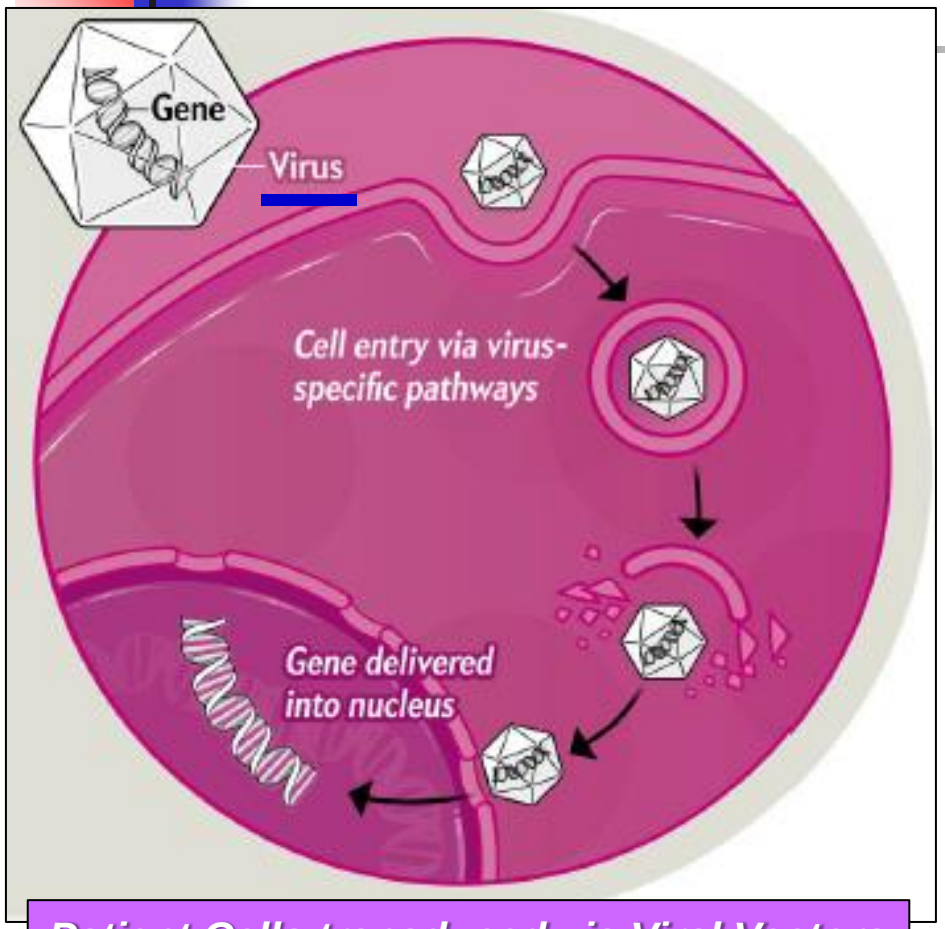
WAVE 5
Gene Therapy

patient is the 'bioreactor'

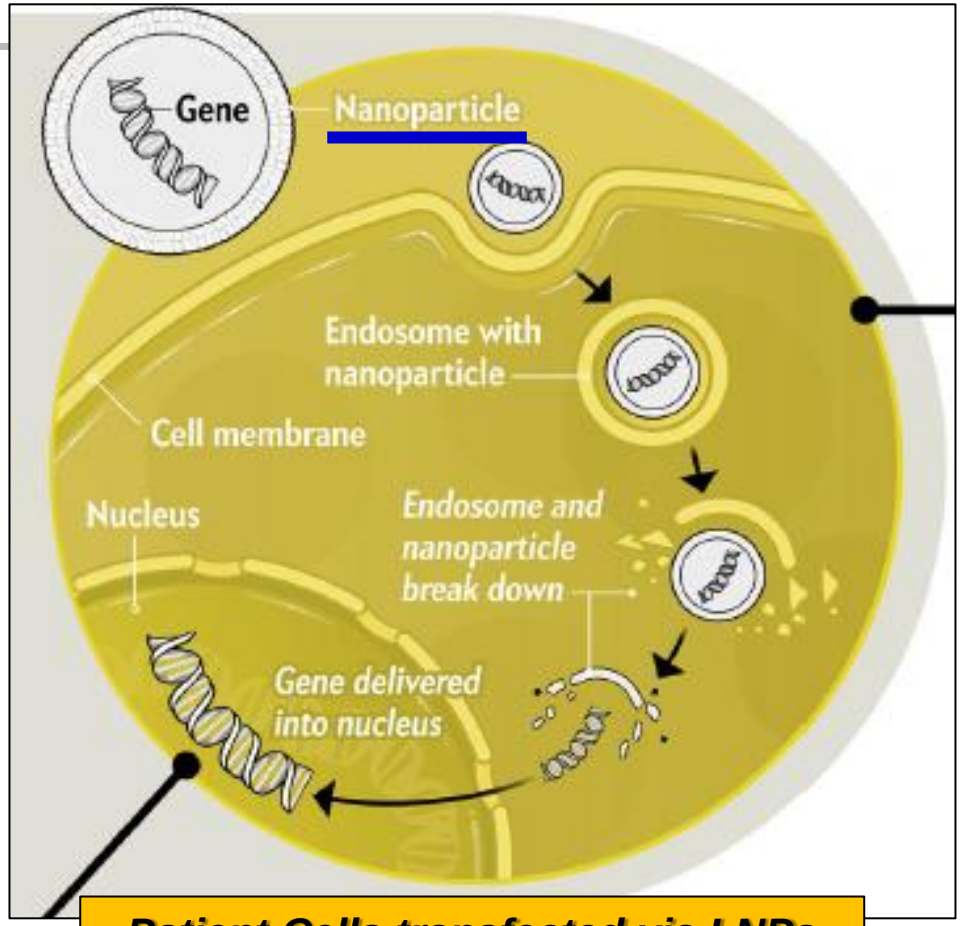
(limited discussion on these gene-based biopharmaceuticals in this course due to time)

Gene Therapy of Humans

(two common DNA/RNA insertion approaches)



Patient Cells transduced via Viral Vectors
(AAV or LV containing gene)

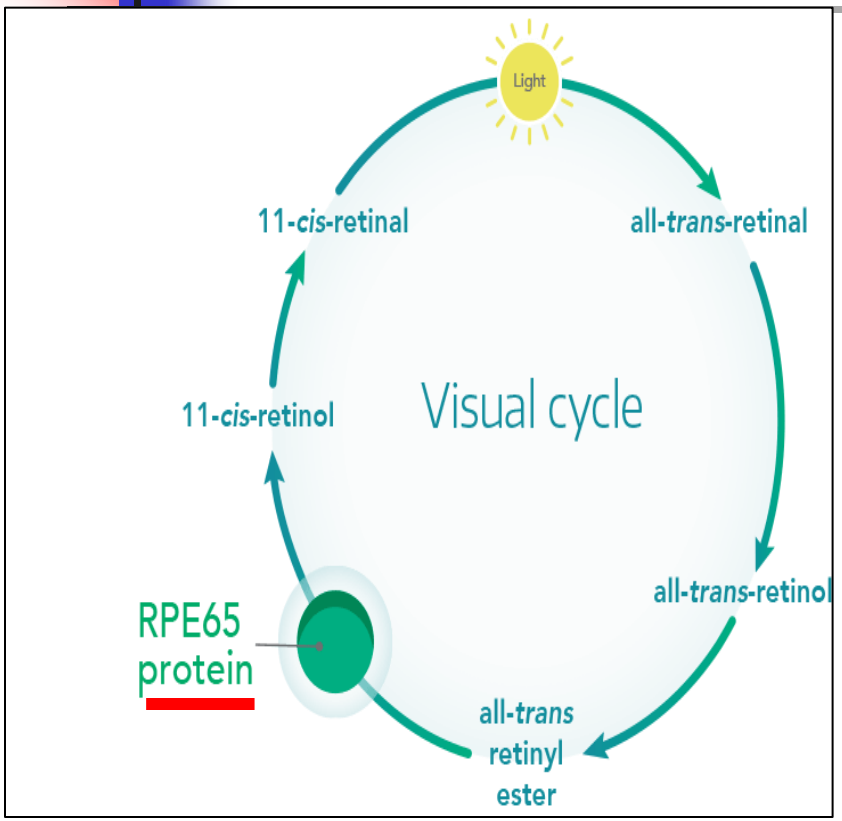


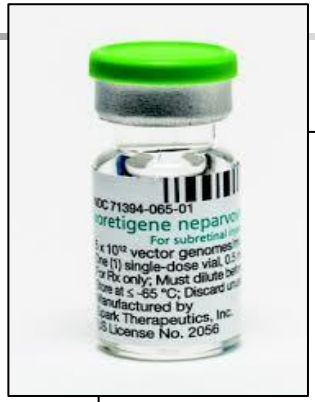
Patient Cells transfected via LNPs
(lipid nanoparticles encapsulating gene)

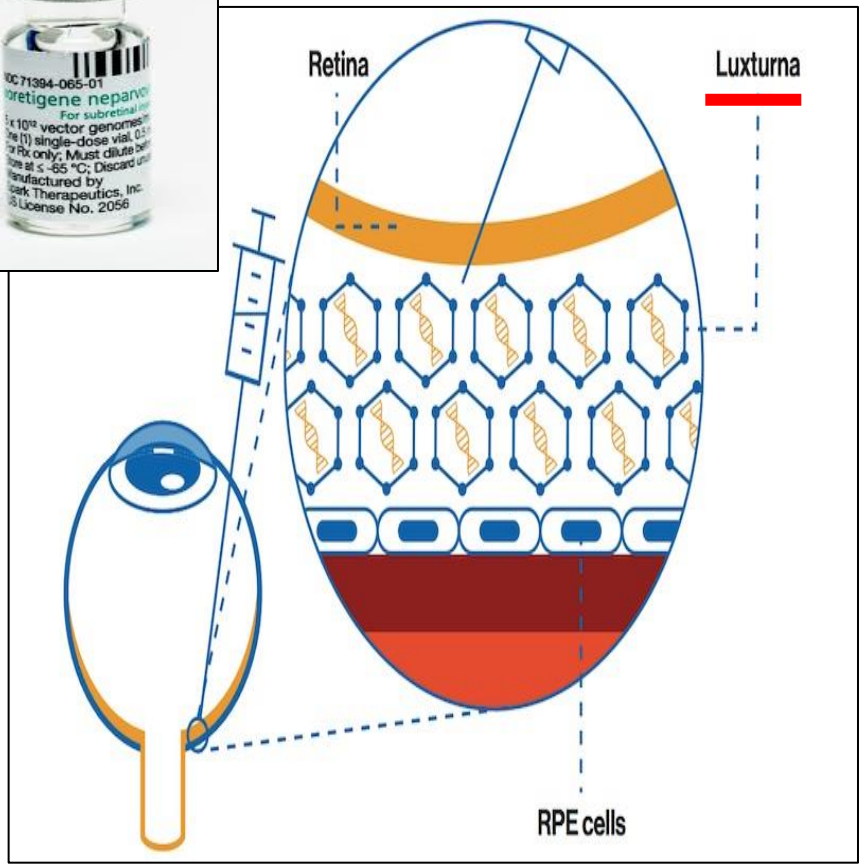
In Vivo Gene Restoration

Spark Therapeutics LUXTERNA

Adeno-associated virus (AAV) vector (with RPE65 gene) to restore vision







Intraocular injection

Note, ~25 genes are associated with loss of vision; RPE65 gene is only one of them

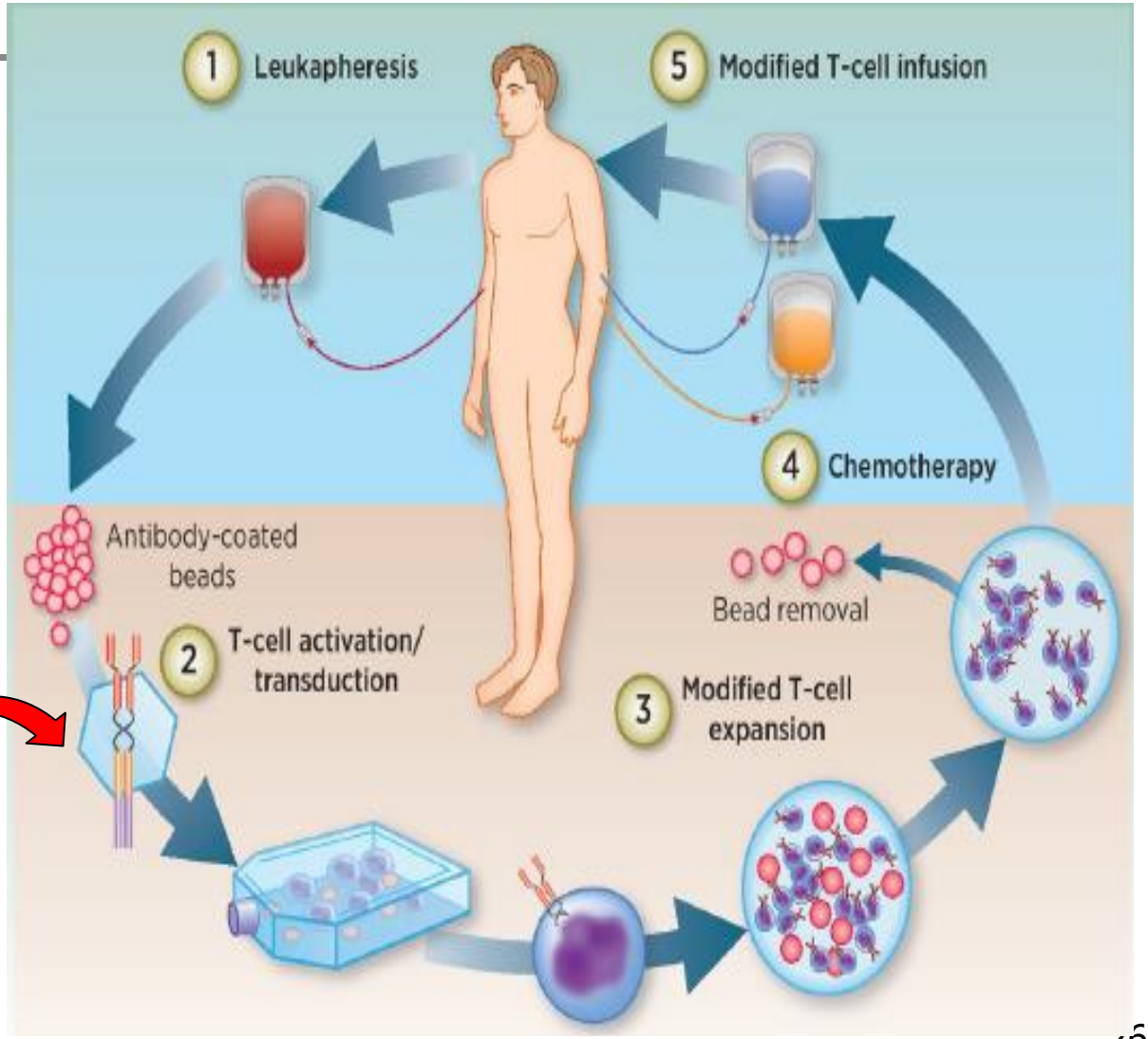
Ex Vivo Gene Addition

Novartis KYMRIAH

autologous T-cells genetically modified to bind to CD19-containing leukemia cells

(CAR – chimeric antigen receptor)

Genetically engineered lentivirus to add a gene to the human T-cells



Wave 5 – a tsunami or just another wave?

Most biopharmaceutical companies have jumped in!

GILEAD

Kite
A GILEAD Company

NOVARTIS

avexis

Roche

Spark THERAPEUTICS

Bristol-Myers Squibb

JUNO THERAPEUTICS

janssen
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

BIOMARIN

bluebirdbio

AMGEN

Orchard therapeutics

BAYER

Most vendors and CMOs have jumped in!

Lonza

FUJIFILM Diosynth biotechnologies

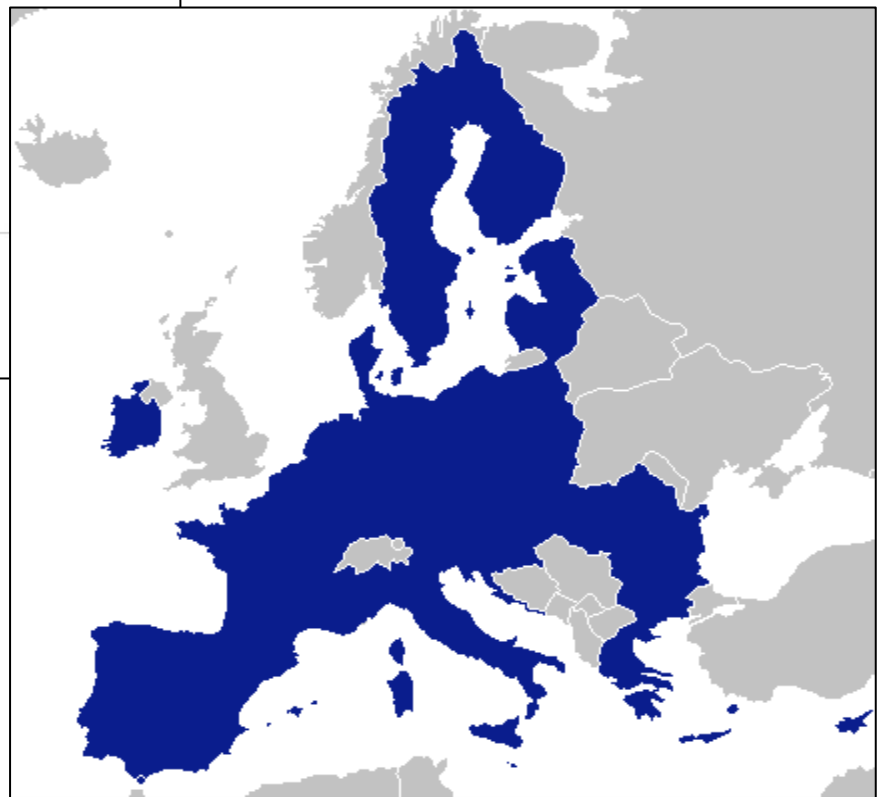
ThermoFisher SCIENTIFIC

Catalent BIOLOGICS

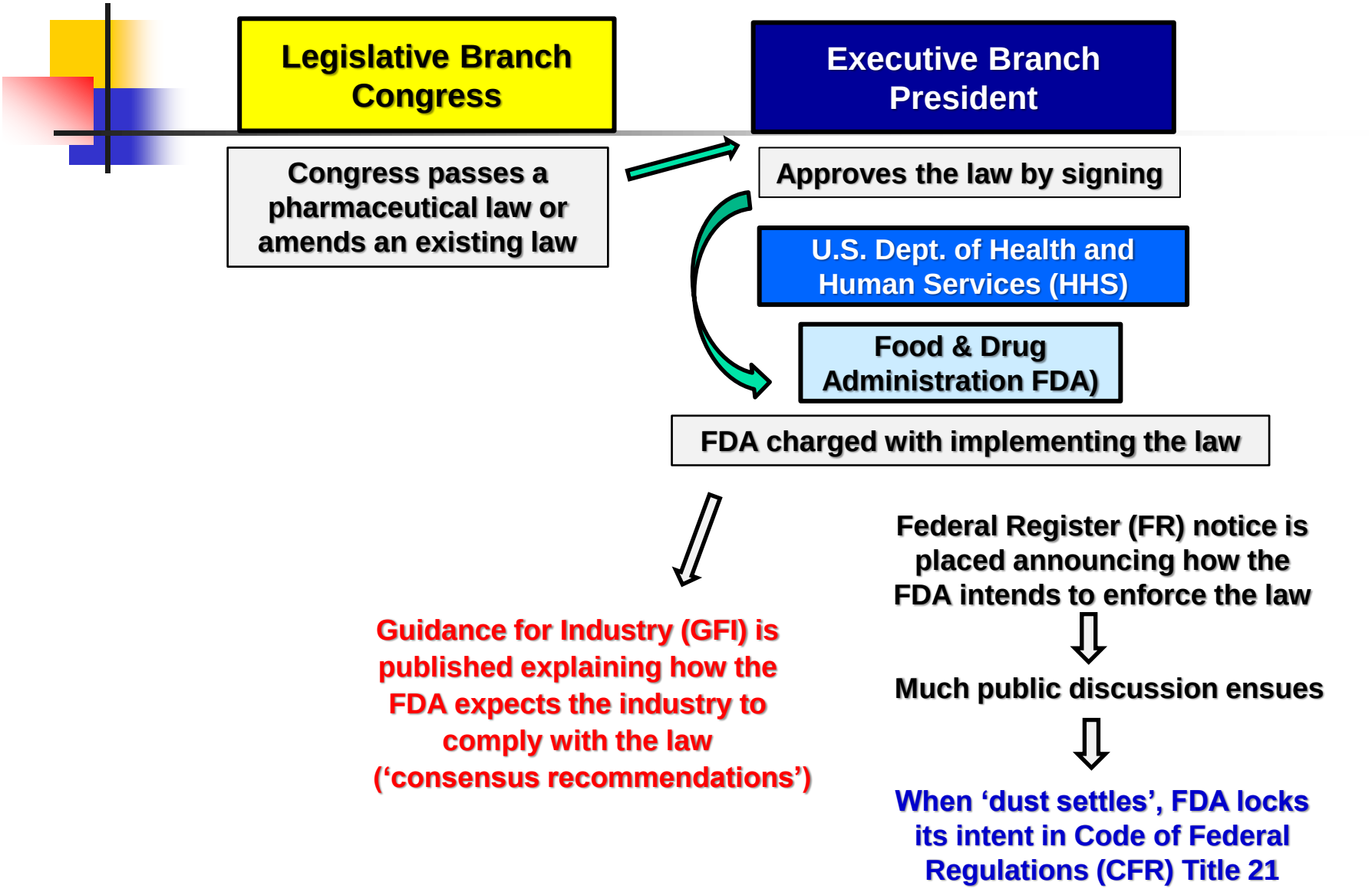
Miltenyi Biotec

Regulatory Authority Landscape for Biopharmaceuticals

(USA and EU to be discussed; but there are many others)



United States Pharmaceutical Legislation



1938 Food Drug & Cosmetics (FD&C) Act

Pathway to Commercialization for CHEMICAL DRUGS in FD&C Act

New Drug Application (NDA) Pathway

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

CMC format today: eCTD Module 3

→

New Drug Application (NDA)
21 CFR 314
[market approval]
FDA regulates

CMC format today: eCTD Module 3

But almost immediately after 1938 …

- ***Congress became aware that certain drug types (referred to as 'biologicals') did not fit well under the FD&C Act:***
  - ***Many 'biologicals' at that time consisted of undefined or impure mixtures***
  - ***These 'biologicals' required more testing than for the other chemical drugs under the FD&C Act***
  - ***These 'biologicals' required a tighter control over the manufacturing process than for the other chemical drugs under the FD&C Act***

U.S. Congress reacted and passed a 2nd law →

1944 Public Health Services (PHS) Act

Pathway to Commercialization for BIOLOGICALS in PHS Act

Biologic License Application (BLA) Pathway

Investigational New Drug (IND)	Biologic License Application (BLA)
21 CFR 312	21 CFR 600-680*
[human clinical studies]	[market approval]
FDA regulates	FDA regulates
CMC format <u>today</u>: eCTD Module 3	CMC format <u>today</u>: eCTD Module 3

[* PHS Act is linked to FD&C Act 21 CFR 211 (cGMPs) and 21 CFR 314 (administrative procedures)]

Biological product defined by 'specific product type'

CFR changes in biological product type 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)~~'*

Analogous = 'comparable in certain respects'
(applies today to gene therapy biopharmaceuticals)

FDA's regulation of 'Protein' vs 'Peptide'

FDA interprets the term "protein" to mean any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size.

FDA interprets the statutory definition of "biological product" such that any amino acid polymer composed of 40 or fewer amino acids (i.e., a "peptide") is outside the scope of the term "protein."

A "peptide" is not a "biological product" and will continue to be regulated as a drug under the FD&C Act unless the peptide otherwise meets the statutory definition of a "biological product" (e.g., a peptide vaccine)

The "Deemed To Be a License" Provision of the BPCI Act Q&A March 2020

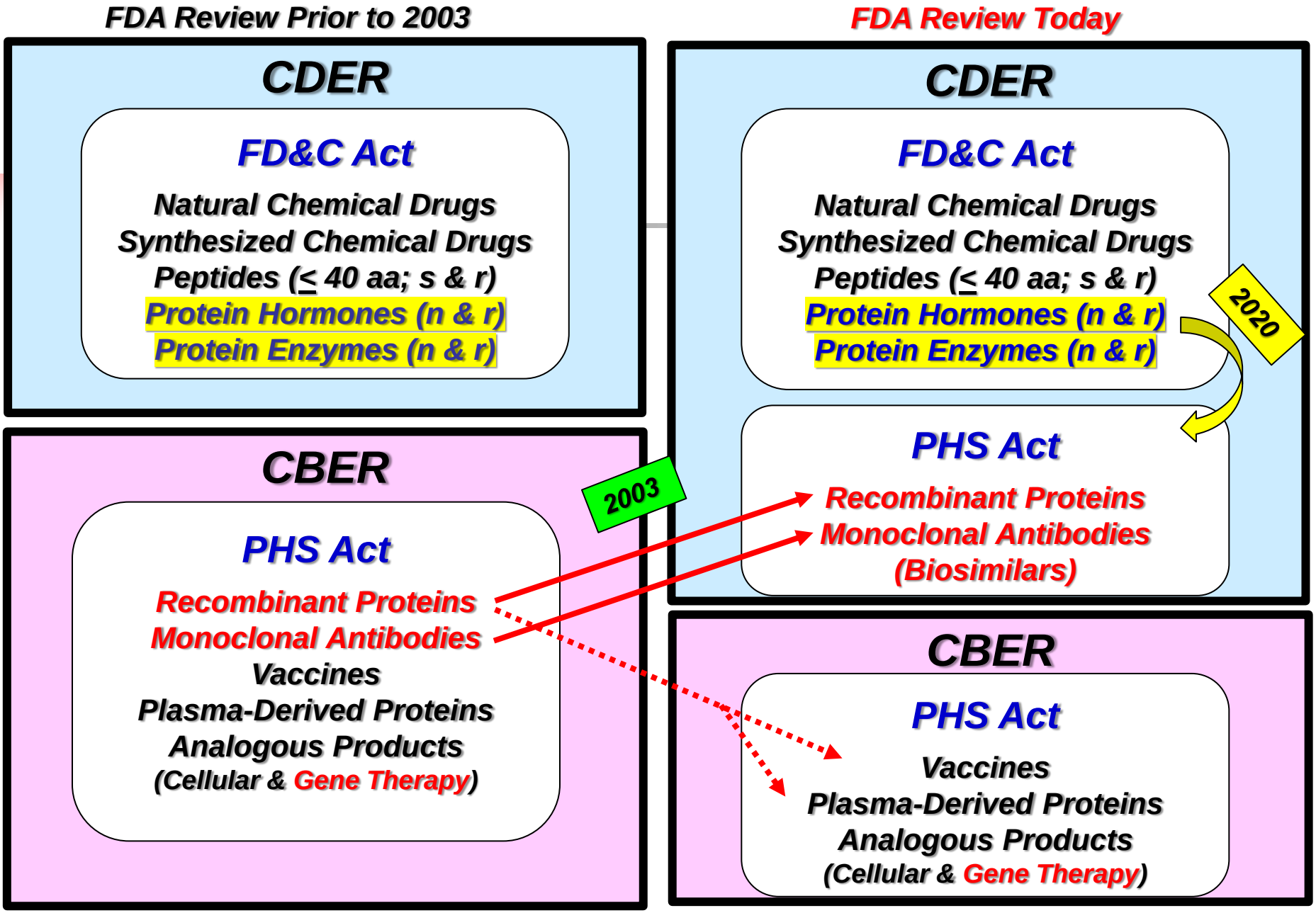
Two primary FDA Centers involved with review and approval of biopharmaceuticals

Center for Drug Evaluation and Research (CDER)

Center for Biologics Evaluation and Research (CBER)

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

has changed over time …

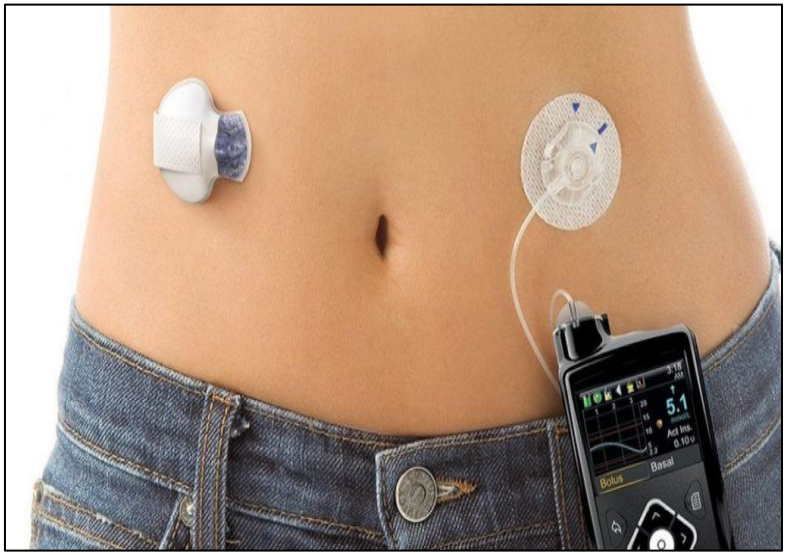


n - natural r - recombinant s - chem synthesized aa - amino acids

A 3rd FDA Center now frequently involved with biopharmaceutical combination products

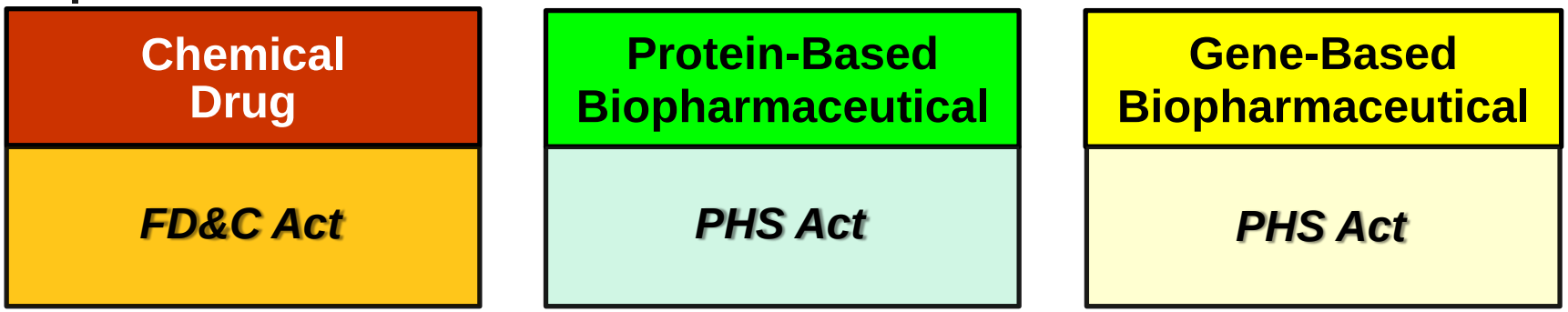
(typically a secondary consult for CDER/CBER)

Center for Devices and Radiological Health (CDRH)



(more on combination products later)

What major differences are there in the CMC regulatory requirements between the two pharmaceutical laws?

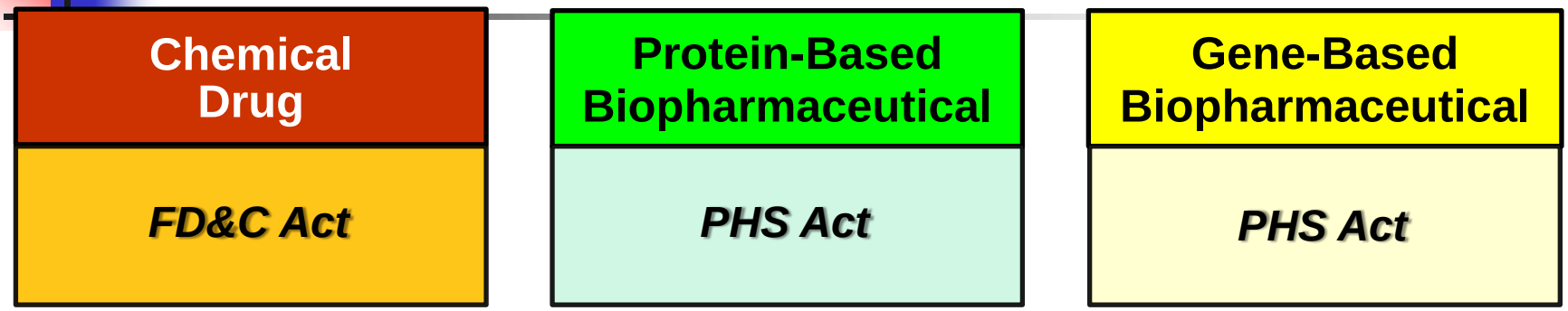


Administrative Regulatory Affairs – CMC

No!

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

What major differences are there in the CMC regulatory requirements between the two pharmaceutical laws?



CMC Regulatory Compliance Requirements

No! *– not during clinical development*

Yes! *– only after market approval, for PHS Act products*

1) *extra test requirement to release commercial batches*
2) *FDA can require pre-release review of commercial batches*
3) *FDA can add a bioqualifier to commercial INN*

1) Extra test requirement to release labelled commercial batches

610.14 Identity.
The contents of a final container of each filling of each lot shall be tested for identity after all labeling operations shall have been completed. The identity test shall be specific for each product in a manner that will adequately identify it as the product designated on final container and package labels and circulars, and distinguish it from any other product being processed in the same laboratory. Identity may be established either through the physical or chemical characteristics of the product, inspection by macroscopic or microscopic methods, specific cultural tests, or in vitro or in vivo immunological tests.

a physical or chemical or biological or immunological content test – after labelling!

LEGALLY REQUIRED FOR ALL BIOLOGICALS

Recombinant Proteins

Monoclonal Antibodies

Biosimilars

Gene Therapy

Case Example (mAb)

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

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.

***not* a FD&C Act requirement (chemical drugs)**

***not* an EMA requirement (for any pharmaceutical)**

2) FDA can require pre-release review of commercial batches

§ 610.2 Requests for samples and protocols; official release.

(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,

recombinant proteins, monoclonal antibodies, biosimilars

(not a FD&C Act requirement for chemical drugs)

(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:

vaccines, plasma-derived proteins, cell & gene therapies

varies by biopharmaceutical product type →

FDA pre-release of Commercial THERAPEUTIC Recombinant Proteins, Monoclonal Antibodies, and Biosimilars

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.

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 VACCINES
Recombinant Proteins
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).

SHINGRIX (Zoster Vaccine Recombinant, Adjuvanted) October 20, 2017

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).

as stated in CBER market approval letters

FDA pre-release of Commercial THERAPEUTIC In Vivo Gene-Based Biopharmaceuticals required!

rAAV

LUXTURNA (voretigene neparvovec-rzyl) **December 19, 2017**

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

ZOLGENSMA® (onasemnogene abeparvovec-xioi) May 24, 2019

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

(not an EMA requirement)

FDA team internal discussion on why pre-release

ZOLGENSMA TEAM MEETING SUMMARY

In vivo gene therapy – AAV virus

Application number: 125694/0 **Meeting date & time:** April 10, 2019

Product name: onasemnogene abeparvovec-xioi

Andrew Byrnes explained DCGT's preference for quarterly surveillance instead of lot release due to the large number of lots (approximately 1 per week) and the risk to commercial supply that could be caused by delays in release. Andrew explained that given the relatively short shelf life (effectively only 8 months), routine lot release could delay distribution of the product.

Jay Eltermann expressed that all products are subject to lot release, but case by case exemptions have been granted, e.g., CAR-T cells. Jay explained that this product has attributes that support the need for routine lot release - it is not a patient specific product, it is a novel product from a manufacturer with little experience, and there appear to be testing issues. It therefore cannot be under surveillance. AveXis will need to establish an acceptable lot release history (longer than 5 years), accumulate stability data, and demonstrate the manufacturing process is well controlled before submitting a supplement to request surveillance as an alternative to routine lot release.

Maryna Eichelberger explained that lot release would give CBER confidence with the product, and regardless if the protocols are electronic or paper, they come to DPMQ/PRB. They are reviewed by the Product Office (PO) and DBSQC reviewers. Paper protocols are physically routed to sequential reviewers and therefore if paper protocols are submitted, it could delay the release. AveXis could send electronic protocols after BLA approval. The Testing Plan (TP), a CBER internal document, determines the LRS routing. There are no PDUFA time lines for lot release. However, the Lot Release Branch (LRB) is committed to releasing lots within 30 business days of protocol receipt. Jay mentioned that LRS captures tests which are released, but no test data is captured in LRS.

3) FDA can add a bioqualifier to the commercial INN

World Health Organization

INN – international nonproprietary name – assigned by WHO

each INN is a unique name assigned to an active pharmaceutical ingredient (API)

BIOLOGICAL BIOQUALIFIER – a FDA-designated suffix (4 lowercase letters)

This guidance describes FDA's current thinking on the need for biological products licensed under the Public Health Service Act (PHS Act) to bear a *nonproprietary name*[2] that includes an FDA-designated suffix. Under this naming convention, the nonproprietary name designated for each *originator biological product*, *related biological product*, and *biosimilar product* will be a proper name that is a combination of the *core name* and a distinguishing suffix that is devoid of meaning and composed of four lowercase letters.[3] The suffix format described in this guidance is applicable to originator biological products, related biological products, and biosimilar products previously licensed and newly licensed under section 351(a) or 351(k) of the PHS Act.

Nonproprietary Naming of Biological Products **January 2017**

An applicant should propose a suffix composed of four lowercase letters for use as the distinguishing identifier included in the proper name designated by FDA at the time of licensure (see section VI of this guidance). Such submissions can be made during the investigational new drug application (IND) phase[16] or at the time of BLA submission. An applicant should submit up to 10 proposed suffixes, as described in this section, in the order of the applicant's preference.

FDA	EMA
Enspryng (monoclonal antibody)	
satralizumab-mwge	satralizumab
Byooviz (Lucentis biosimilar)	
ranibizumab-nuna	ranibizumab
PreHebrio (Vaccine)	PreHebri (Vaccine)
hepatitis B vaccine (recombinant)	hepatitis B surface antigen
Zolgensma (in vivo gene therapy virus)	
onasemnogene abeparvovec-xioi	onasemnogene abeparvovec
Abecma (ex vivo gene therapy cells)	
idecabtagene vicleucel	idecabtagene vicleucel

FDA

always applied to recombinant proteins, monoclonal antibodies, biosimilars and in vivo gene therapy biopharmaceuticals

not applied to chemical drugs or chemical generics

not applied to vaccines or ex vivo gene therapy biopharmaceuticals

EMA

not applied to any pharmaceutical

European Pharmaceutical Legislation

European Parliament (EP)

Final approval of laws

European Commission (EC)

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

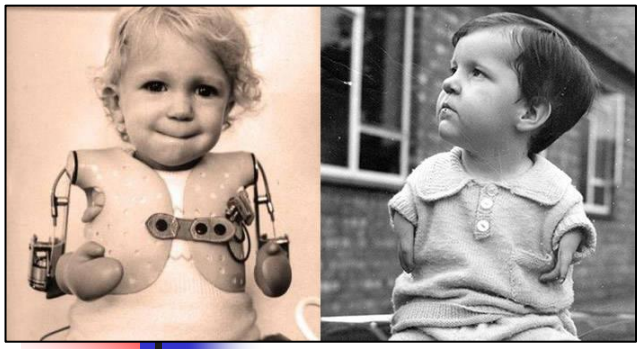
National Competent Authority (NCA)

Review/evaluation of medicines during human clinical development

European Medicines Agency (EMA)

Review/evaluation of medicines for market approval

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



Pathway to Commercialization for Medicines in EU

Clinical Trial Application (CTA)

[human clinical studies]

CMC format: Investigational Medicinal Product Dossier (IMPD)

Marketing Authorisation Application (MAA)

[market approval]

CMC format: eCTD Module 3

NCAs regulate

(country-by-country review)

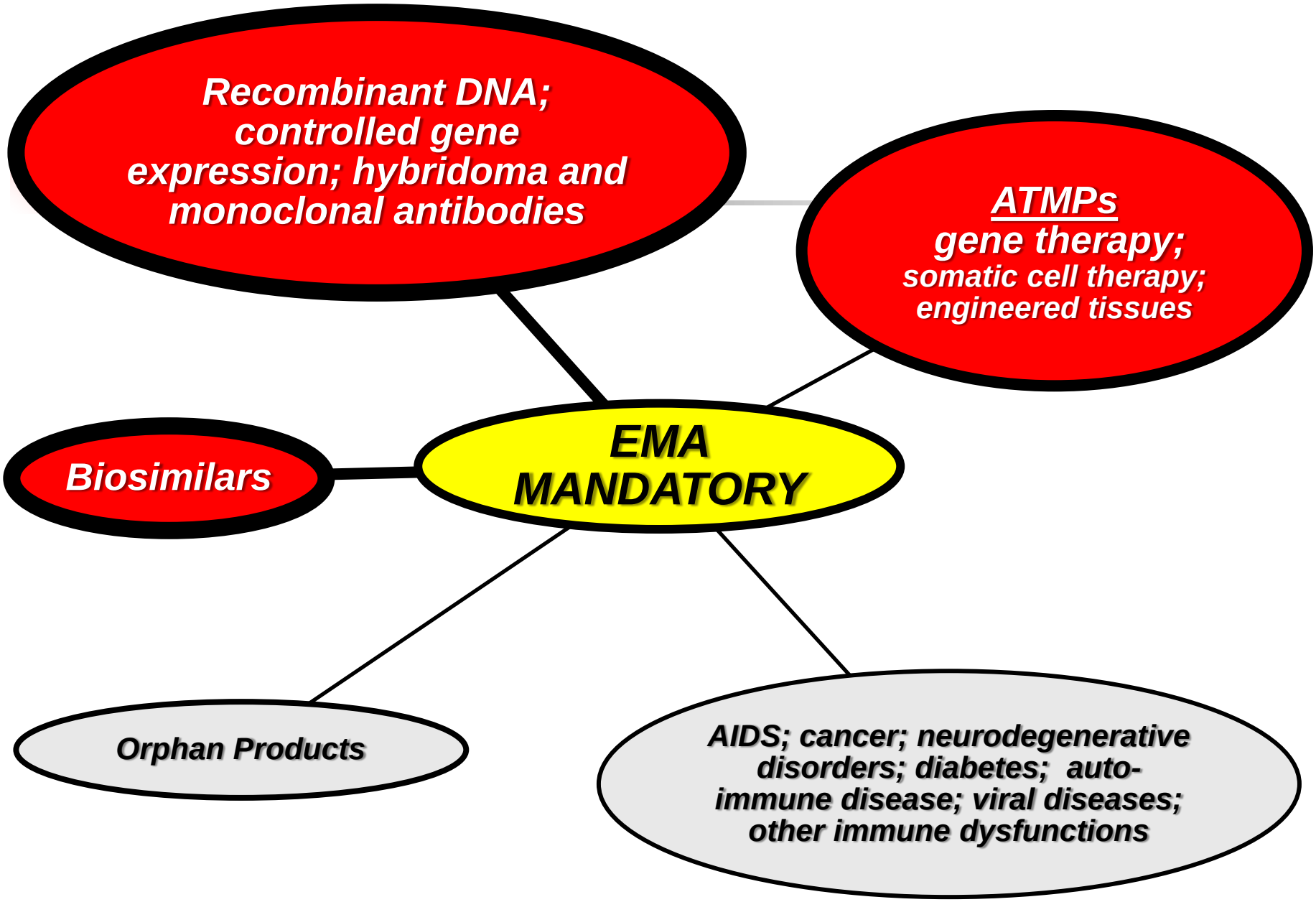
Directive 2001/20/EC
allows each country to choose how to implement the act

Clinical Trial **Regulation** (536/2014)
in transition until 2023

EMA regulates

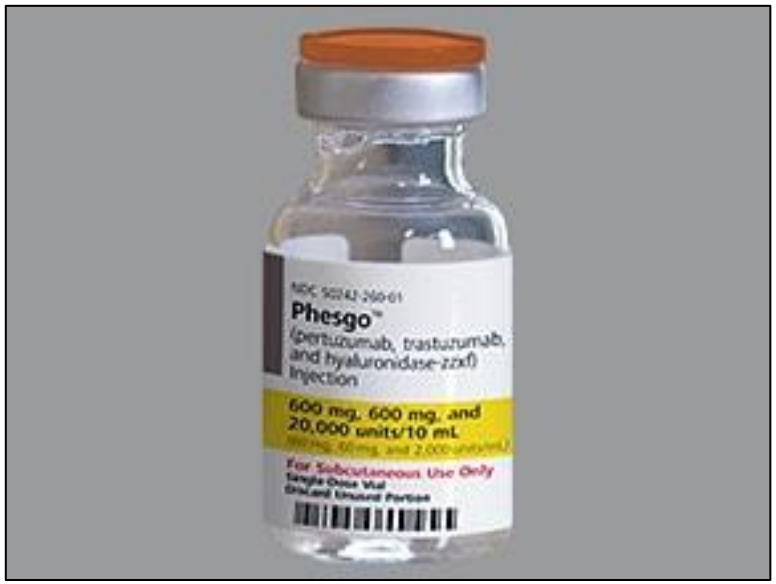
(centralized review)

Regulation EC 726/2004
a binding legislative act; must be uniformly applied across EU


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

Many other pharmaceutical regulation landscapes around the world!
(Fortunate to have FDA and EMA!)

Biopharmaceuticals are NOT Chemical Drugs



4 major areas of difference that impact CMC regulatory compliance!

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

1 of 4: Differences in Synthesis

Chemical Drug	Protein-Based Biopharmaceutical	Gene-Based Biopharmaceutical
• Synthesized using <u>non-living</u> chemical reagents • Organic solvents • Chemical reactions under harsh conditions of temperature and pressure	• (Bio) synthesized using <u>living</u> organisms • Aqueous medium • Protein induction in cell culture conditions (mild temperature and pressure	• (Bio) synthesized using <u>living</u> organisms • Aqueous medium • Gene vector propagated in cell culture conditions (mild temperature and pressure)

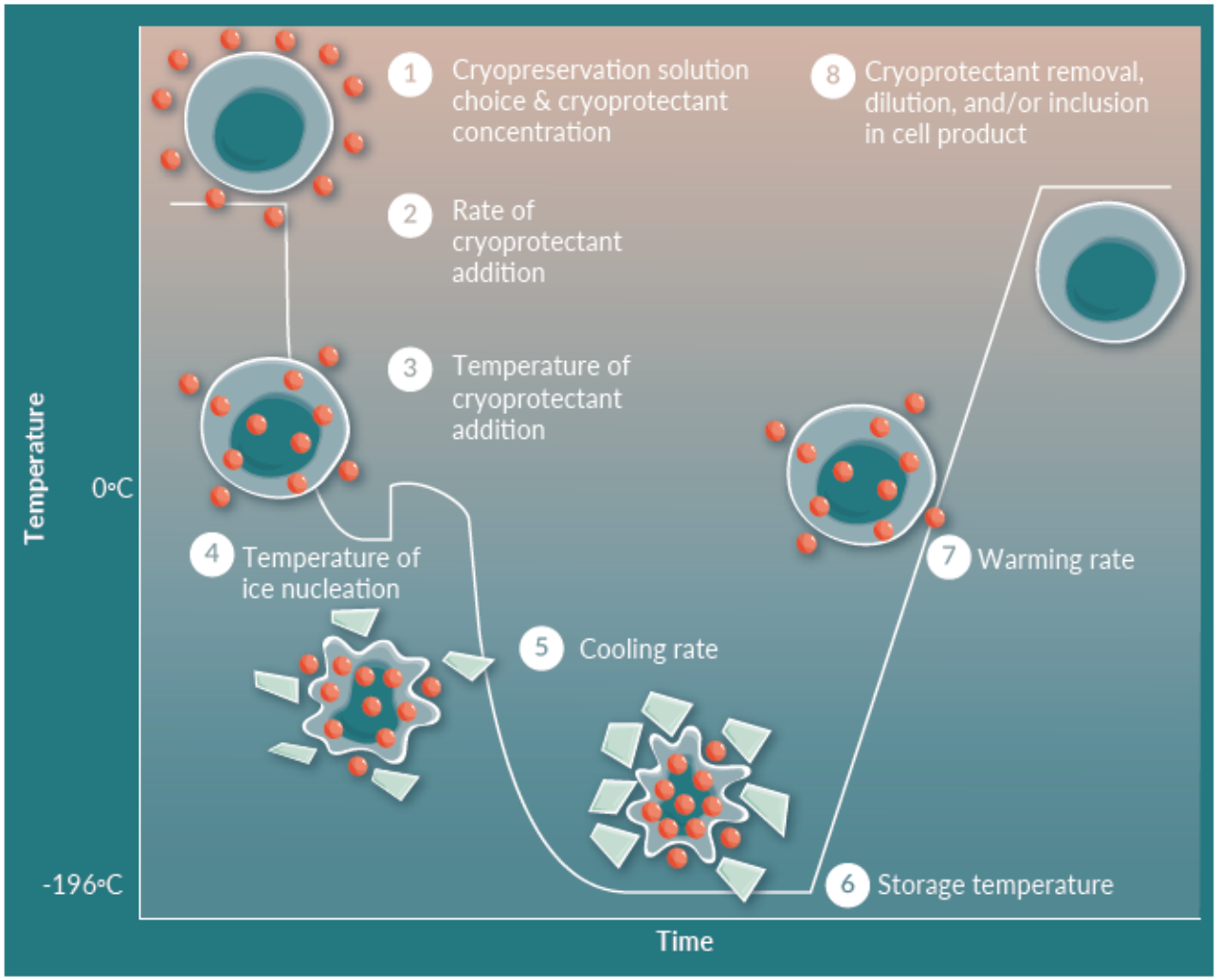
3 major challenges when using a living organism →

Challenge when using living organisms

1a: Keep 'ALIVE'!

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

Critical steps in the cryopreservation process.



Around the clock – 24/7

'life clock' can't be stopped

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

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

controlled freeze (slow)
(to prevent ice inside cell)

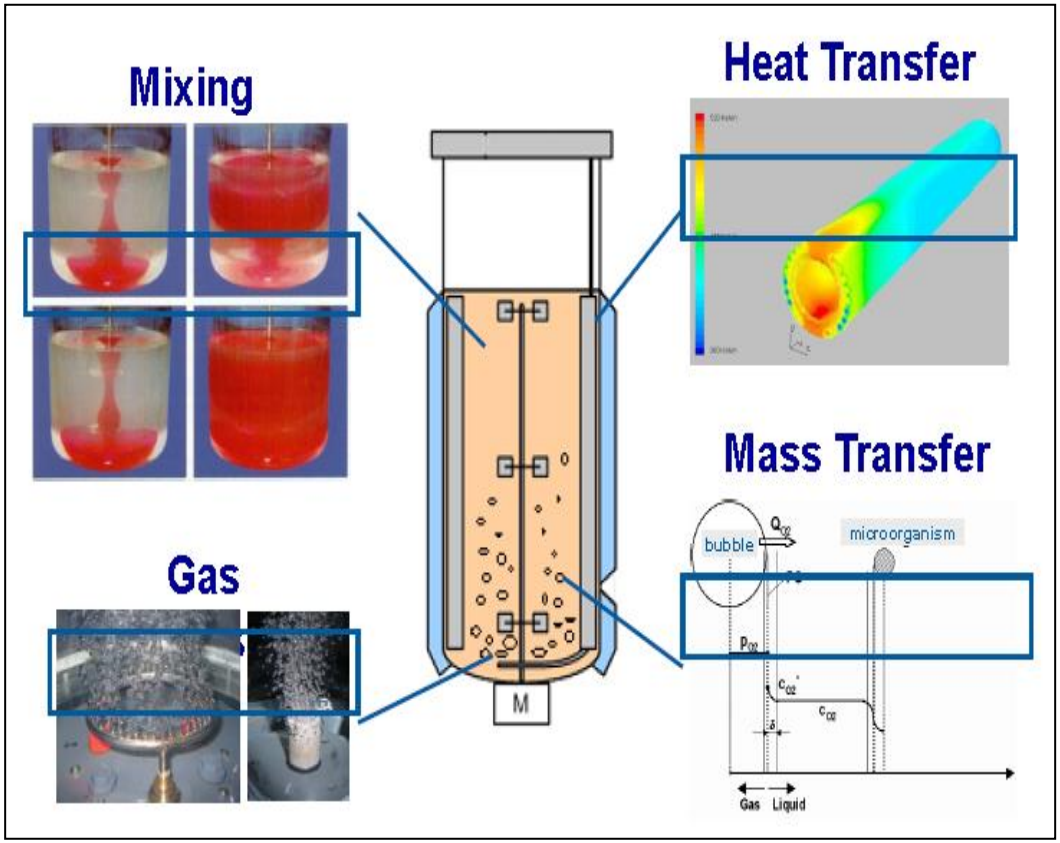
fast thaw

Challenge when using living organisms

1b: Keep 'HAPPY'!

Process control – process scientists earn their salary!

bacterial cells are <u>hardy</u>, mammalian cells are <u>fragile</u>



rapidly growing bacterial cells generate more heat than slowly growing mammalian cells

CO_2 <u>out</u>, O_2 <u>in</u>

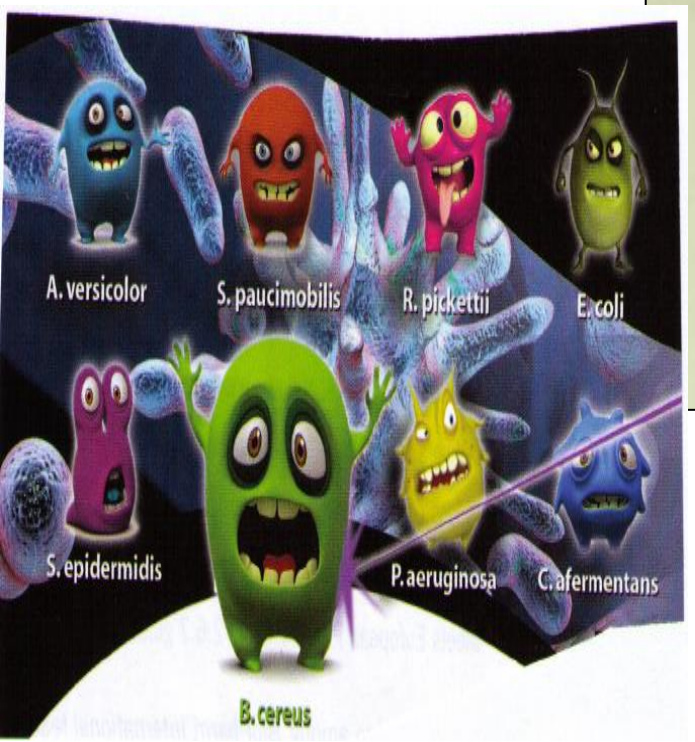
nutrients <u>toward</u>, waste products <u>away</u>

up to 12 critical process parameters that may need to be optimized in the bioreactor

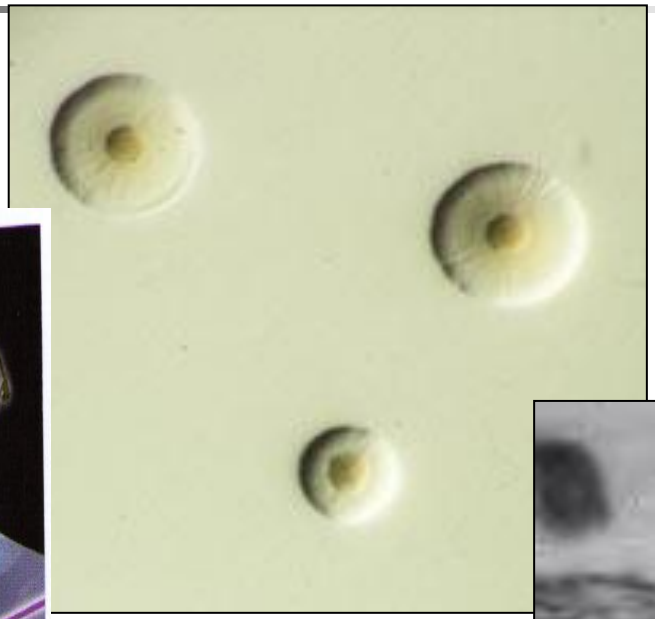
Challenge when using living organisms

1c: Keep 'HEALTHY'!

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

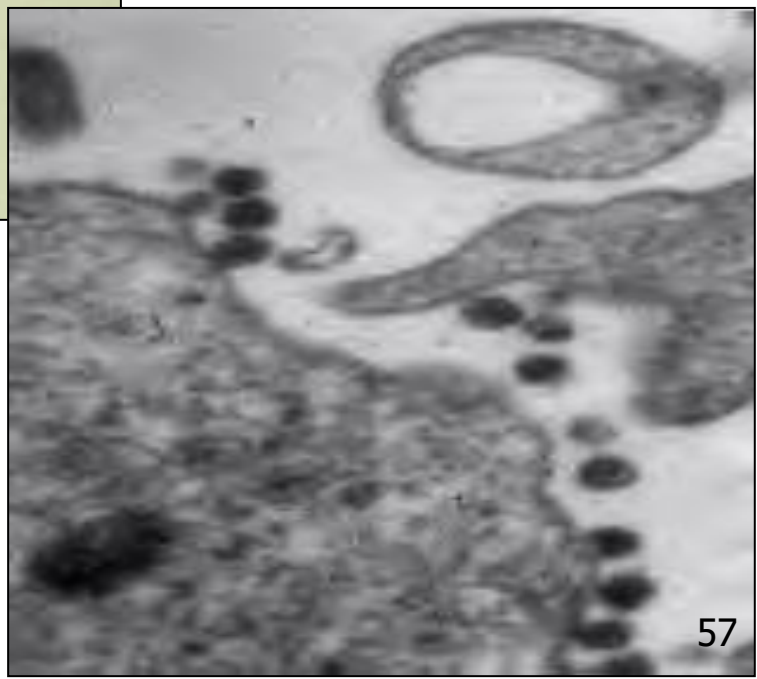


Bacteria/Fungi

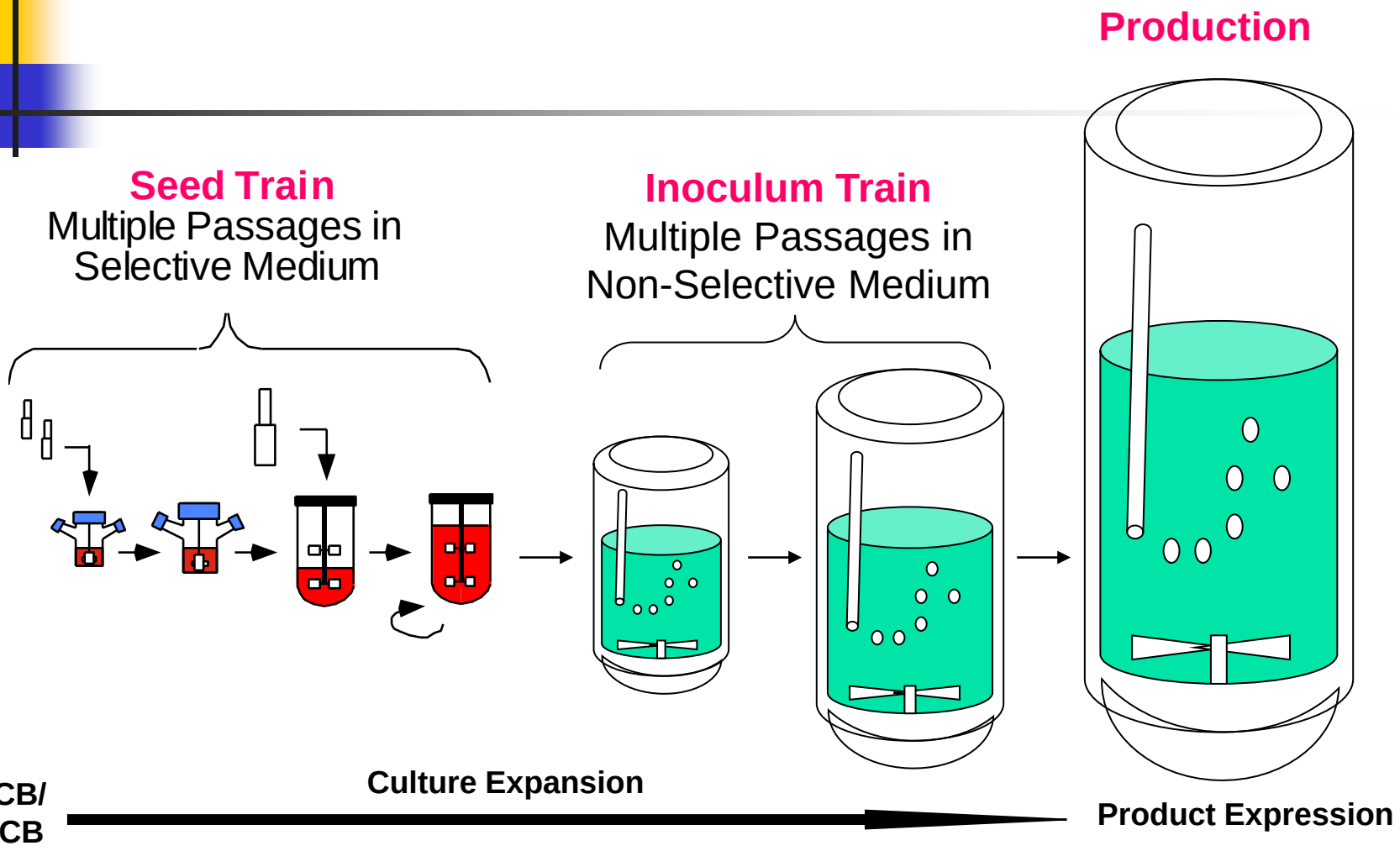


Mycoplasmas

Viruses



Once an adventitious agent contaminates a living organism, proliferation occurs and <u>all further downstream steps are impacted</u>!



(must be kept 'healthy' for several months)

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

2 of 4: Impact of the Manufacturing Process

Chemical Drug	Protein-Based Biopharmaceutical	Gene-Based Biopharmaceutical
• Product can be produced independent of the manufacturing process • Basis for chemical generics	• Product can be produced somewhat independent of the manufacturing process • Basis for biosimilars	• "Process is the product"

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

impact of manufacturing process on mAbs ***video*** → ***Amgen***

Amgen 5 min

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

3 of 4: Molecular Structure Complexity

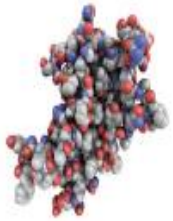
Chemical Drug	Protein-Based Biopharmaceutical	Gene-Based Biopharmaceutical
• Molecular structure can be simple or somewhat complex	• Molecular structure is complex, with numerous 'molecular variants'	• Molecular structure is very complex, many times with undefined variants

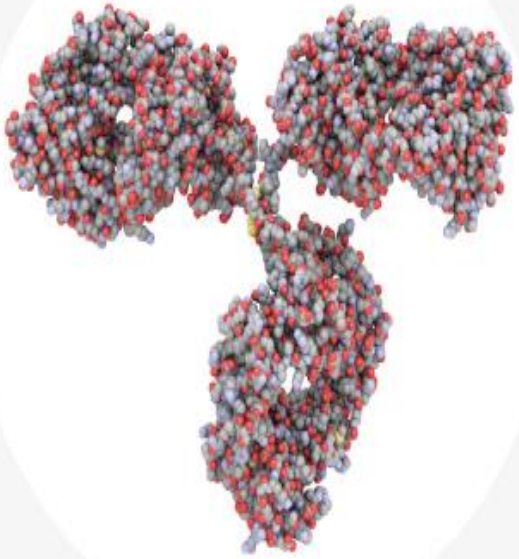
Chemical drugs can be large, just not as large nor as complex as biopharmaceuticals

chemically synthesized
siRNA (small, interfering RNA) for gene silencing

Givlaari
MW 17,250 D

~150 kDa; ~10 nm



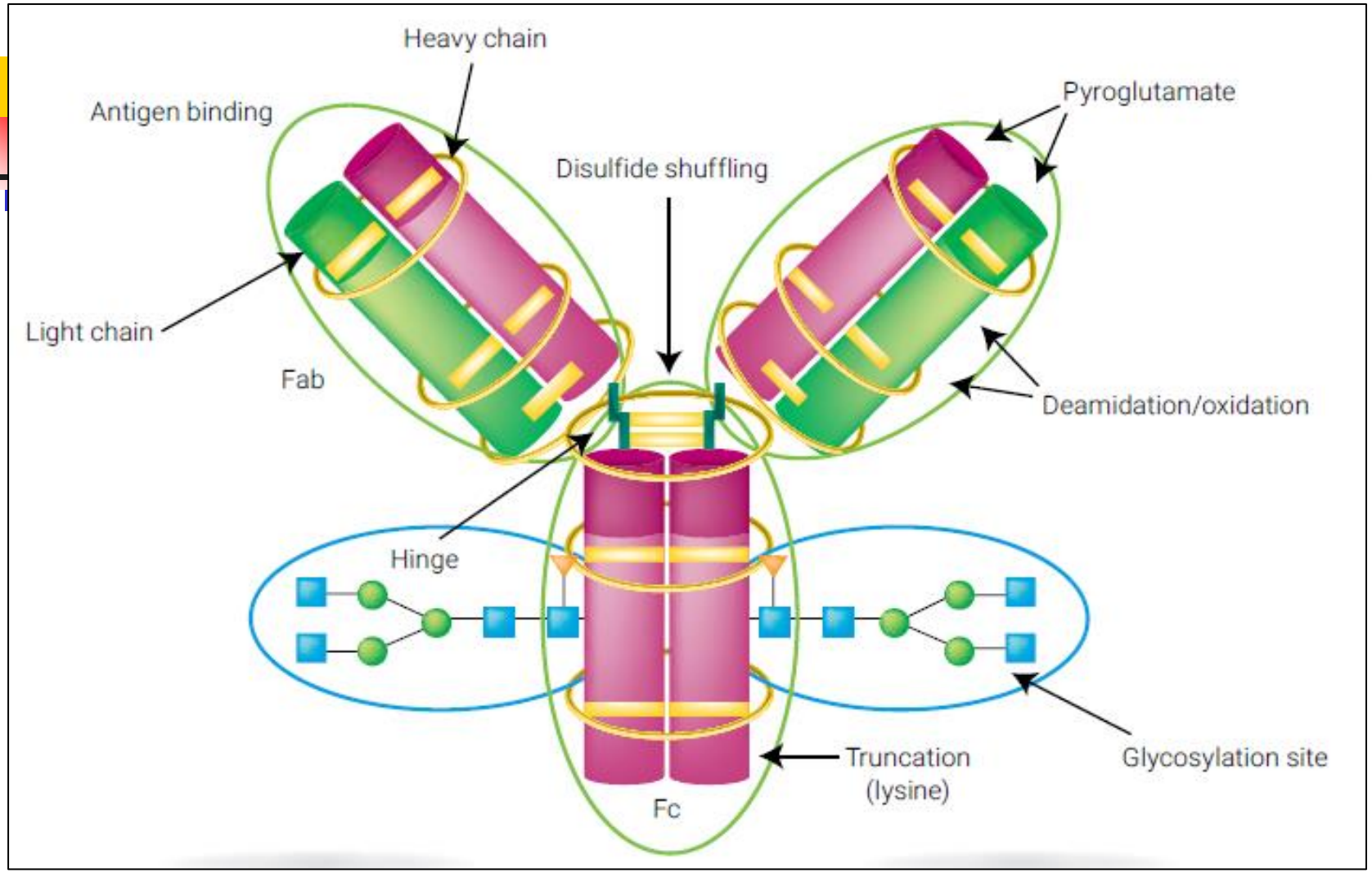


Insulin
5,808 daltons

Growth hormone
22,000 daltons

Monoclonal antibody
150,000 daltons

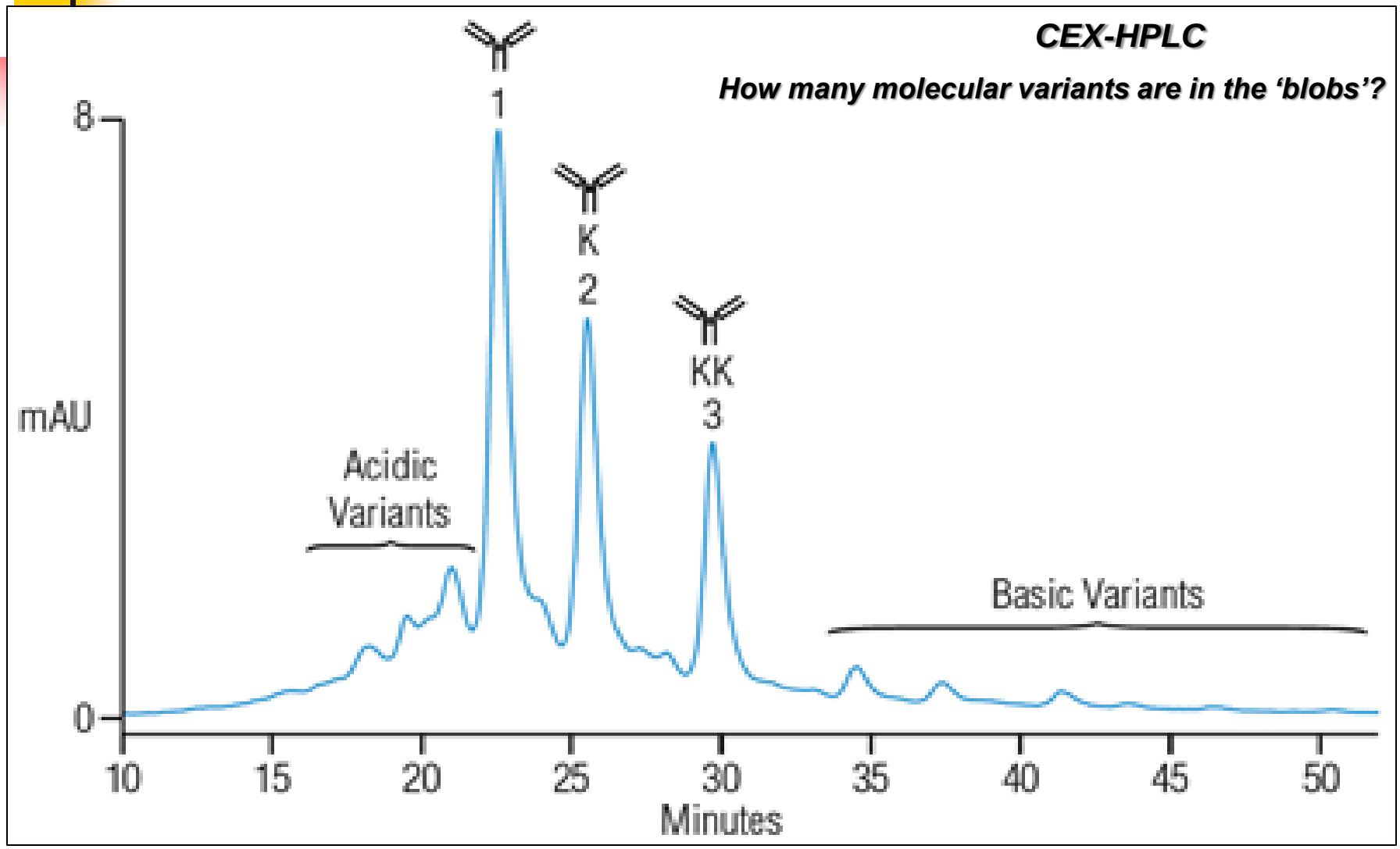
Abundance of molecular variants leads to complexity!



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 for a mAb → 100 million!

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



The size of biopharmaceuticals means they are recognized by the body's immune system – which means their complexity can lead to patient safety immunogenicity concerns

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

Therapeutic proteins are recognized by the human immune system. This recognition is often followed by an immune response to therapeutic proteins. This potentially harmful immune response is complex and, in addition to ADA formation, involves T cell activation and innate immune responses.

Important factors influencing the immunogenicity of therapeutic proteins include the origin (e.g. foreign or human) and nature of the active substance (endogenous proteins, post-translational modifications), significant modifications of the therapeutic protein (e.g. pegylation and fusion proteins), product-related (e.g. degradation products, impurities, aggregates) and process-related impurities (host cell proteins, lipids or DNA, microbial contaminants), formulation (excipients) and the interactions between the drug and/or formulation with the primary product packaging (e.g. containers, closures).

EUROPEAN MEDICINES AGENCY

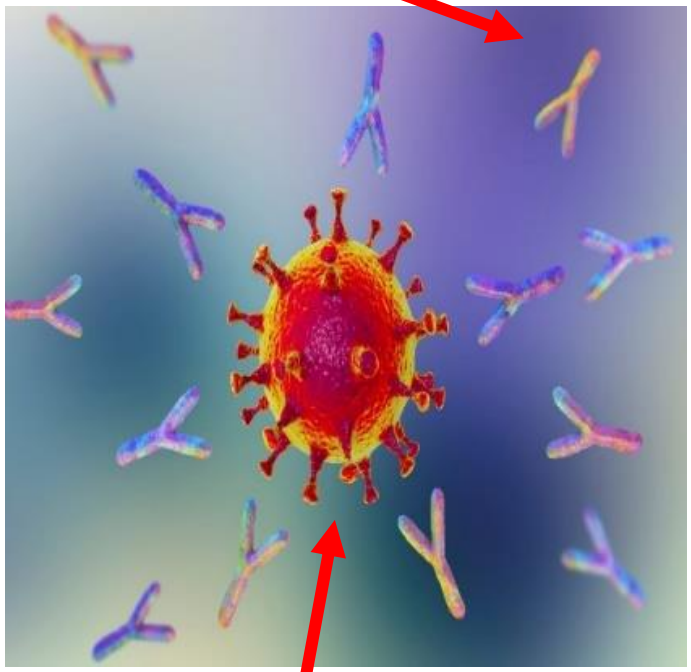
Guideline on Immunogenicity assessment of therapeutic proteins

18 May 2017
EMEA/CHMP/BMWP/14327/2006 Rev 1

Height of biopharmaceutical size and complexity

gene therapy viruses and genetically engineered cells

Protein (10 nm)



Virus (25 nm – 100 nm)

proteins + nucleic acids

Cell (10,000-100,000 nm)

~20,000 genes

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

4 of 4: Biosimilars are NOT Bio-Generics

Chemical Drug	Protein-Based Biopharmaceutical	Gene-Based Biopharmaceutical
• Generics drugs are 'equivalent' in quality to innovator chemical drugs • Bioequivalence study	• Biosimilars are 'highly similar' in quality to innovator biopharmaceuticals • Comprehensive CMC, Non-Clinical & Clinical Studies	• No biosimilars (yet)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Commission

Biosimilars in the EU

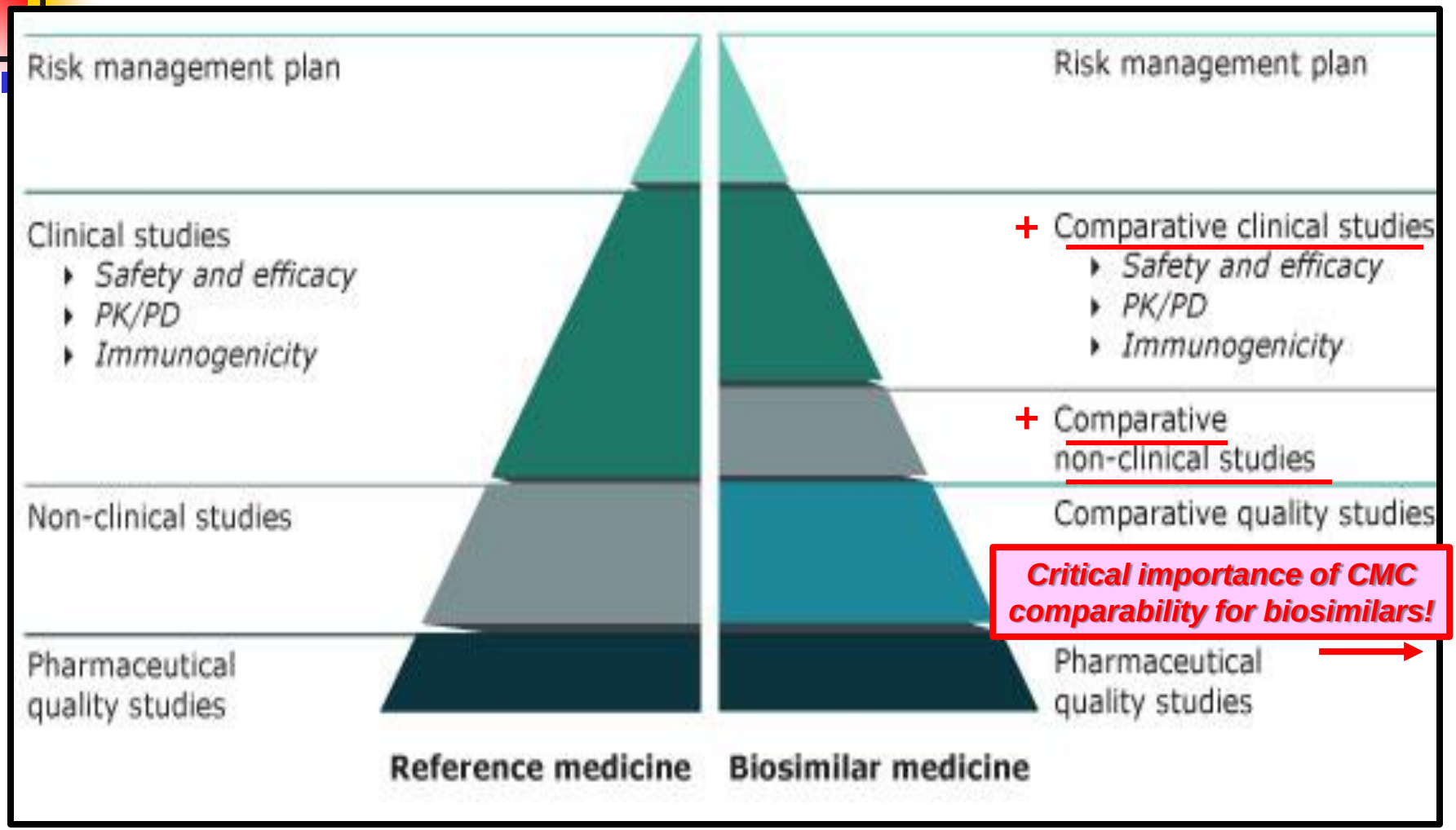
Information guide for healthcare professionals

Why biosimilars are not considered generic medicines

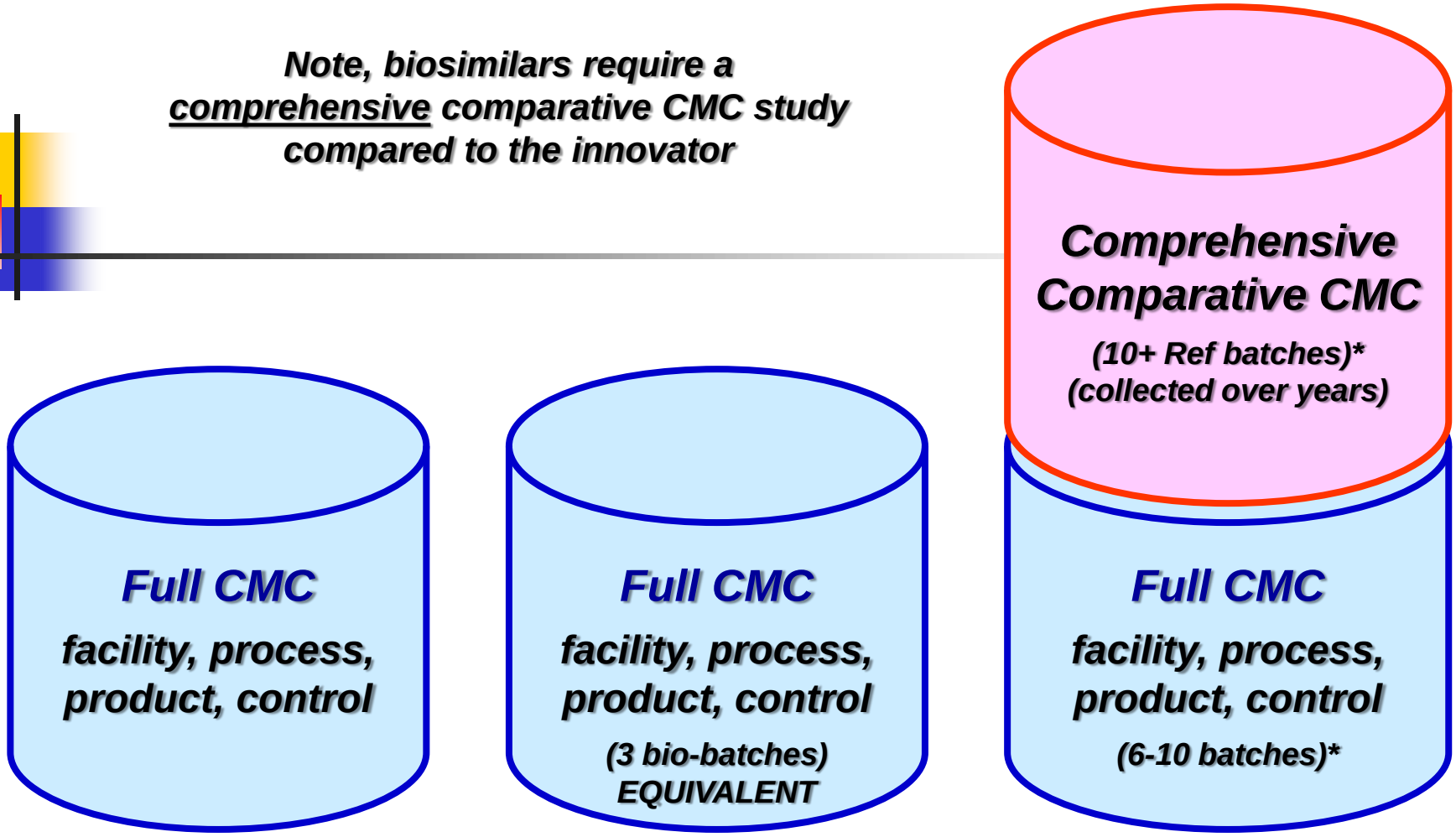
A biosimilar is not regarded as a generic of a biological medicine. This is mostly because the natural variability and more complex manufacturing of biological medicines do not allow an exact replication of the molecular microheterogeneity.

Consequently, more studies are needed for regulatory approval of biosimilars than for generics to ensure that minor differences do not affect safety or efficacy. Table 3 compares development and characteristics of generics and biosimilars.

"Highly similar" demonstrated by comprehensive analytical comparability, + comprehensive nonclinical + comprehensive clinical comparability studies



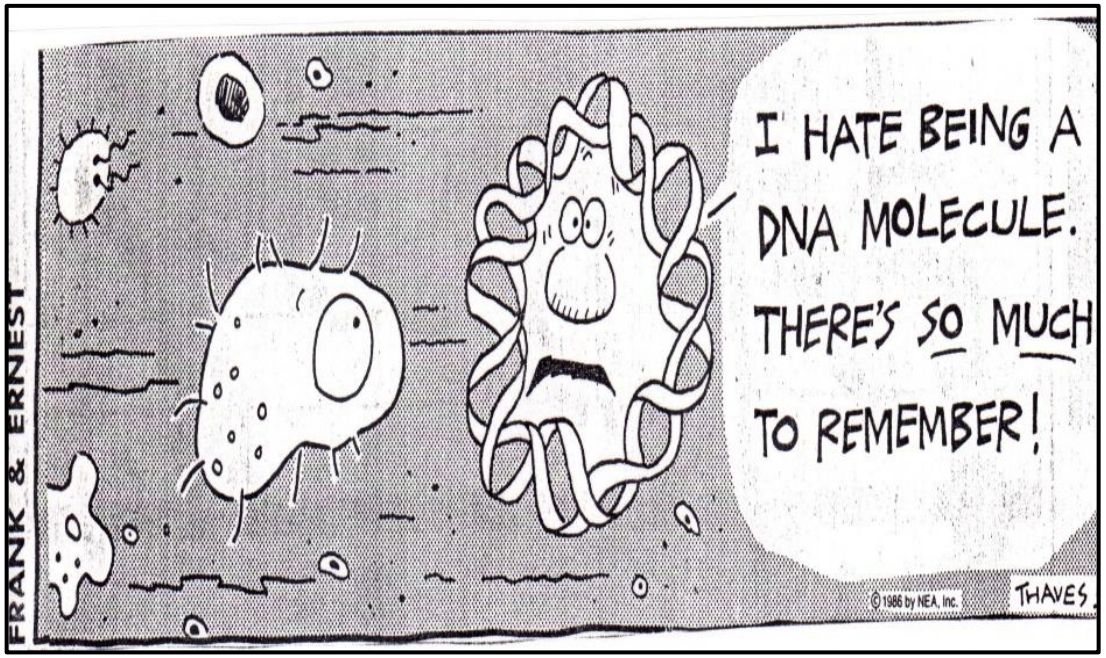
Note, biosimilars require a <u>comprehensive</u> comparative CMC study compared to the innovator



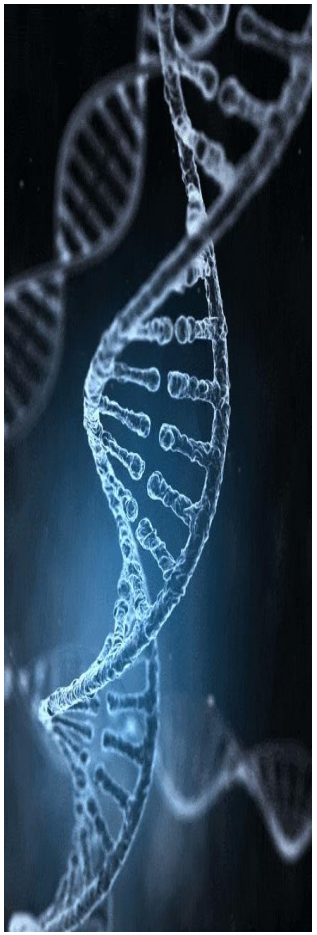
**FDA GfI Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations (2019)*

Summary of CMC Regulatory Compliance is Challenging for Biopharmaceuticals

- ✓ *An increasing diversity of biopharmaceuticals*
- ✓ *Regulatory authority systems are in place (FDA/EMA) to regulate these evolving manufacturing processes and products*
- ✓ *Biopharmaceuticals have different CMC regulatory compliance concerns compared to chemical drugs*



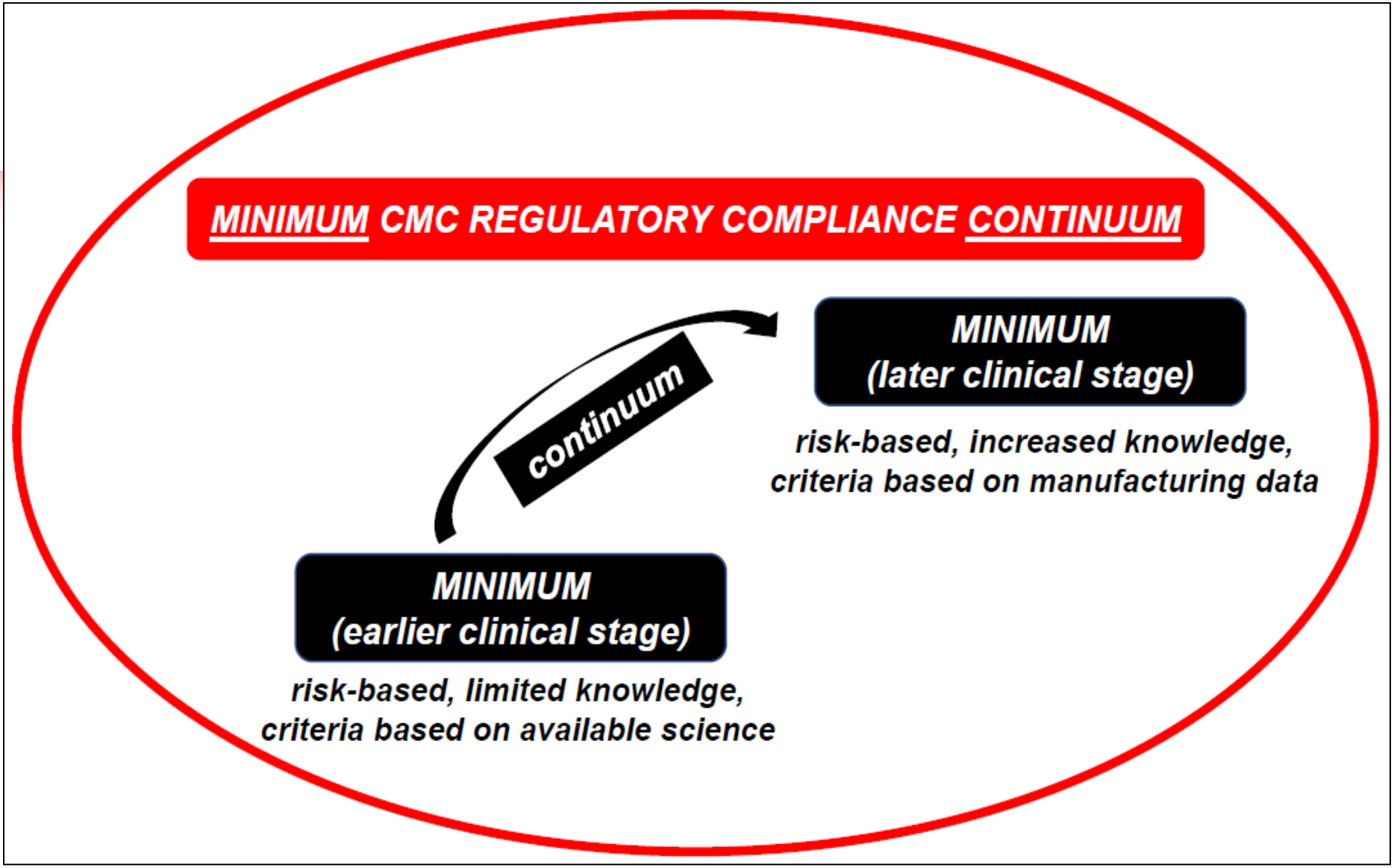
QUESTIONS??



Course Outline

2. Risk-Managed Biopharmaceutical CMC Regulatory Compliance Strategy

- *'MINIMUM CMC regulatory compliance CONTINUUM'*
- *Three (3) interactive CMC components protecting patients*
- *Regulatory authority recommended risk-based approach (QbD/QRM)*



A risk-based approach that is a lifesaver for biopharmaceuticals!

'MINIMUM CMC regulatory compliance CONTINUUM'

explained

"minimum" – "the least quantity assignable"

the lowest threshold of CMC regulatory compliance that must be achieved – cannot go below – at given stages of clinical development

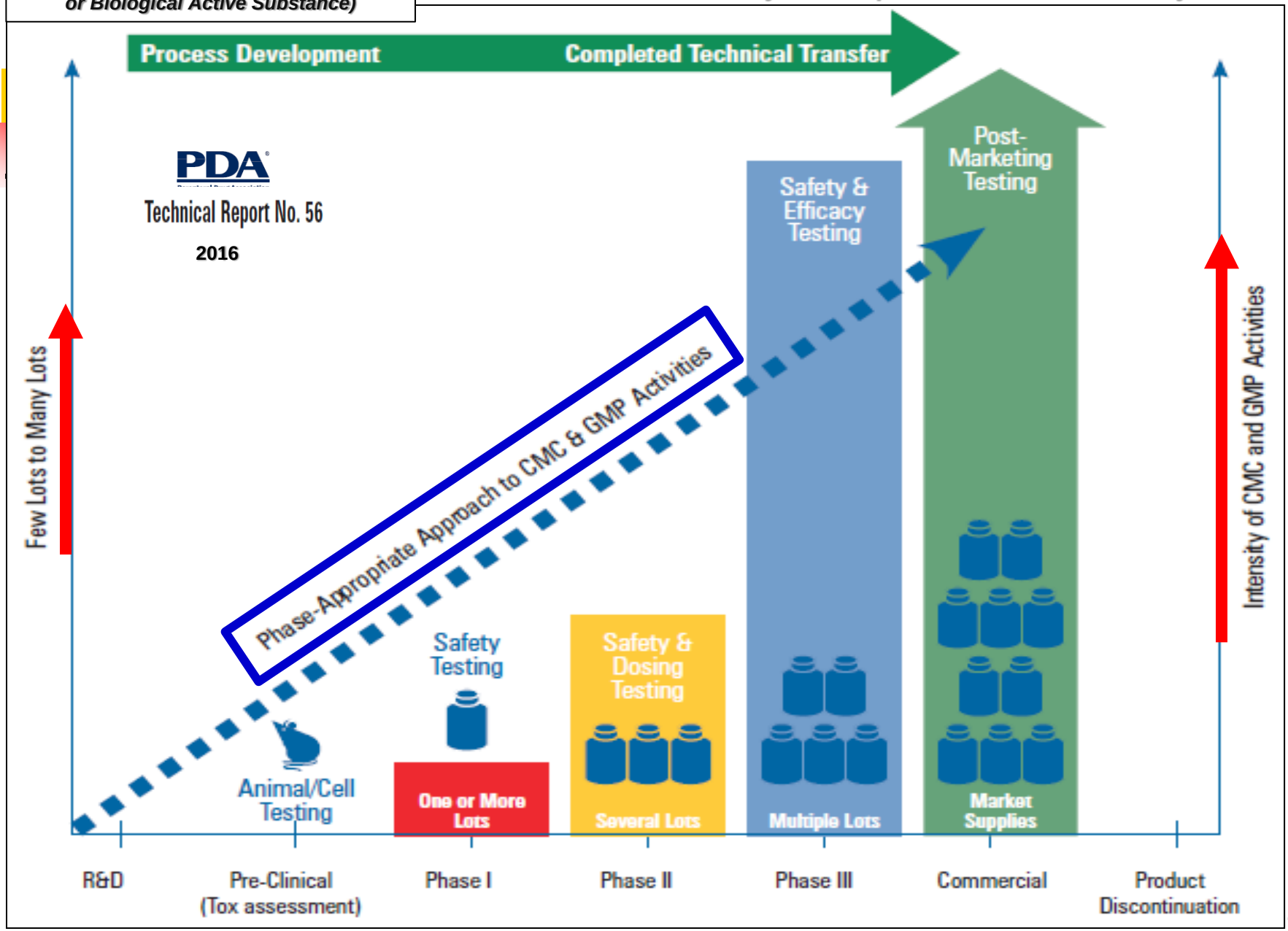
"continuum" – "a coherent whole characterized as a progression of values or elements varying by degrees"

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

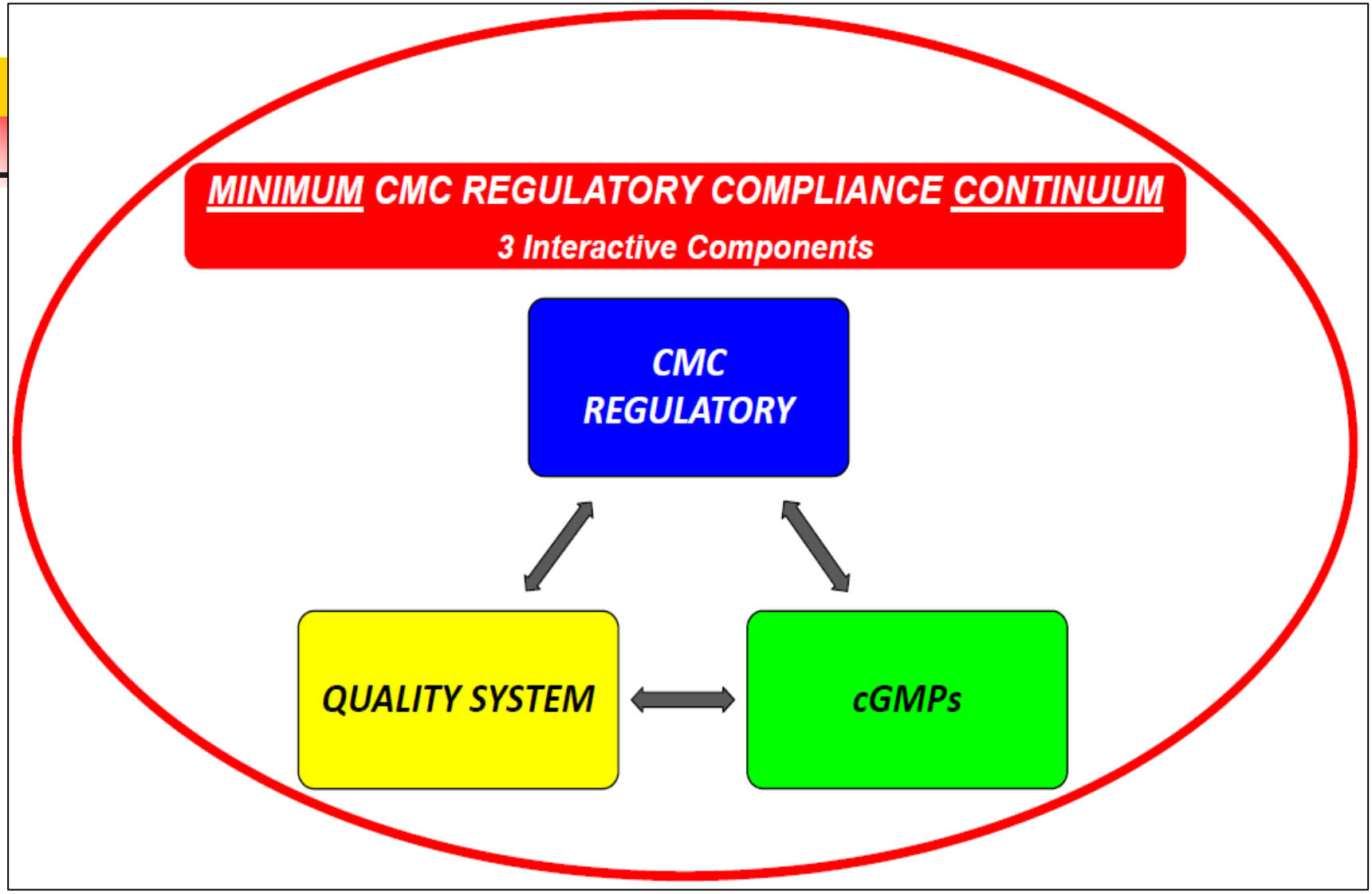
Application of Phase-Appropriate Quality System and cGMP to the Development of Therapeutic Protein Drug Substance (API or Biological Active Substance)

'minimum CMC regulatory compliance continuum'

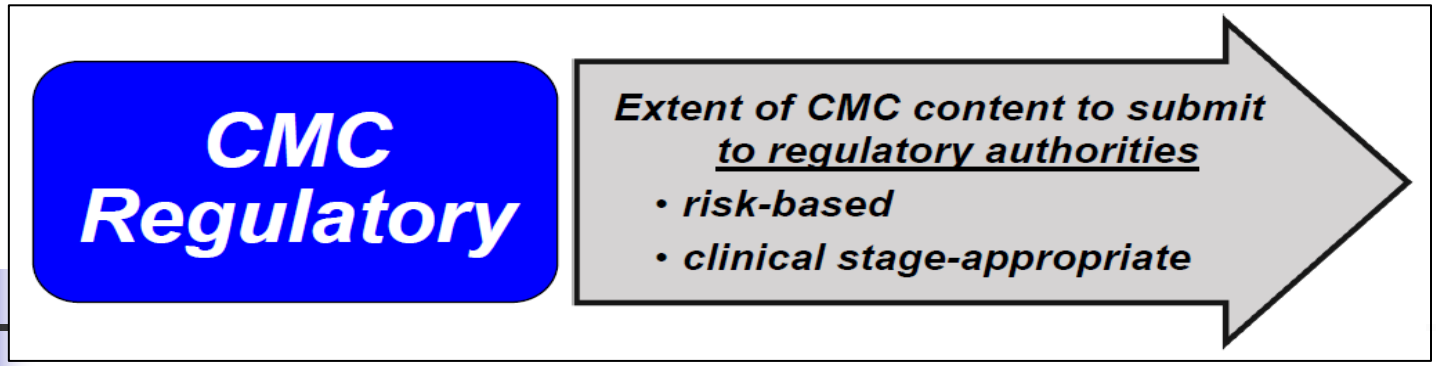
embraced by the biopharmaceutical industry!



as applied by the regulatory authorities!



each component is risk-based, clinical stage-appropriate, flexible



Basic CMC Regulatory information to be submitted to regulatory authorities

Drug Substance (DS, API)	Drug Product (DP)
Manufacturer & Sites of Manufacture	Manufacturer & Sites of Manufacture
Manufacturing Process Definition	Manufacturing Process Definition
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)	

ICH M4Q(R1)

EMA/FDA guidance on CMC Regulatory content to be included in submissions

recombinant proteins and monoclonal antibodies

EMA

- ***Guideline on Development, Production, Characterization and Specification for Monoclonal Antibodies and Related Products (2016)***
- ***Guideline on the Requirements for Quality Documentation Concerning Biological Investigational Drug Medicinal Products in Clinical Trials (2022)***

FDA

- ***Guidance for Industry: For the Submission of CMC Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody for In Vivo Use (2016)***
- ***Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (2017)***

gene therapy biopharmaceuticals

EMA

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

FDA

- ***Guidance for Industry: Chemistry, Manufacturing & Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) (2020)***

International Council for Harmonisation

ICH harmonisation for better health

CMC Regulatory content in submissions – consensus guidelines

(immensely helpful for decades)

USA/EU/Japan + UK/Brazil/China/8 other countries + 20 observing countries

"Q" CMC

(specific focus on recombinant proteins & mAbs)

- Q5A(R1) *Viral Safety Evaluation* [1999]
- Q5B *Analysis of the Expression Construct in Cells* [1995]
- Q5C *Stability Testing of Biotech Products* [1995]
- Q5D *Derivation and Characterization of Cell Substrates* [1997]
- Q5E *Comparability of Biotech Products* [2004]
- Q6B *Specs for Biotechnological/Biological Products* [1999]

ICH considered developing CMC Regulatory content guidelines for gene-based biopharmaceuticals – but abandoned in 2011 due to limited resources

CMC REGULATORY

Regulatory authorities concur, that for CMC Regulatory, the extent of CMC content to be included in the submissions needs to be risk-based, clinical stage-appropriate, and flexible!

(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 recognizes that modifications to the method of preparation of the new drug substance and dosage form and changes in the dosage form itself are likely as the investigation progresses. Therefore, the emphasis in an initial Phase 1 submission should generally be placed on the identification and control of the raw materials and the new drug substance. Final specifications for the drug substance and drug product are not expected until the end of the investigational process.

(iii) As drug development proceeds and as the scale or production is changed from the pilot-scale production appropriate for the limited initial clinical investigations to the larger-scale production needed for expanded clinical trials, the sponsor should submit information amendments to supplement the initial information submitted on the chemistry, manufacturing, and control processes with information appropriate to the expanded scope of the investigation.

FDA 21 CFR 312.23

Classroom Work Problem

'minimum CMC regulatory compliance continuum'

applied to CMC Regulatory content

REFERENCE 1

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

Read: Where in this EMA guideline are risk-based, clinical stage-appropriate or flexibility phrases applied to the level of CMC Regulatory content to be submitted in the IMPD?

Examples: 'limited data', inherently preliminary' , 'as knowledge and experience increases' , etc.

read & fill-in table

TEAM DISCUSS

Classroom Work Problem

(20 minutes to read/fill-in)
(10 minutes to discuss)

REFERENCE 1

'minimum CMC regulatory compliance continuum'
CMC Regulatory

EMA Guideline IMPD CMC Section		*Risk-Based, Clinical Stage-Appropriate, Flexibility CMC Regulatory content to be submitted in IMPD*
S.2.2	*Description of Manufacturing Process & Process Controls*	
S.2.4	*Control of Critical Steps*	
S.2.5	*Process Validation*	
S.2.6	*Manufacturing Process Development*	
S.4.1	*Specifications*	
S.4.5	*Justification of Specification*	
S.7	*Stability*	
P.2	*Pharmaceutical Development*	

Illustration: 'minimum CMC regulatory compliance continuum'

CMC Regulatory: risk-based, flexibility assignment of specifications

Early Stage Clinical Development → **Late 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.*

FDA U.S. FOOD & DRUG ADMINISTRATION

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

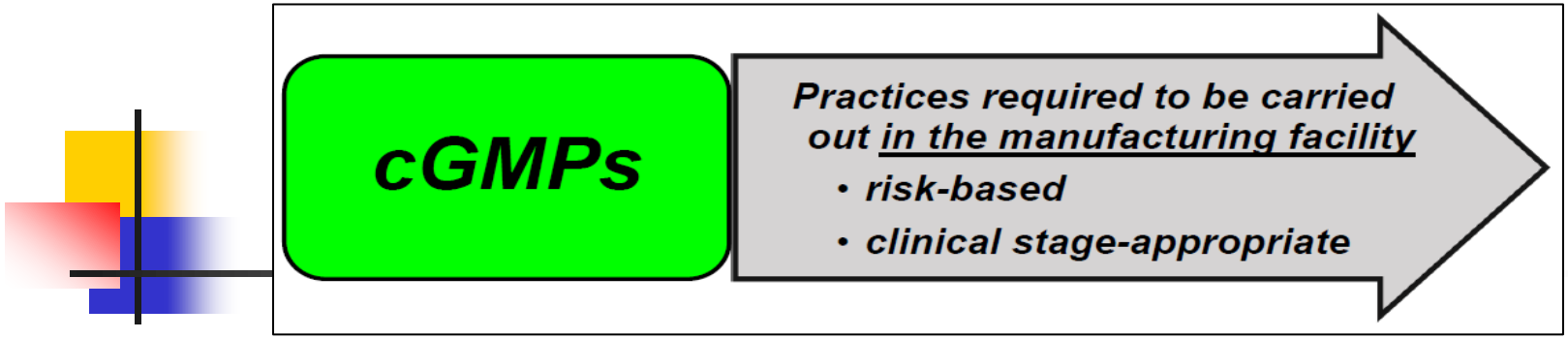
Critical Quality Attribute	Early Stage Clinical Specification	Justification
Purity by CE-SDS	≥ 95%	'Industry Standard'
Monomer by SEC-HPLC	≥ 95%	'Industry Standard'
Endotoxin by LAL	NMT 5 EU/ patient kg/hour	USP Safety Limit
Residual Host Cellular DNA	NMT 10 ng/dose	WHO Safety Limit
Residual Host Cell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

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 CE-SDS	Based on statistical analysis of manufactured batches
Monomer by SEC-HPLC	
Endotoxin by LAL	
Residual Host Cellular DNA	
Residual Host Cell Proteins (HCPs)	



GMPs are not optional, but required from First-in-Human (FIH) onwards!

V. RECOMMENDED CGMP FOR PHASE 1 INVESTIGATIONAL DRUGS

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.

FDA U.S. FOOD & DRUG ADMINISTRATION

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

cGMPs

Regulatory authorities concur, that for cGMPs, the requirements need to be risk-based, clinical stage-appropriate and flexible!

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.

It is important to note that CGMPs are minimum requirements. Many pharmaceutical manufacturers are already implementing comprehensive, modern quality systems and risk management approaches that exceed these minimum standards.

FDA U.S. FOOD & DRUG ADMINISTRATION

Facts About the Current Good Manufacturing Practices

FDA website

FDA general guidance on flexible cGMPs during early clinical stage development

We recommend the following steps to establish the appropriate manufacturing environment for phase 1 investigational drugs:

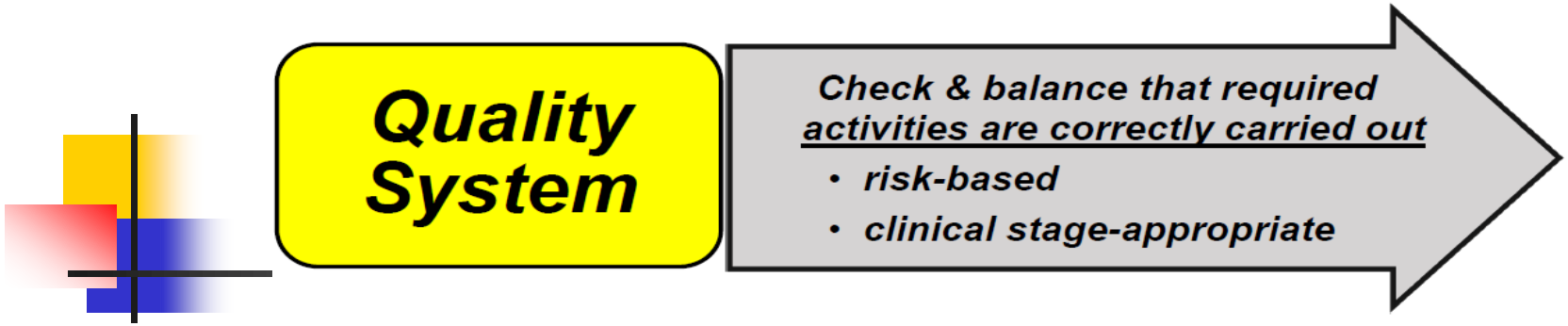
- A comprehensive and systematic evaluation of the manufacturing setting (i.e., product environment, equipment, process, personnel, materials) to identify potential hazards
- Appropriate actions prior to and during manufacturing to eliminate or mitigate potential hazards to safeguard the quality of the phase 1 investigational drug

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). For example, some academic institutions have developed shared manufacturing and testing facilities that can be used by institutional sponsors.

FDA U.S. FOOD & DRUG ADMINISTRATION

Guidance for Industry
CGMP for Phase 1 Investigational Drugs July 2008



- ***'Quality System' refers to 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***
- ***'Quality System' is to ensure that the required CMC Regulatory commitments and the required cGMPs are appropriately and adequately carried out by the manufacturing and quality control staff***
- ***'Quality System' is to ensure that data obtained from the early phases of a clinical trial can be used in subsequent phases of clinical development***

Responsibilities under the Quality Unit

Every manufacturer should establish a written plan that describes the role of and responsibilities for QC functions.[8] For example, a written plan should provide, at a minimum, for the following functions.

- Responsibility for examining the various materials used in the manufacture of a phase 1 investigational drug (e.g., containers, closures, in-process materials, raw materials, packaging materials, and labeling) to ensure that they are appropriate and meet defined, relevant quality standards
- Responsibility for review and approval of manufacturing procedures, testing procedures, and acceptance criteria
- Responsibility for releasing or rejecting each batch of phase 1 investigational drug based on a cumulative review of completed manufacturing records and other relevant information (e.g., procedures were followed, product tests performed appropriately, acceptance criteria met)
- Responsibility for investigating unexpected results or errors that occur during manufacturing or from complaints received and initiation of corrective action, if appropriate.

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.

check and balance

Quality System

Major pressure point for the Quality Unit today …

(short staffing, replacement and staff)

Due to the challenge of the biopharmaceutical manufacturing processes and the complexity of the products, staff training takes on an extremely important role. It is required that there be an adequate number of personnel with appropriate qualifications and appropriate practical experience relevant to the intended operations. The Quality Unit needs to ensure that such training is taking place. There are three main areas of training required:

- ***All personnel should receive training on the principles of GMP that affect them and receive initial and periodic training relevant to their tasks***
- ***There should be appropriate (and periodic) training in the requirements specific to the manufacturing, testing, and traceability of the product***
- ***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***

Because training is time-intensive and expensive, senior management must be supportive of this requirement.

Classroom Work Problem

REFERENCE 1

'minimum CMC regulatory compliance continuum'

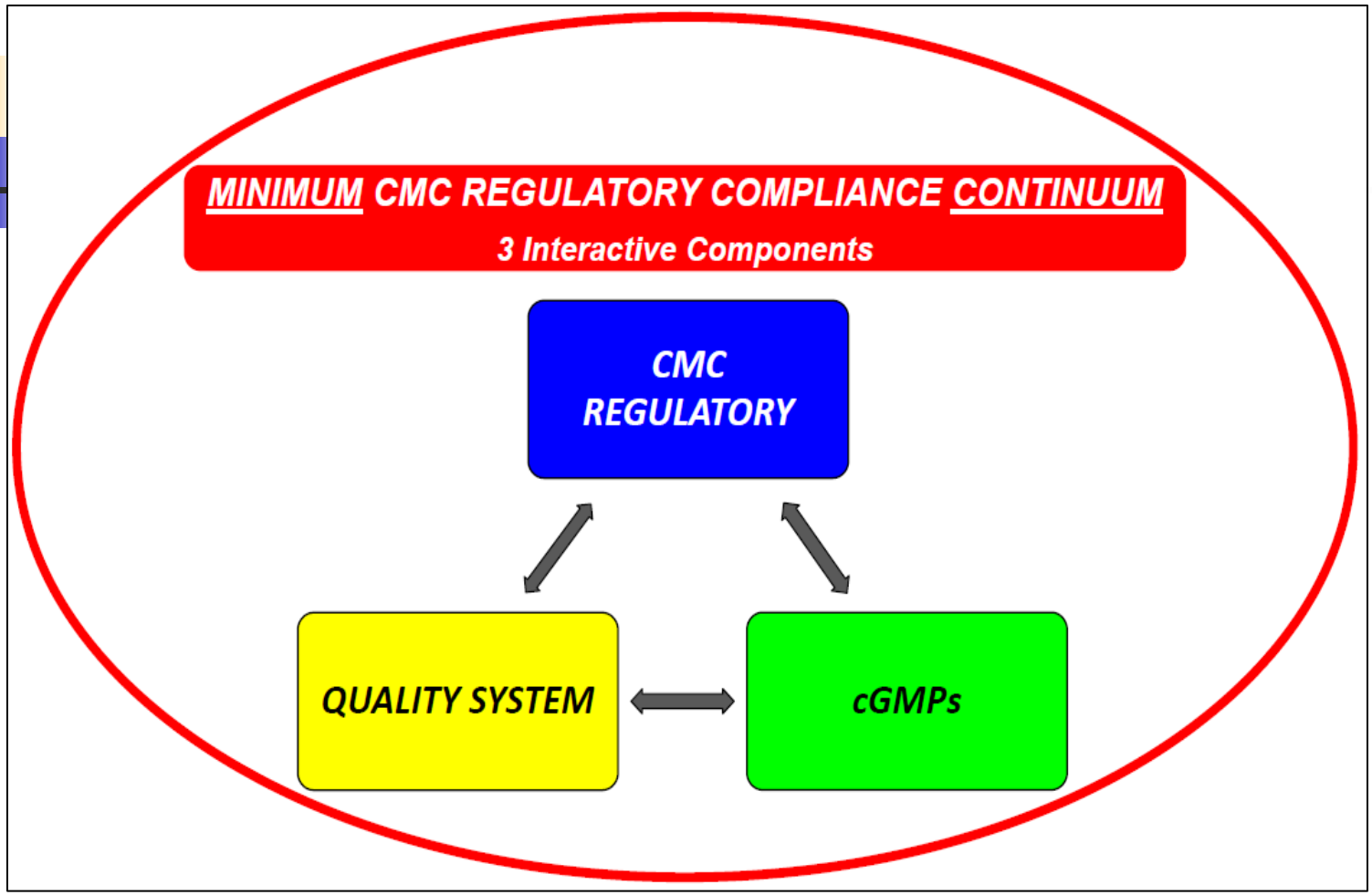
ACKNOWLEDGED by regulatory authorities

IMPD CMC Section		EMA CMC Guideline for Biologic IMPS Risk-Based CMC Content Required to Be Submitted
S.2.2	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.2.4	Control of Critical Steps	Tests and acceptance criteria for the control of critical steps in the manufacturing process should be provided…. It is acknowledged that due to limited data at an early stage of development (phase I/II) complete information may not be available.
S.2.5	Process Validation	Process validation data should be collected throughout development, although they are not required to be submitted in the IMPD.
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.

more

IMPD CMC Section		EMA CMC Guideline for Biologic IMPS Risk-Based CMC Content Required to Be Submitted
S.4.1	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.4.5	Justification of Specification	It is acknowledged that during clinical development, the acceptance criteria may be wider and may not reflect process capability.
S.7	Stability	Progressive requirements will need to be applied to reflect the amount of available data and emerging knowledge about the stability of the active substance during the different phases of clinical development. By phase III the applicant should have a comprehensive understanding of the stability profile of the active substance.
P.2	Pharmaceutical Development	For early development there may be only limited information to include in this section

risk-based, clinical stage-appropriate, flexible



Critical role of 'senior management' in making this effective!

2. MANAGEMENT RESPONSIBILITY

Leadership is essential to establish and maintain a company-wide commitment to quality and for the performance of the pharmaceutical quality system.

2.1 Management Commitment

(a) *Senior management* has the ultimate responsibility to ensure an effective pharmaceutical quality system is in place to achieve the *quality objectives,* and that roles, responsibilities, and authorities are defined, communicated and implemented throughout the company.

(b) Management should:

(1) Participate in the design, implementation, monitoring and maintenance of an effective pharmaceutical quality system;

(2) Demonstrate strong and visible support for the pharmaceutical quality system and ensure its implementation throughout their organisation;

(3) Ensure a timely and effective communication and escalation process exists to raise quality issues to the appropriate levels of management;

(4) Define individual and collective roles, responsibilities, authorities and inter-relationships of all organisational units related to the pharmaceutical quality system. Ensure these interactions are communicated and understood at all levels of the organisation. An independent quality unit/structure with authority to fulfil certain pharmaceutical quality system responsibilities is required by regional regulations;

(5) Conduct management reviews of process performance and product quality and of the pharmaceutical quality system;

(6) Advocate continual improvement;

(7) Commit appropriate resources.

Senior management sets the level of corporate risk tolerance across the minimum CMC regulatory compliance continuum!

(risk levels in between)

risk adverse

'plodders'
slow and thorough
unexpected problems not tolerated

While slow is good, competition is not waiting around!

risk tolerant

'wild west'
correct problems on the fly
press CMC team to go forward

Sometimes moving too fast leads to overlooking risk warning signs!

Corporate Risk Acceptance Level

What message is senior management sending to the CMC Team?

'must stay on schedule – no excuses'
'don't worry, that can't happen to us'
'just find a way to deal with it – we can fix later'

Senior management controls the resources to fund the activities across the minimum CMC regulatory compliance continuum!

Case Example: Consequence of inadequate senior management leadership over their CMC regulatory compliance strategy

Genzyme Temporarily Interrupts Production at Allston Plant

Senior management press release

Release Date:
Tuesday, June 16, 2009 8:30 am EDT

(Because pediatric orphan drug recombinant protein enzymes shortages resulted, Genzyme had to go public with contamination)

Terms:

Dateline City:
CAMBRIDGE, Mass.

"only a minor delay"

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Genzyme Corporation (NASDAQ: GENZ) today announced that it has detected a virus that impairs cell growth in one of six bioreactors at its Allston Landing manufacturing facility. The company has decided to temporarily interrupt bulk production at the plant to sanitize the facility. Genzyme is collaborating with regulatory agencies as it works to resume production. The company expects the plant to be fully operational by the end of July.

since 2003

The virus strain, Vesivirus 2117, has not been shown to cause human infection. It is known to interfere with the growth of CHO cells used to produce biologic drugs and was likely introduced through a nutrient used in the manufacturing process. Genzyme has now confirmed that this virus was the cause of declines in cell productivity at its Allston and Geel facilities in two previous instances in 2008, which were subsequently fully addressed. The company was able to detect the virus in this case using a highly specific assay it developed after standard tests were unable to identify the cause of the previous productivity declines. Genzyme is adding steps to increase the robustness of its raw materials screening and viral removal processes.

If this was fully addressed in 2008, why did it happen again in 2009?

Genzyme Press Release Sept 2009 – 3 months later!

- This effort required replacement of many fixtures at Allston Landing. As a result of this effort, the entire U.S. inventory of sanitary ball valves was depleted. The inventory of food grade ceiling tile caulk in the northeastern US was also depleted. The factory that supplied T-tube installation for this effort was required to run three shifts to meet demand.
- Five miles of insulation, one mile of copper tubing and fittings, and 660 feet of sanitary tubing and fittings were sanitized or replaced. Several key vessels were replaced during this period also.
- More than 700 fluorescent light lenses were removed and replaced. In addition, approximately 3,253 valve diaphragms, 36,625 gaskets, 267 HEPA filters, 233 ball valves and 358 rebuild kits were used.

- ***First shipment of newly manufactured orphan recombinant proteins ship – January 2010 (6 month delay)***
- ***Consent decree signed with FDA – May 2010*** ***Sanofi buys Genzyme – February 2011***

sanofi

Excellent reference on prospectively developing a virus contamination response plan

Kiss, R., Dehghani, H., et.al., *Virus Contamination in Biomanufacturing: Risk Mitigation, Preparedness, and Response*; PDA Technical Report 83 (2019)

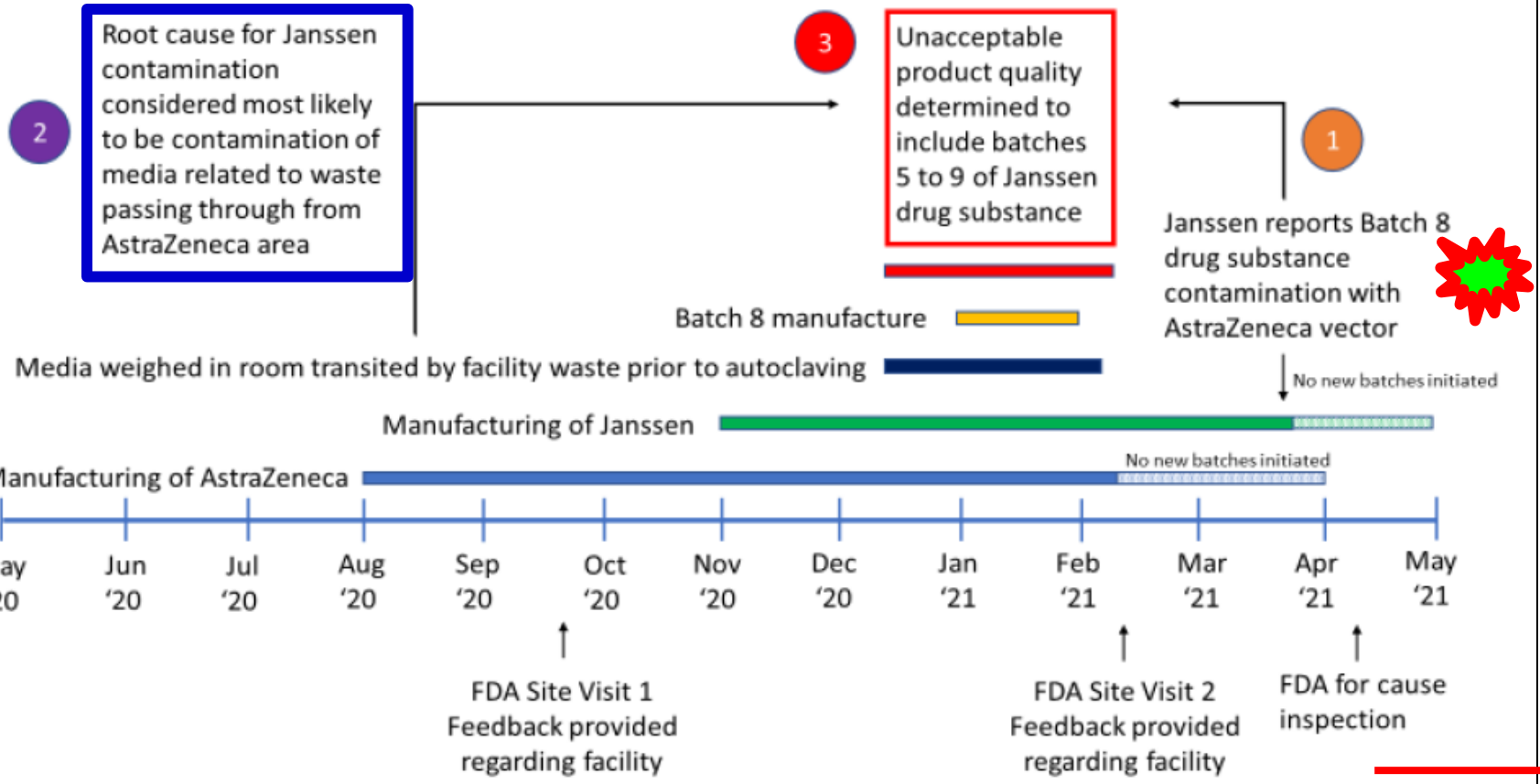
Case Example: Consequence of inadequate senior management leadership over their corporate CMC regulatory compliance strategy

Emergent BioSolutions

BDS manufacturer for 2 genetic virus vaccines (COVID-19)

J&J – human adenovirus
AZ – chimpanzee adenovirus

Figure 1: Timeline Related to Batches GMP 5 through 9



HOUSE COMMITTEE ON
OVERSIGHT AND REFORM
CHAIRWOMAN **CAROLYN B. MALONEY**

Committees' Report on Emergent BioSolutions Uncovers Extensive Vaccine Manufacturing Failures, Deliberate Efforts to Hide Deficiencies

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." Internally, one Emergent executive posed questions on the state of the Bayview facility, asking, "When will all these trash going to be out of here? Trash are piling up." During a staff briefing, FDA acknowledged, "Clearly, in retrospect, they hired a lot of individuals not as familiar with vaccine manufacturing, that did not have adequate training to do so."

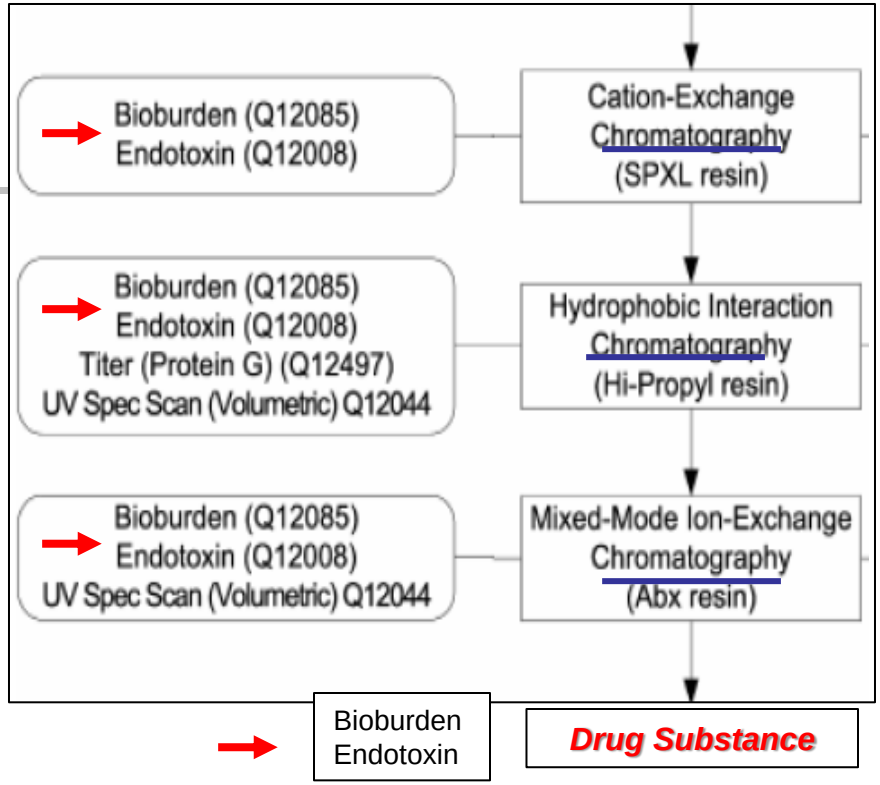
Nearly 400 million doses of coronavirus vaccines have been destroyed as a result of Emergent's failure to meet or maintain quality standards.[1] The Committees' investigation revealed that due to poor quality control approximately 240 million vaccine doses had to be destroyed in late 2020 and early 2021—

But it is just not Senior Management, it is also the leadership of the CMC Teams over the CMC regulatory compliance strategy!

Question Raised by 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?



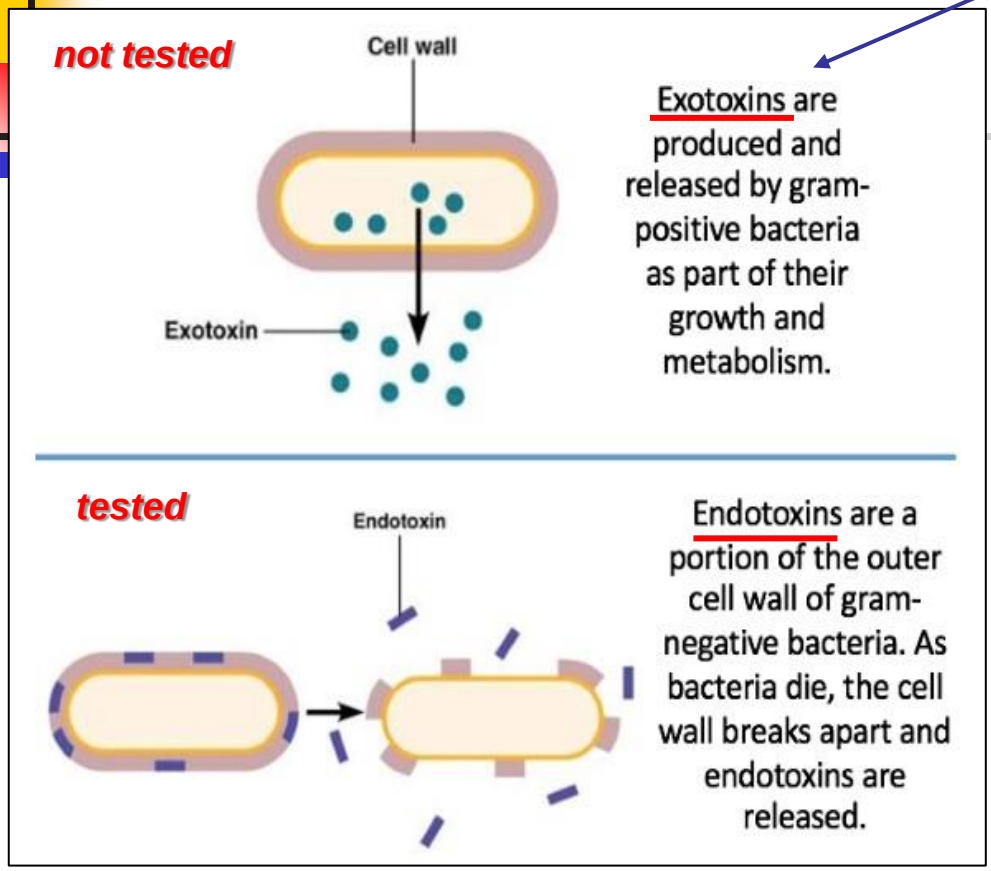
Risk Assessment (QA/ QC/ Mfg/ Dev/ Reg Affairs):

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

Perception: why do regulatory authorities insist on the testing?

What possible problem/ patient harm could occur?

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!

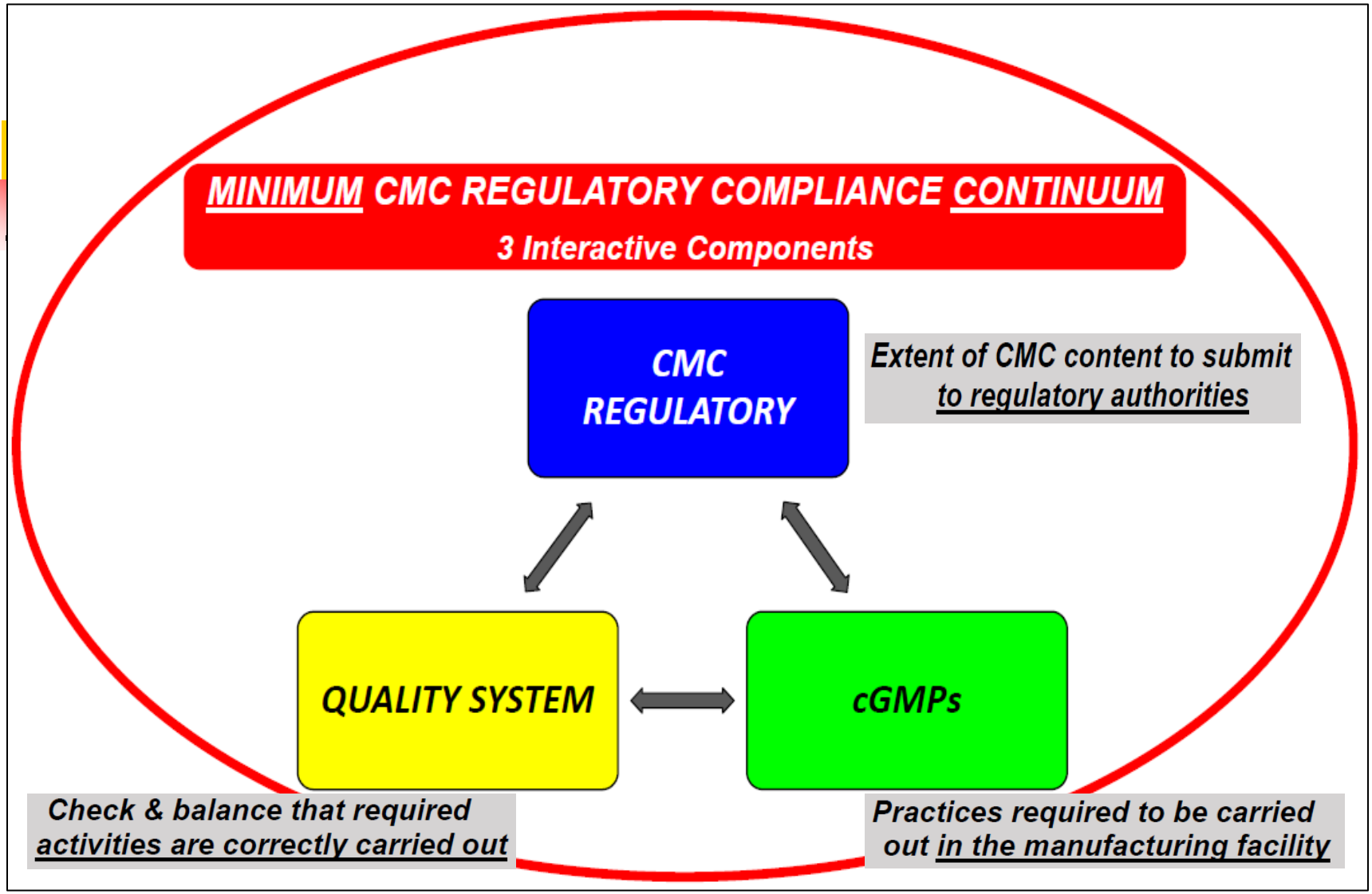
Might we miss a high level of excreted exotoxins at an in-process purification step if not bioburden/endotoxin tested?

(patient safety)

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!



risk-based, clinical stage-appropriate, flexible

QUESTIONS?

Strategic risk-based approach highly recommended by the regulatory authorities for the control over biopharmaceuticals

Quality by Design (QbD) elements

Quality Risk Management (QRM) tools for prioritization

(a short practical presentation)

Two Strategic Risk-Based Control Guidelines

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

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 are the Process Development and Analytical Development groups in the development of the biopharmaceutical manufacturing process and control of the biopharmaceutical product?

development genetics → MCB
cell culture optimization → cell productivity
purification process design → impurity profile
characterization of the product

Does Development fully understand that what they do can impact successful entry into clinical development and/or successful market approval?

ICH Q9 Quality Risk Management (QRM) 2006

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.

ICH Q9 (R1) at step 2 (2022)

QRM	***QRM***
project management tools to mitigate/control risks	***statistical analysis tools to identify/prioritize risks***
Risk Ranking and Filtering (RRF)	***Control Charts (Shewhart)***
Failure Mode Effects Analysis (FMEA)	***Process Capability Analysis (Cpk)***
Preliminary Hazard Analysis (PHA)	***Design of Experiments (DOE)***

QbD/QRM is the language of communication with regulatory authorities

not mandatory, but highly recommended ('expected')

Process evaluation involved the initial identification of CQAs through an evaluation of the Quality Target Product Profile (QTPP) and CQAs of the finished product. This was followed by a preliminary hazard analysis and a risk assessment to identify areas of focus and potential CPPs with impact on CQAs, respectively. Potential CPPs, classified as high risk, were evaluated through process evaluation studies to determine if they had a critical impact on the relevant CQAs. The control strategy is considered acceptable.

QTPP
CQA
CPP
CS

The formulation development was guided by the QTPP and based on prior knowledge regarding the stabilisation of lyophilised monoclonal antibodies and antibody-drug conjugate products. CQAs were identified based on the QTPP. The rationale for the identified CQAs has been provided. The rationale for assigning the parameters as CQAs is based on the influence of the individual CQA on safety and/or efficacy and stability of the finished product.

QTPP
CQA

Enhertu
trastuzumab deruxtecan
ADC

Daiichi Sankyo

Assessment report

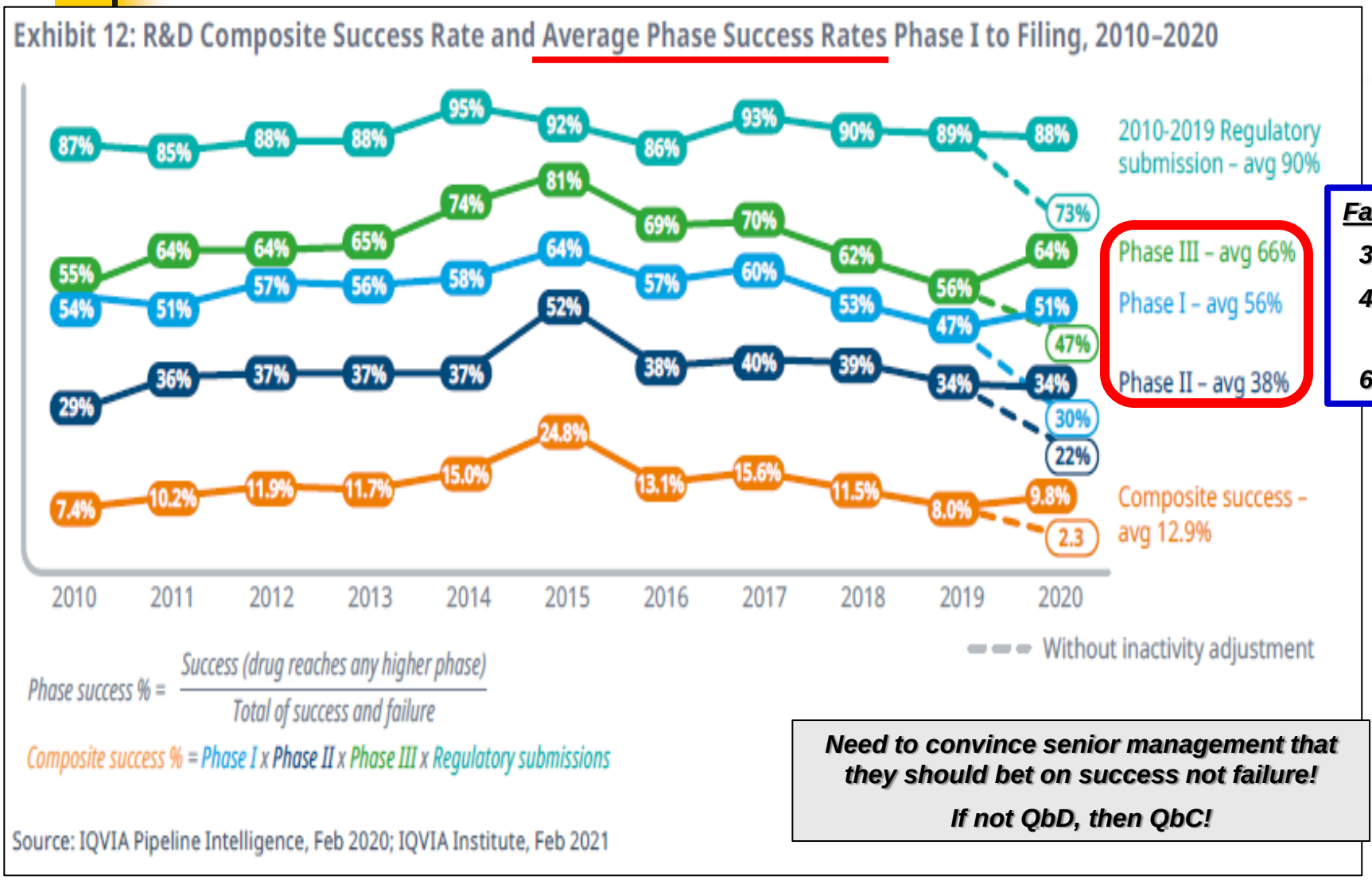
EUROPEAN MEDICINES AGENCY

10 December 2020
EMA/2446/2021

(why reluctance)

Senior management reluctance to fund QbD/QRM

The Development budget for obtaining this scientific understanding needs to be funded early in clinical development, when clinical success is unknown



Failure
34%
44%
62%

Need to convince senior management that they should bet on success not failure!

If not QbD, then QbC!

QTPP • Quality Target Product Profile

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)

(changeable by executive management)

Quality Target Product Profile (QTPP):

A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product.

(CMC direction on what needs to be done to achieve the TPP for the company)

The QTPP is the target to be shared across by CMC team members

(Development, QC, QA, Manufacturing, CMC RA, etc.)

QTPP Example

N-mAb

GENERAL PROPERTIES	
Indication	N-mAb is a humanized IgG1 antibody intended as a treatment for indolent non-Hodgkin's Lymphoma (NHL) in an adult population only.
Safety	Only infusion- or injection-related side effects
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. Although N-mAb was designed so that the B cell killing is primarily through ADCC activity, involvement of CDC activity cannot be completely ruled out.
Relevant Post-Translational Modifications, Impurities, & Degradants (see details below)	Glycosylation/Galactosylation: pCQA – Efficacy Glycosylation/Fucosylation: pCQA – Efficacy (ADCC) Glycosylation/High Mannose: pCQA – Efficacy (PK/PD) Deamidation at Asn325: pCQA – Efficacy (ADCC) HMW species: pCQA - Safety (Immunogenicity) Host Cell Protein (HCP): pCQA - Safety (Immunogenicity)

TPP

	Must Have at Launch	Nice to Have for Life Cycle Extension
Route of Administration	IV administration at a weekly dose of 2 mg/kg	SC injection at a weekly dose of 150 mg
Dosage Form	Sterile liquid formulation in a single-use vial containing 1 mL	Sterile liquid formulation in a pre-filled single-use syringe containing 1 mL
Dosage Strength	75 mg/mL	150 mg/mL
Stability	2-year stability at 5 °C 14-day stability at 25 °C	3-year stability at 5 °C 30-day stability at 25 °C

ADCC Antibody-dependent cell-mediated cytotoxicity

CDC Complement-dependent cytotoxicity

MOA Mechanism of action

What does this communicate to the CMC team on what they have to accomplish?

The QTPP – a project management tool – to guide the direction of development

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

Case Example

EPAR

Jemperli dostarlimab GlaxoSmithKline

25 February 2021
EMA/176464/2021

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.

The development of finished product manufacturing process started with the early phase clinical presentation, manufactured at WuXi Biologics (WuXi) in China. For the late phase clinical trials and commercial presentation, a higher protein content per vial was targeted (50 mg/mL dostarlimab, with 10.0 mL delivered volume), with no change in product formulation. In addition, the stored conditions were changed from -40ºC to -80ºC. The comparability of the two storage conditions was demonstrated by stability studies.

CQA • Critical Quality Attributes

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

impact on patient safety ↕ ***(changeable as scientific understanding about the product increases)***

ICH Q8(R2)

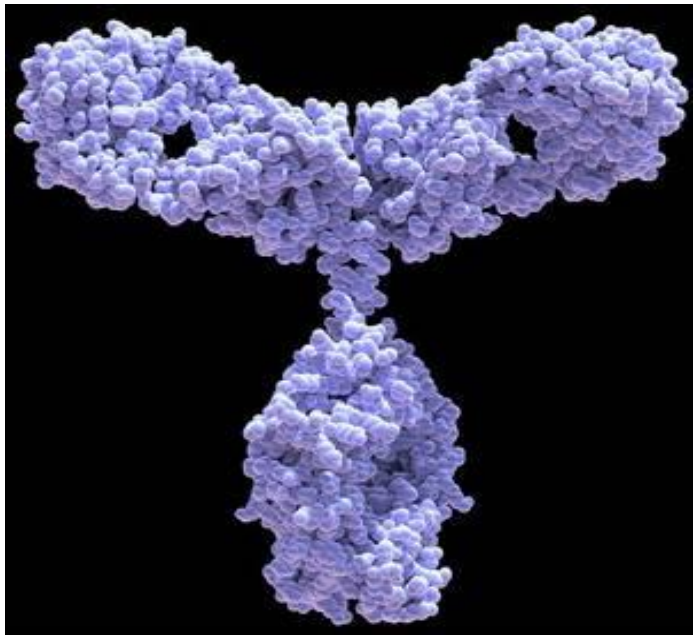
Critical Quality Attribute (CQA):

A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

A CQA forces the focus onto those quality attributes, properties or characteristics of the product that are most important (i.e., those that are related to patient safety)!

3 Step Process: QA → CQA

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



Monoclonal Antibody

List all quality attributes, characteristics, properties of the biopharmaceutical

30+

Quality Attributes (QAs) of Biopharmaceuticals		
PHYSIOCHEMICAL PROPERTIES	**PRIMARY STRUCTURE**	**HIGHER ORDER STRUCTURES (HOS)**
Intact Molecular Mass	Amino Acid Primary Structure	Secondary Structure
Isoelectric Point	C-Terminal Variants	Tertiary Structure
Molecular Weight Profile	N-Terminal Variants	Quaternary Structure
Molecular Size Profile	Internal AA Sequence Variants	Thermodynamic Properties
Molecular Charge Profile	Disulfide Bridges	Aggregation/Particles
POST-TRANSLATIONAL MODIFICATIONS		**IMPURITIES**
Amino Acids	**Carbohydrates**	**Process-Related**
Oxidation (Met)	N-Glycosylation Site(s)	Host Cellular DNA
Deamidation (Asn)	Glycosylation Site Occupancy	Host Cell Proteins (HCP)
Isomerization	N-Glycan Profile	Cell Culture Media Residuals
Disulfide Scrambling	Galactosylation Profile	Buffer/Surfactant Residuals
Glycation	Sialylated Glycans	Leachables (e.g., Protein A)
FUNCTIONAL ACTIVITY(IES) (OBLIGATORY CQAs)		
Biological Activities		**Immunochemical Activities**
Potency (typically cell-based bioassay)		Binding to specific receptor(s)

Quality Attributes (QAs) of Biopharmaceuticals	
COMPENDIAL REQUIREMENTS (OBLIGATORY CQAs)	
GENERAL	**ADVENTITIOUS AGENT SAFETY**
Visual Appearance (USP) (Physical State, Color, Clarity) Appearance (EP) (Degree of Coloration, and Opalescence)	Absence of Adventitious Virus Absence of Adventitious Mycoplasma
Protein Content/Concentration	Bioburden Control (Drug Substance) Sterility (Injectable Drug Product)
Extractable Volume	Bacterial Endotoxin
Osmolality	**PATIENT SAFETY**
pH	Particulate Matter
Residual Moisture (if lyophilized) Reconstitution Time (if lyophilized)	

Note, obligatory CQAs do not need any risk assessment, all other QAs need a criticality risk assessment

3 Step Process: QA → CQA

Step 2 of 3: Rank ALL QAs for 'Criticality'

Monoclonal Antibody ***30+ Quality Attributes (QAs)***

- ***Eliminate QAs that are not relevant***
  - ***e.g., glycosylation (if mAb Fab fragment)***
- ***From scientific experience/literature, some QAs can be deemed Non-Critical?***
  - ***C-Terminal Lysine Truncation***
- ***ICH Q9 – Apply Risk Management Tools for Ranking***
  - ***Risk Ranking & Filtering (RRF): Impact x Uncertainty***
  - ***Failure Modes Effect Analysis (FMEA): Occurrence x Severity x Detection***

Two Most Common Tools Risk Assessment Tools

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

  RISK SCORE = Impact Risk level x Uncertainty Risk level

  Impact Risk: 1 → n highest level (n can be 3, 5, 10 or …)

  Uncertainty Risk: 1 → n highest level (n can be 3, 5, 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

With Risk Management Tools – always best to start easy!

RRF

n = 3

Keep it simple!

Risk Ranking & Filtering (RRF) Example

Risk Level	Impact (Severity) Risk
1 Low	No patient impact
2 Medium	Minimal, but manageable, patient impact
3 High	Significant to catastrophic patient impact

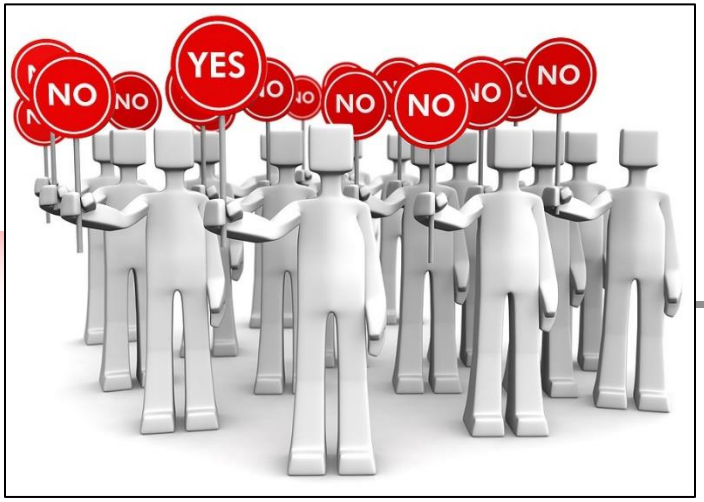
Risk Level	Uncertainty Risk
1 Low	Clinical experience or extensive literature available on this attribute
2 Medium	Minimal clinical experience or literature available on this attribute
3 High	No clinical experience or in-house data on this attribute

For EACH of the 30+ Quality Attributes (QAs)

as a CMC team agree on an Impact Risk Level and an Uncertainty Risk Level; then multiply the two risk levels to reach a Risk Score for each QA

Genentech uses a more refined RRF approach: I: 2-20 U: 1-7 RS: 2-140

N. Alt et al. / Biologicals 44 (2016) 291–305



What is the <u>weakest link</u> in Risk Management?

<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: QA → CQA

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

Impact Risk	Uncertainty Risk		
	1 Low	2 Medium	3 High
1 Low	1 x 1 = 1	1 x 2 = 2	1 x 3 = 3
2 Medium	2 x 1 = 2	2 x 2 = 4	2 x 3 = 6
3 High	3 x 1 = 3	3 x 2 = 6	3 x 3 =9

Risk Scores > 2 → CQA

Risk Scores 1 to 2 → Non-CQA

whatever risk threshold is set for CQAs will have to be defended

Illustration only: applied to a specific biopharmaceutical

Risk Scores 1 to 2 → Non-CQA

Risk Scores > 2 → CQA

Impact Risk	Uncertainty Risk		
	1 Low	2 Medium	3 High
1 Low		Residual Surfactants*	Residual Host Cell DNA
2 Medium	C-Terminus Lysine	Methionine Oxidation	Aggregation
3 High	Protein Content	Residual Host Cell Proteins	Potency

** Non-CQAs will be treated as CQAs until enough manufacturing evidence is obtained that the residuals are acceptably low and consistently maintained!*

CQAs ←→ QAs can shift as new understanding, control becomes available

• Critical Process Parameters

CPP

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

impact on CQAs

(changeable as scientific understanding about the process increases)

ICH Q8(R2)

Critical Process Parameter (CPP):

A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.

A biopharmaceutical manufacturing process will have many hundreds of process parameters!

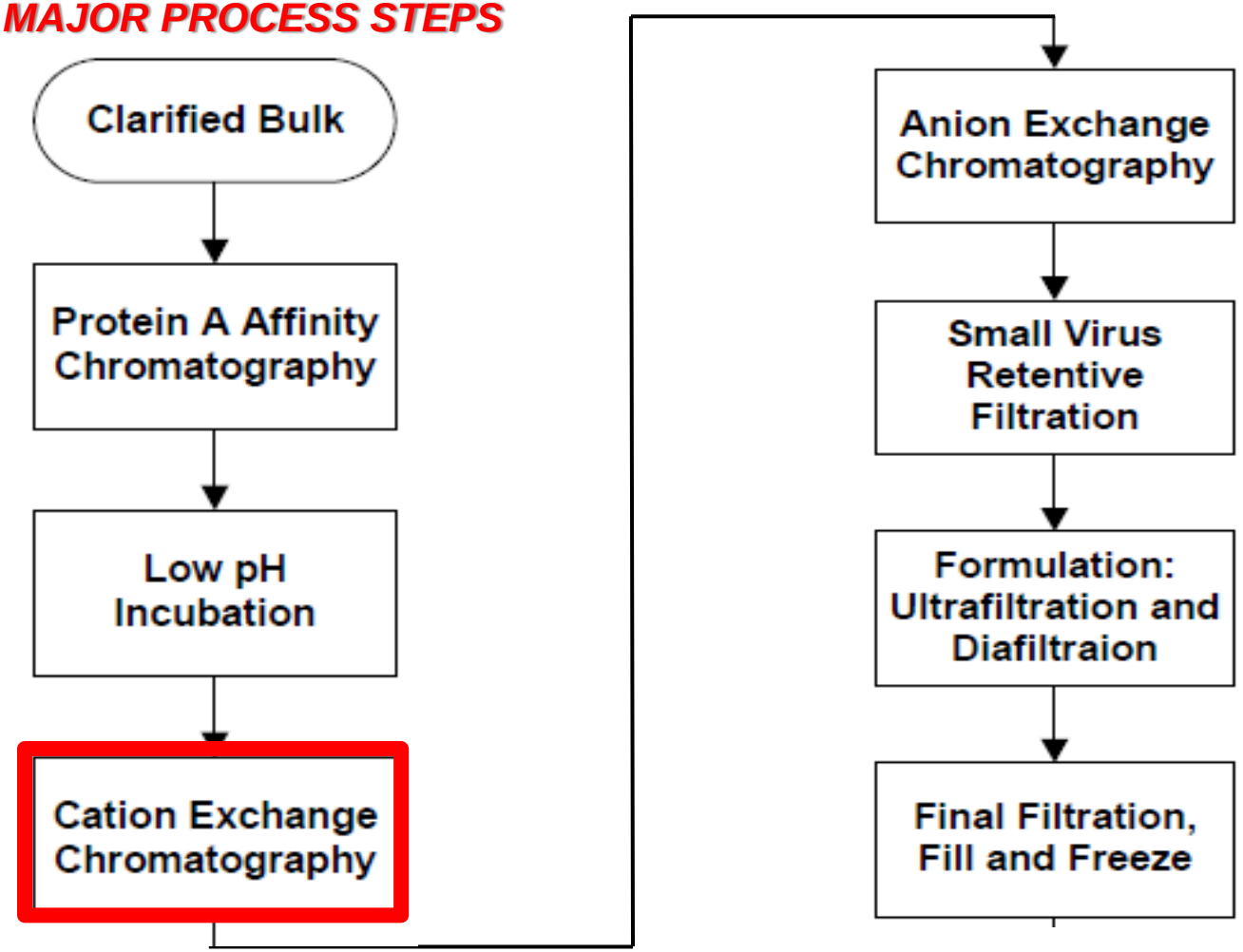
but which ones will be CPPs?

Illustrated using a mAb purification process

3 Step Process: PP → CPP

Step 1 of 3: Identify ALL Process Parameters (PPs)

7 MAJOR PROCESS STEPS



selecting 1 process step

Each manufacturing process has many 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
Column Resin
Bind/Elute

- Sanitization
- Neutralization
- Equilibration
- Loading
- Wash
- **Elution**
- Strip
- Equilibration
- Storage

Process Parameters
Maximum Product Load
Column Length
Eluent Composition
Eluent pH
Eluent Flow Rate
Peak Collection Start
Peak Collection End

7 PPs for 1 sub-step of 1 process step!

3 Step Process: PP → CPP

Step 2 of 3: Rank ALL PPs for 'Level of Criticality'

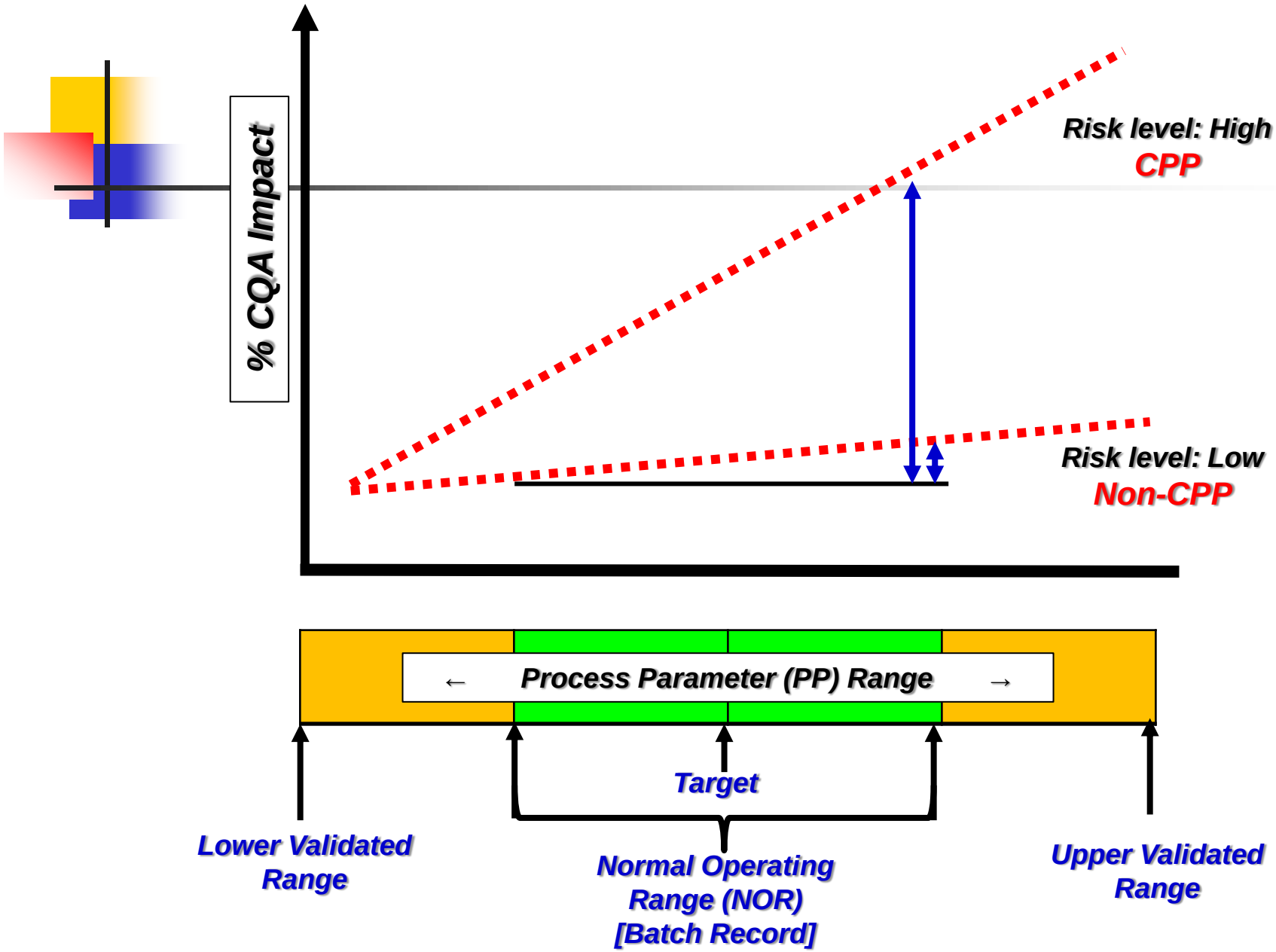
Biopharmaceutical Manufacturing Process

100's Process Parameters (PPs)

- ***IF* scientific experience/literature is available, some PPs can be deemed as Non-Critical**
- **ICH Q9 – Risk Management Formal Tools for Ranking**
  - **Risk Ranking & Filtering (RRF) – % CQA IMPACT***
  - **Failure Modes Effect Analysis (FMEA) – RISK PRIORITY NUMBER**
  - **……**

*

Risk Level	% CQA Impact
Low	No significant % impact on CQAs of this PP
Medium	Large change of this PP (or a small change in combination with other factors) has a significant % impact on CQAs
High	Small to moderate change of this PP has a significant % impact on CQAs


% CQA Impact
Risk level: High
CPP
Risk level: Low
Non-CPP
← Process Parameter (PP) Range →
Target
Lower Validated Range
Normal Operating Range (NOR) [Batch Record]
Upper Validated Range

3 Step Process: PP → CPP

Step 3 of 3: Set threshold for 'Critical'

simple example

Risk Level	% CQA Impact	Assigned Criticality
Low	No significant % impact on CQAs of this PP	Non-CPP
Medium	Large change of this PP (or a small change in combination with other factors) has a significant % impact on CQAs	CPP or Non-CPP
High	Small to moderate change of this PP has a significant % impact on CQAs	CPP

Whatever risk levels are assigned and whatever CPP threshold is set, will have to be defended to the regulatory authority

Note, most important that the impact of the PP needs to be assessed across the breadth of relevant CQAs at each specific process step

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[1] ***CPP Non-CPP***	Range assessed during process development studies	Validated Range	Clinical Study Range	Justification of the proposed commercial acceptable range[2]

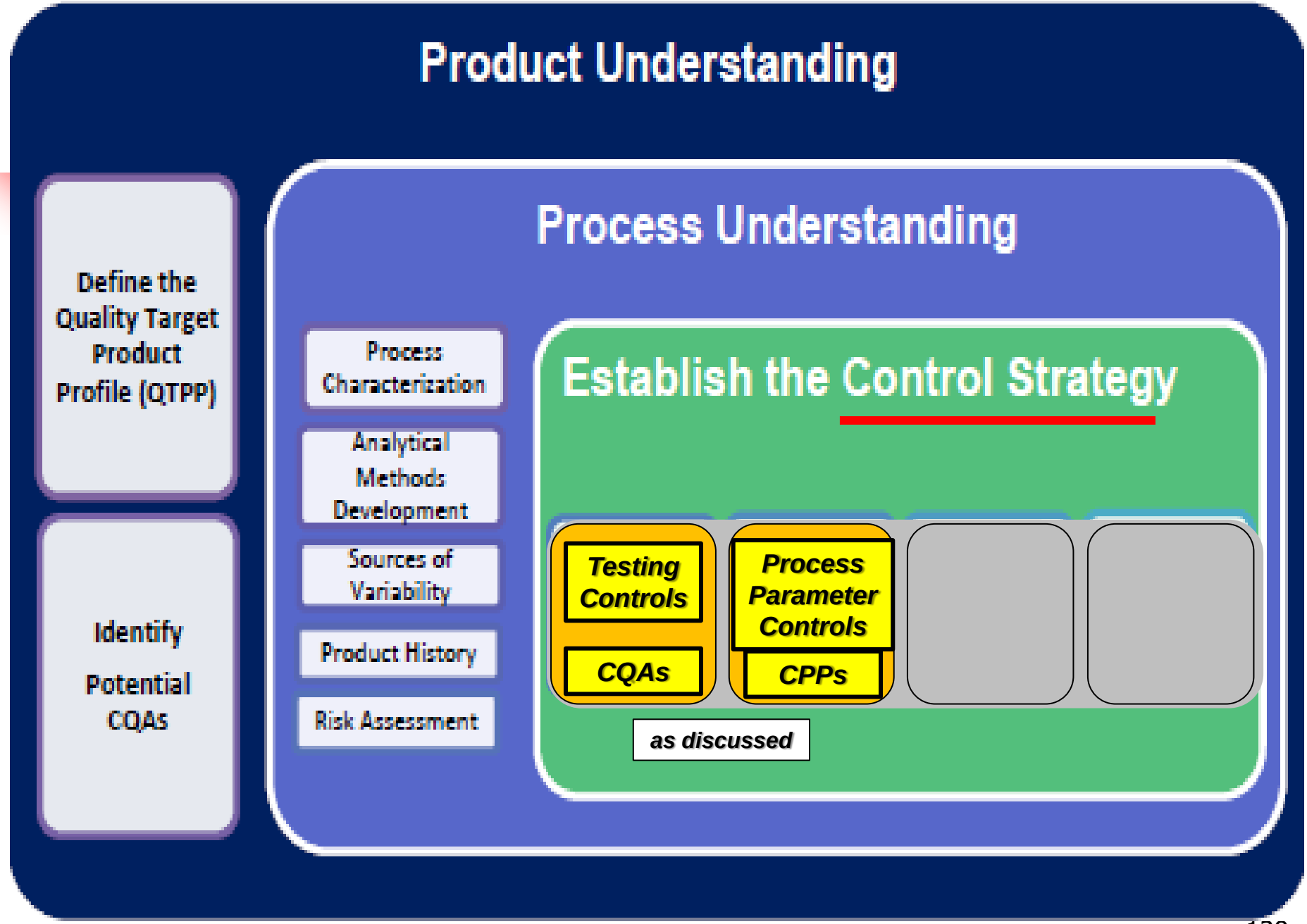
[1]For example, critical process parameter, key process parameter, non-critical process parameter, as described in module 3.

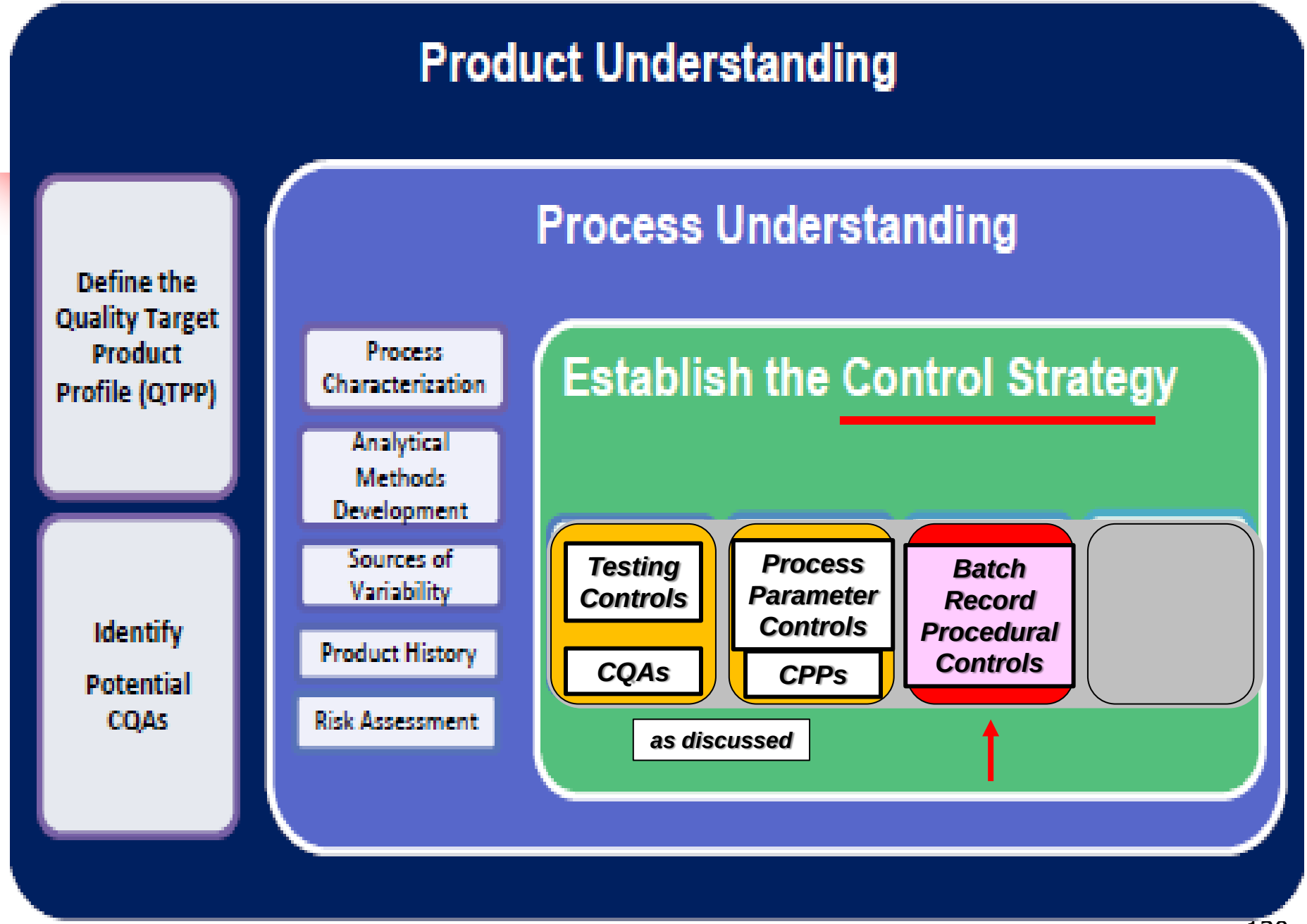
[2]Provide a brief summary description (e.g., "development range", "validation range", or "platform experience"). To link to additional description for justification you may additionally include a link or reference to the appropriate section of the eCTD with more detail.

Control Strategy:

A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10)

The Control strategy is much more 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
Testing Controls
CQAs
Process Parameter Controls
CPPs
as discussed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Product History
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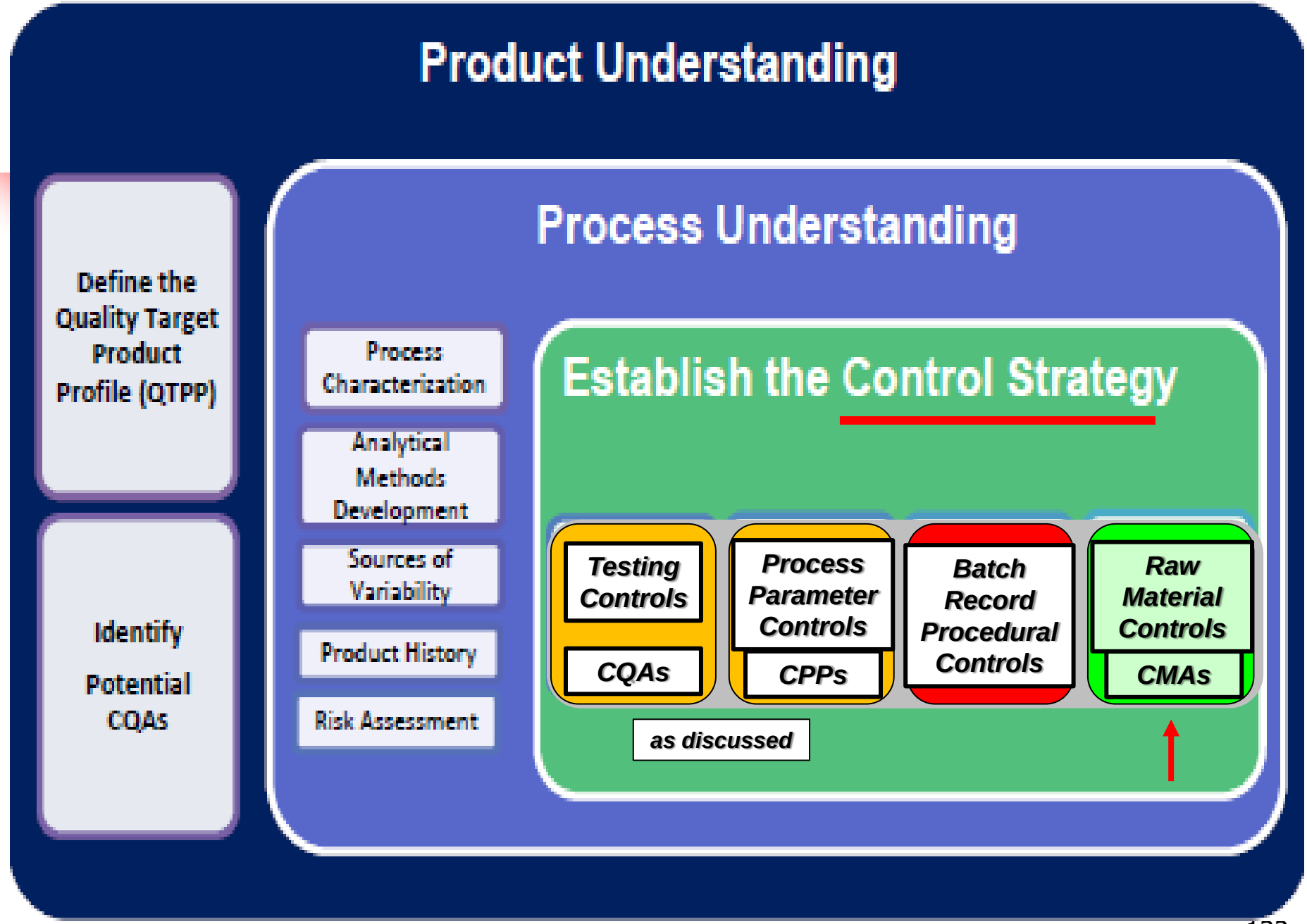
Testing Controls
CQAs
Process Parameter Controls
CPPs
Batch Record Procedural Controls
as discussed

Procedural Controls (Process Flow in PBRs)	How the manufacturing process is designed to obtain the required product quality

PBR – production batch record

Examples

- **Limit on the length of time in bioreactor production phase**
  - Protein titer might can keep increasing over a longer production time (but at a lower cell productivity); loss of % cell viability keeps decreasing (cell lysing due to age) over longer production times
    - this leads to increased impurity buildup (e.g., host cell DNA and host cell proteins) → increasing pressure on downstream purification steps
- **Arrangement of purification chromatography steps**
  - Lots of chromatography 'polishing' steps – AEX, CEX, HIC, SEC
    - which column arrangement obtains maximum removal of process-related impurities?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Process Characterization
Analytical Methods Development
Sources of Variability
Product History
Risk Assessment
Establish the Control Strategy
Testing Controls
CQAs
Process Parameter Controls
CPPs
Batch Record Procedural Controls
Raw Material Controls
CMAs
as discussed

Critical Material Attributes (CMAs)	Identify Critical Raw Materials that can impact CQAs

Raw materials are the reagents used in the manufacturing process but are not part of the final drug product

Case example of a Critical Raw Material in the cell culture medium impacting the glycosylation composition CQA

the four PPQ batches. Evaluation of CQAs, IPCs, and performance parameters demonstrated that the manufacturing process is consistent throughout the process. A shift in glycosylation profile (sum of afucosylation and G0F) was observed between v1.0 clinical and v1.0 PPQ batches. This shift was assigned to increased levels of trace element manganese impurity. As a result, a manganese acceptance criterion was implemented and a verification batch was produced, showing glycosylation levels comparable to previous v1.0 clinical manufacturing runs.

Polivy (polatuzumab vedotin) Roche EPAR 14 November 2019 EMA/CHMP/690748/2019

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[1] ***RISK***	Source[2] ***ORIGIN***	Analytical method[3]	Proposed control strategy[4]	Justification of the proposed control strategy[5]

[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.

For more information on QbD for biopharmaceuticals

free, downloadable

NIIMBL

ISPE has A-mAb (2009)

N-mAb – A Case Study to Support Development and Adoption of Integrated Continuous Bioprocesses for Monoclonal Antibodies (NIIMBL, 2022)

NIIMBL.force.com/s/n-mab

Alliance for Regenerative Medicine

Project A-Gene – A Case Study Based Approach to Integrating QbD Principles into Gene Therapy CMC (ARM, 2021)

ALLIANCERM.org/manufacturing/a-gene-2021

QbD: What about 'Design Space" for Biopharmaceuticals

"Regulatory Flexibility" vs "Residual Risk"

- ***Regulatory Flexibility*: ability to control the manufacturing process changes without regulatory authority involvement**
  - **The dream for the industry**

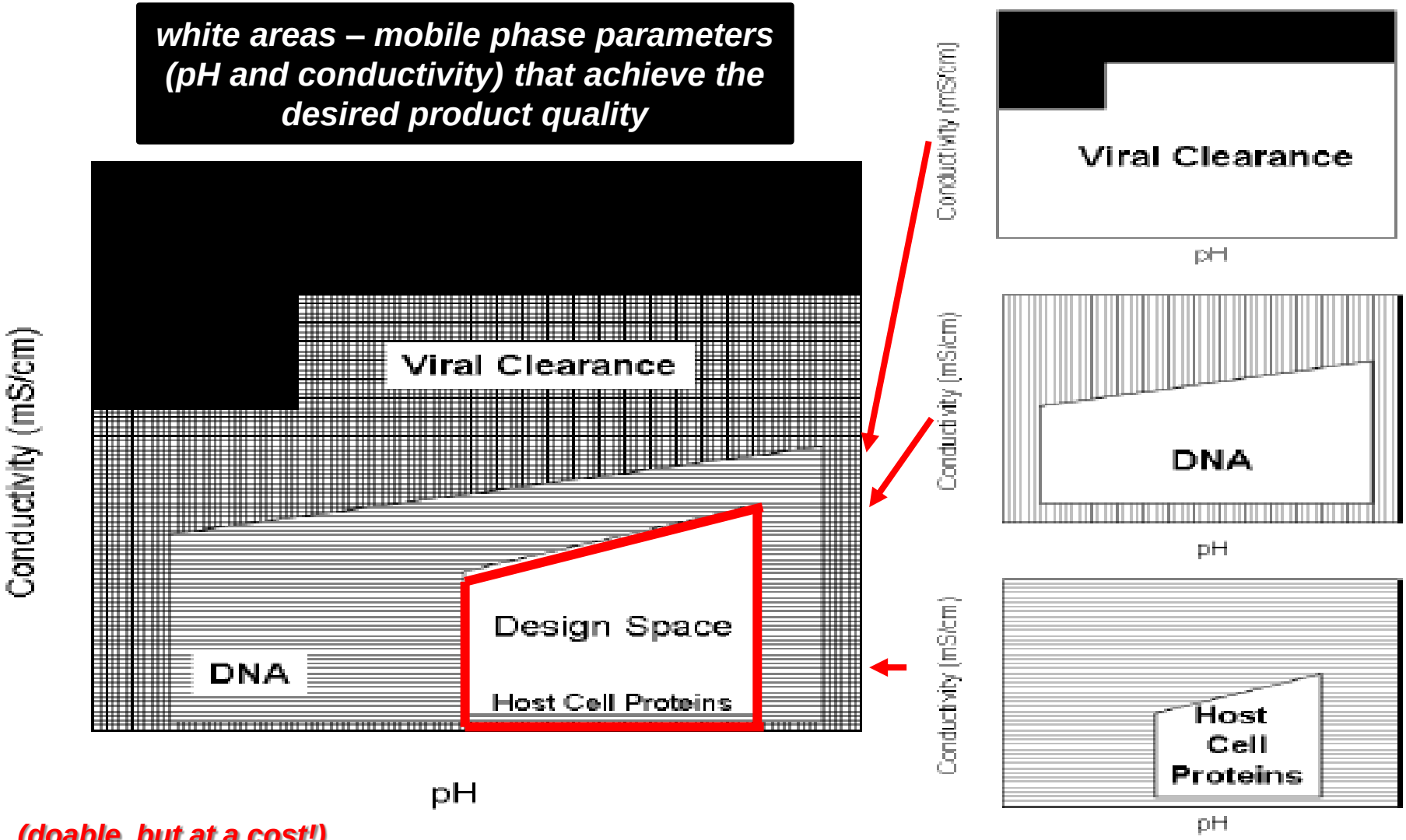
- ***Residual Risk*: potential for *unexpected negative* changes to CQAs**
  - **The more complex the process/product (e.g., biologics) the more challenging to know either which potential changes may occur or to predict the impact of an unexpected change**

Regulatory Flexibility is *inversely proportional* to the level of Residual Risk!

Design Space applied to an Individual Manufacturing Process Step is Doable

(Anion Exchange Chromatography Step of a Monoclonal Antibody) ICH Q11

white areas – mobile phase parameters (pH and conductivity) that achieve the desired product quality



(doable, but at a cost!)

Design Space applied to an Analytical Test Method is Doable!

Manufacturing Process	*Analytical Method*
Quality Target Product Profile (QTPP)	*Analytical Target Profile (ATP)*
Critical Quality Attributes (CQAs)	*Link to CQAs*
Critical Process Parameters (CPPs)	*Method Operational Design Region (MODR)*
Control Strategy	*Analytical Control Strategy*

ANALYTICAL PROCEDURE DEVELOPMENT
Q14

Example of Design Space Applied to an Individual Test Method

(Potency Assay for a Monoclonal Antibody)

Skyrizi risankizumab AbbVie 28 February 2019
EMA/191996/2019

The applicant has applied QbD principles in the development of the active substance and the finished product and their manufacturing process. A design space is claimed for the potency assay and multivariate ranges for several factors are registered for the method. The available data supports the proposed design space for the assay.

Design Space applied to the Overall Biopharmaceutical Manufacturing Process

(only one public example)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Genentech GAZYVA (obinutuzumab) 11/01/2013

Upon review of the supporting data, the design space as proposed in BLA 125486 was found to be acceptable. The Agency would like to reiterate that in addition to the information described in the application, it is our expectation that plans for implementation of the design space for the commercial process are documented within the firm's Quality System. Such quality systems may include plans for handling movements within the design space (e.g., change control procedures, plans for updating batch records). In accordance with ICH Q8(R2), while the Agency does not expect any regulatory notification for movements within the design space, any other changes in the manufacturing, testing, packaging, or labeling or manufacturing facilities for GAZYVA (obinutuzumab) will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

Gazyvaro 22 May 2014
EMA/CHMP/231450/2014

Quality by Design (QbD) principles have been applied during the development of obinutuzumab. The design space of obinutuzumab includes all the unit operations, the process parameters describing the operation of each of the unit operations, and the raw materials used. The design space is limited by the Multivariate Acceptable Ranges (MARs) for all process parameters (CPPs and non-CPPs) described in the

(doable, but at great cost!) ROI?

Non-pharmaceutical illustration of QbD

QbD

Critical Materials

Source Material: _____

Container: _____

As you watch the video

Identify the CQAs

Thickness_____

Texture_____

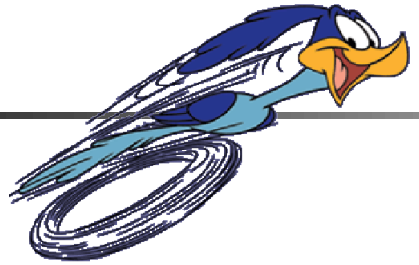
Identify the CPPs to achieve CQAs

Thickness_____

Texture_____

Pringles crisps – Enhanced Approach (QbD) – using continuous manufacturing – QTPP? CQAs? CPPs? 5 min

Clinical Expediting Significantly Impacts the Minimum CMC Regulatory Compliance Continuum



Exciting clinical speed opportunities to shorten the timelines …

… but stresses the CMC Team!

Migration to a Shorter, 'SEAMLESS', Clinical Development Program

FDA: Breakthrough Therapy designation

FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014)

(also Fast Track, Accelerated Approval, Priority Review)

EMA: Primary Medicine (PRIME) designation

EMA European Medicines Agency Guidance on Interactions in the Context of PRIME (May 2018)

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.

FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014)

EMA reveals where it MIGHT BE willing to accept higher CMC residual risk in MAA submissions

(when PRIME expedited)

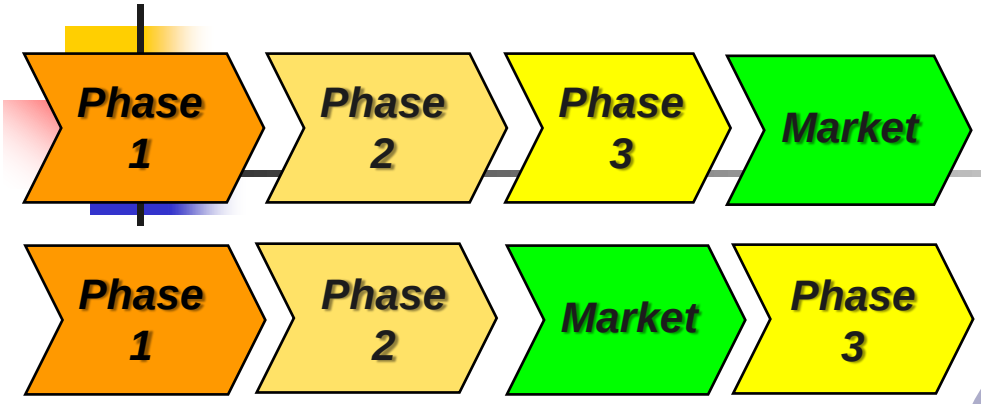
Module 3	POTENTIAL CMC Flexibility for Long Extensive Time Requirements
Process Validation	Concurrent process validation in place of prospective process validation Deferral to post market approval commitment Decoupling drug substance PPQ from drug product PPQ
Control Strategy	Filing with a more 'constrained' control strategy (augmented with additional testing or tighter controls)
GMP Compliance	Launching from an investigational manufacturing site Aligning Module 3 review with GMP Pre-Approval Inspection Use of Starting Material of lower GMP level
Product Stability	Extrapolation of shelf life from similar biopharmaceutical products
Product Comparability	Prior knowledge to tailor comparability studies Separate assessment of individual process changes

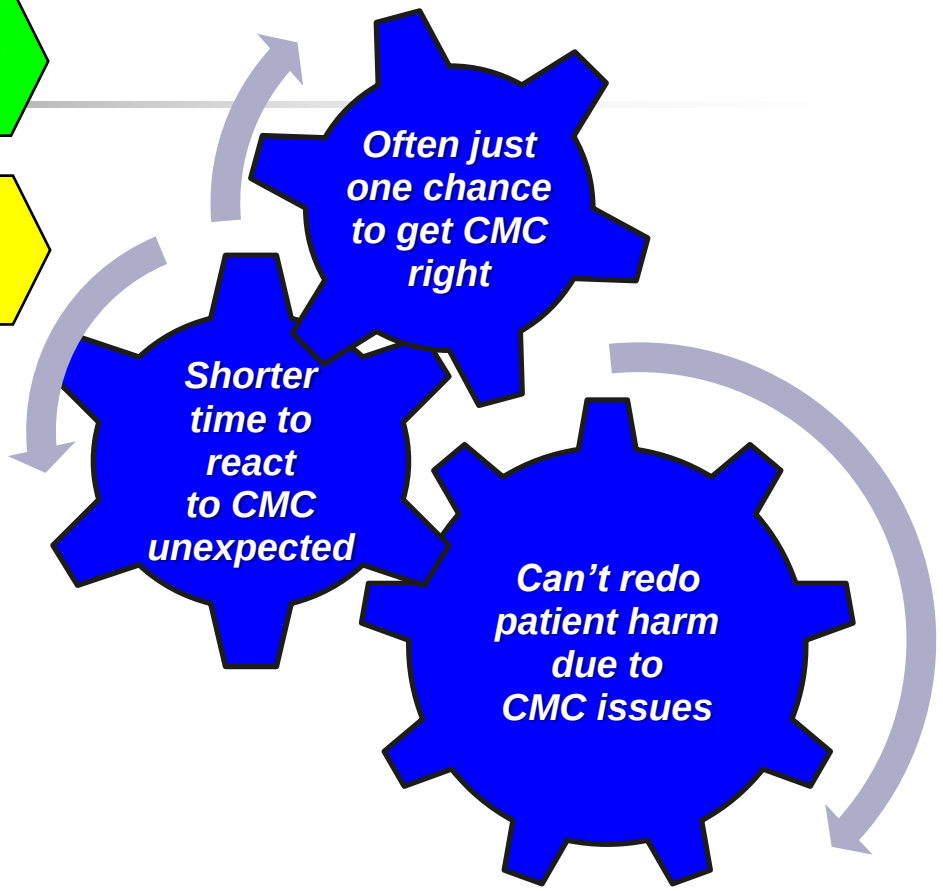
EUROPEAN MEDICINES AGENCY

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

Cautionary Note: Going fast has its benefits and its risks!



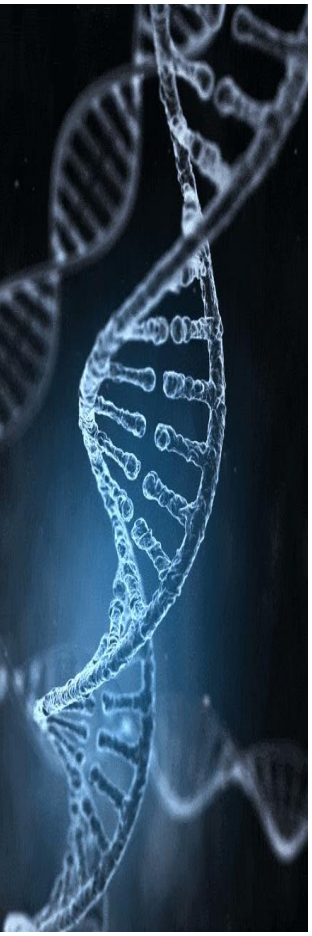


Always a danger if going too fast!

Summary of Risk-Managed Biopharmaceutical CMC Regulatory Compliance Strategy

- ✓ ***Introduction to the risk-based, clinical stage-appropriate, flexible 'minimum CMC regulatory compliance continuum' for biopharmaceuticals***
- ✓ ***The 3 interactive CMCcomponents to protect patients – CMC Regulatory, cGMPs, Quality System***
- ✓ ***Discussion of the regulatory authority recommended risk-based approach (QbD/QRM) – which also serves as our communication language***

QUESTIONS??



Course Outline

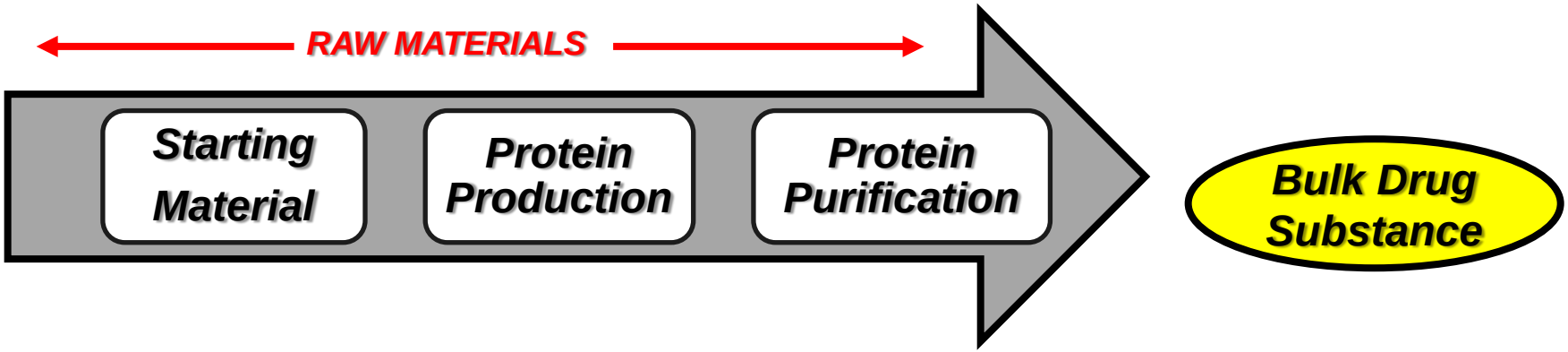
3. Applied Risk-Managed Biopharmaceutical CMC Regulatory Compliance Strategy

- CMC strategy applied across the manufacturing process from raw materials → starting material → protein production → protein purification → bulk drug substance

  (plus a few comments onto the drug product stage)

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 product-contact components used in the manufacturing process, but are <u>not</u> part of the manufactured product

(United States Pharmacopeia (USP) uses the term 'ancillary materials' for raw materials)

- ***Up-Stream Process (USP)***
  - ***Culture media components for cell expansion***
  - ***Antifoam***
  - ***Surfactant/nuclease to lyse cells***
  - ***…***
- ***Down-Stream Process (DSP)***
  - ***Solutions and buffer components used in purification***
  - ***Resins in the purification columns***
  - ***Nanofilters***
  - ***…***

Why raw materials are of such a safety concern to regulatory authorities

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

***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 biopharmaceutical product!*

full CMC content to be provided in submissions

Applied Risk-Management Across the Manufacturing Process

RAW MATERIALS

Risk to Product Quality! Risk to Patient Safety!

(1) Listed, (2) Identified, (3) Justified Quality, (4) Suitable for Intended Use

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.

EUROPEAN MEDICINES AGENCY

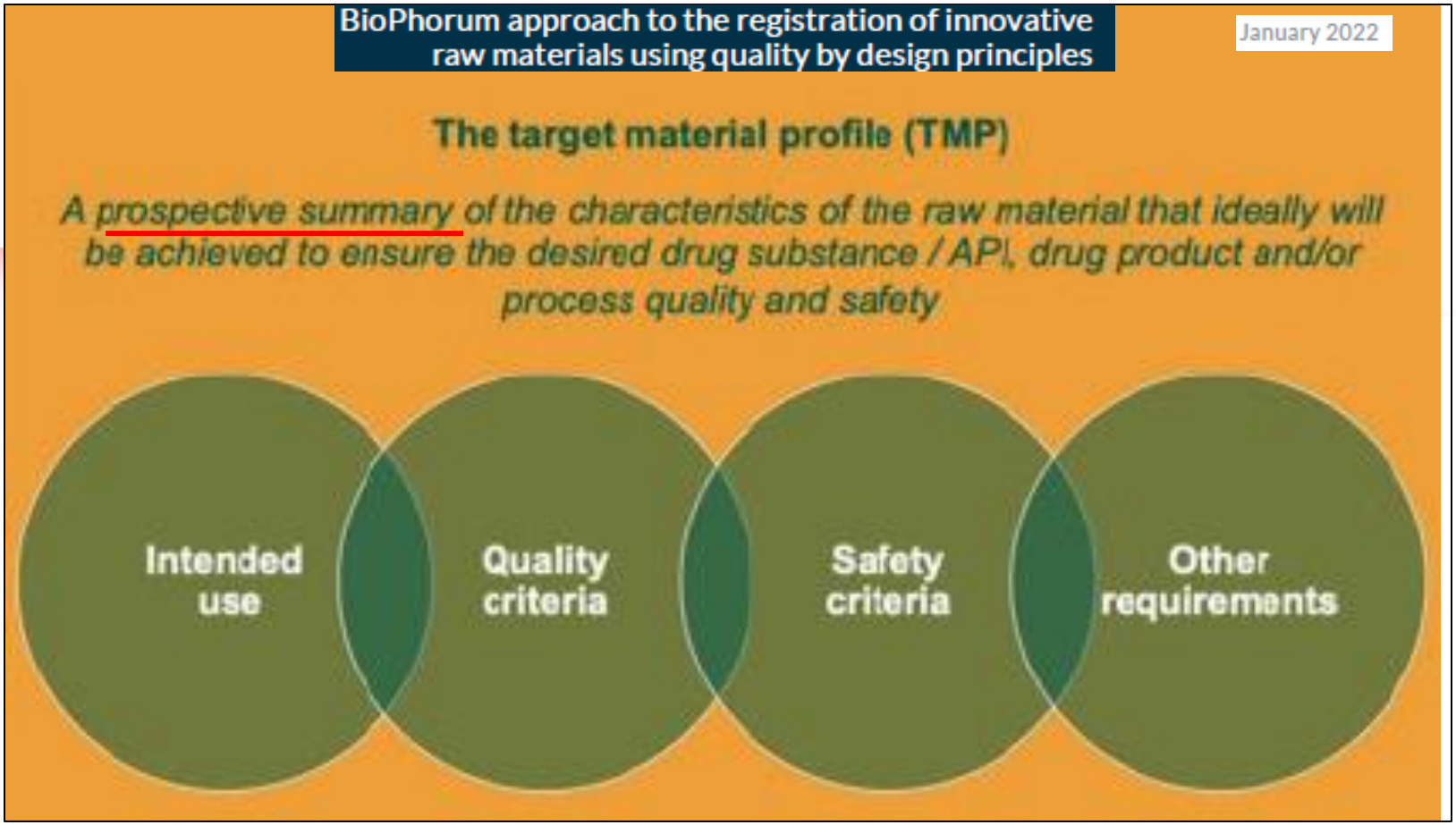
Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials

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

ICH harmonisation for better health

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

M4Q

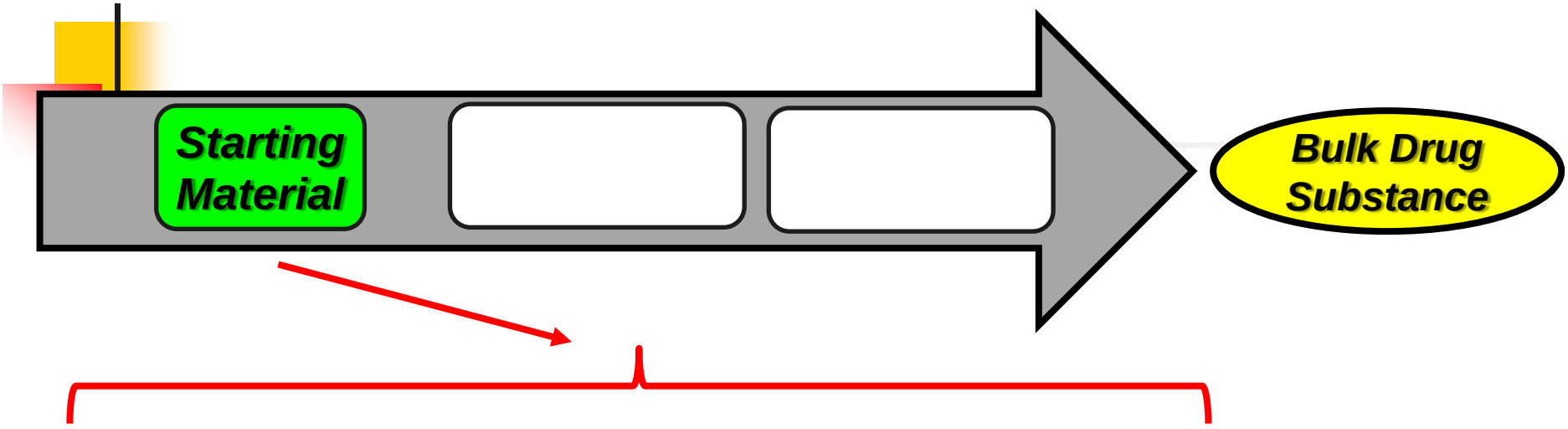


risk assessment approach

risk reduction steps (as needed)

- ***DMF cross reference (when possible or practical) and/or Certificate of Analysis***
- ***Assess lot-to-lot effect on process performance***
- ***Assess removal from final product***
- ***When relevant, confirm certificate of analysis test results critical to product***
- ***Vendor audit***
- ***Upgrade manufacturing process for material to GMP***
- ***Develop stringent internal specifications***

Applied Risk-Management Across the Manufacturing Process



Development Genetics → **Master Cell Bank (MCB)**

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

'recombinant'

contains the genetic capacity to produce the protein of interest

DG → (7-12 month process) → MCB

Starting Materials (ICH Q11)

for chemical drugs

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. Commonly available chemicals used to create salts, esters or other simple derivatives should be considered reagents.

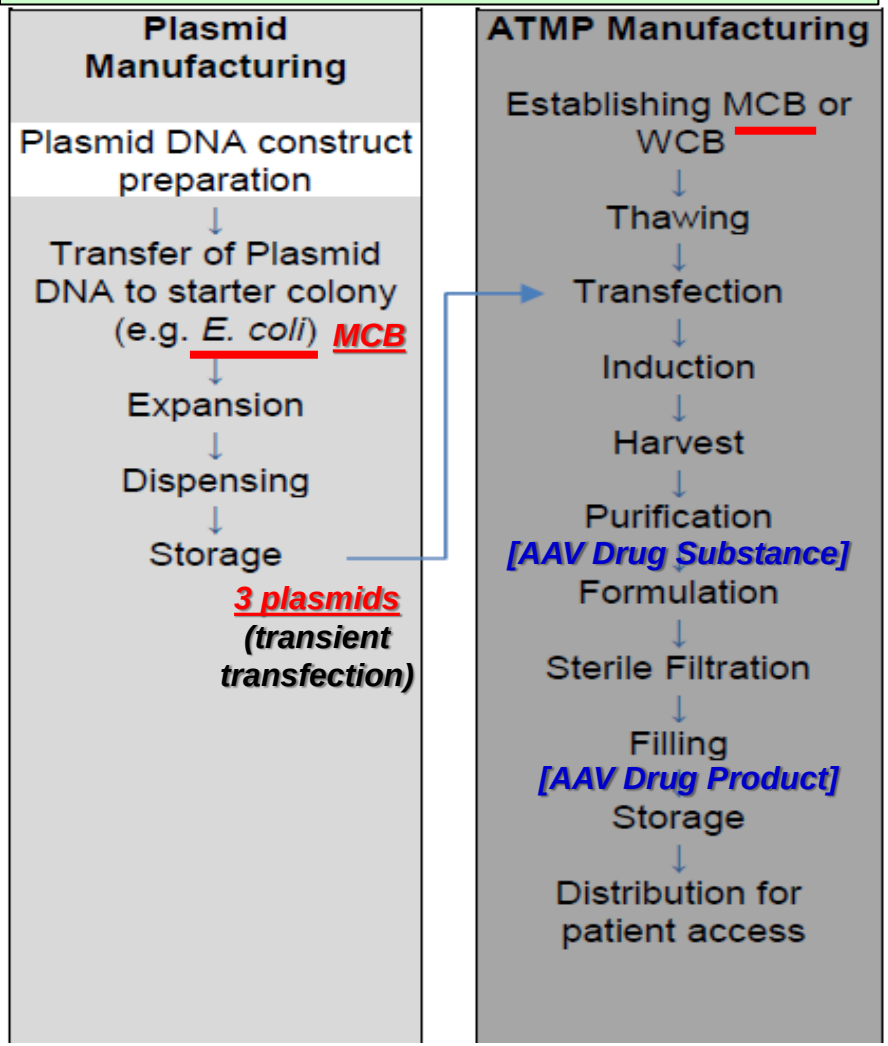
for recombinant proteins and monoclonal antibodies

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. Guidance is contained in ICH Q5A, Q5B, and Q5D.

Cell banks contain the "genetic capability" to express the protein product

Gene-based biopharmaceuticals

Using adeno-associated virus (AAV) vector



In Vivo Gene AAV

multiple Starting Materials

3 Master cell banks (to produce plasmids) + 3 plasmids + Master cell bank (to propagate virus)

Box Color: ***White – outside GMPs*** | ***Light Grey – Principles of GMP*** | ***Dark Grey - GMPs***

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***

cGMP not required, but 'PRINCIPLES OF GMP'

careful written documentation critical!

Development Genetics

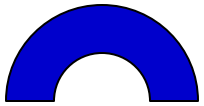
(Step 1 of 2) Stitching together the genetic components

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

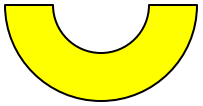
(genes can be further genetic engineered)

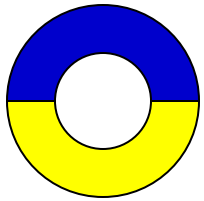
larger piece of DNA (e.g., plasmid, virus) that contains promoters, enhancers and other genetic pieces to allow the gene to function and survive within a foreign host

gene



vector



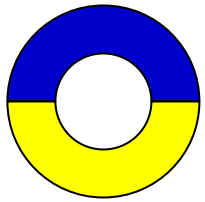


expression construct

(molecular cloning to ensure correct gene and vector sequence)

Development Genetics

(Step 2 of 2) Preparing the Cloned Cell Substrate



expression construct

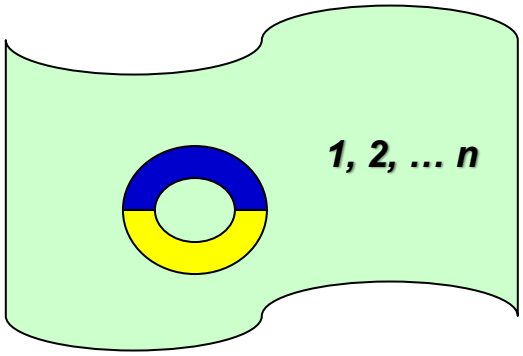
Transduction (virus)

Transfection (plasmid)

Transformation (electroporation)

living host

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



not 1 engineered host cell, but 1000s

CELL CLONING

Cloned genetically engineered single cell expanded → 'cell substrate'

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)*

Transformed cells	→	***Cloning***	→ *Cell Substrate*	→ *MCB*
1000's		*1 transformed cell*		*clonal*

***Regulatory Concern:** A non-clonal cell bank can give rise to outgrowth of a different subpopulations of cells that can generate products with different CQAs*

World Health Organization (WHO)

recommended approach to cloning!

In the process of cloning a cell culture, single cells should be selected for expansion. The cloning procedure should be carefully documented, including the provenance of the original culture, the cloning protocol, and reagents used. Cloning by one round of limiting dilution will not necessarily guarantee derivation from single cells; additional subcloning steps should be performed. Alternatively or in addition to limiting dilution steps the cloning procedure can include more recent technology such as single cell sorting and arraying, or colony picking from dilute seeds into semi-solid media. In any case, the cloning procedure should be fully documented, accompanied by imaging techniques and/or appropriate statistics. For proteins derived from transfection with recombinant plasmid DNA technology a single, fully documented round of cloning is sufficient provided product homogeneity and consistent characteristics are demonstrated throughout the production process and within a defined cell age beyond the production process.

WHO Evaluation of Animal Cell Cultures as Substrates TR978 (2013)

NOTE: strong emphasis on documentation done in R&D!

USP <1042> Cell Banking

why 2 rounds of limiting dilution

LIMITING DILUTION CLONING

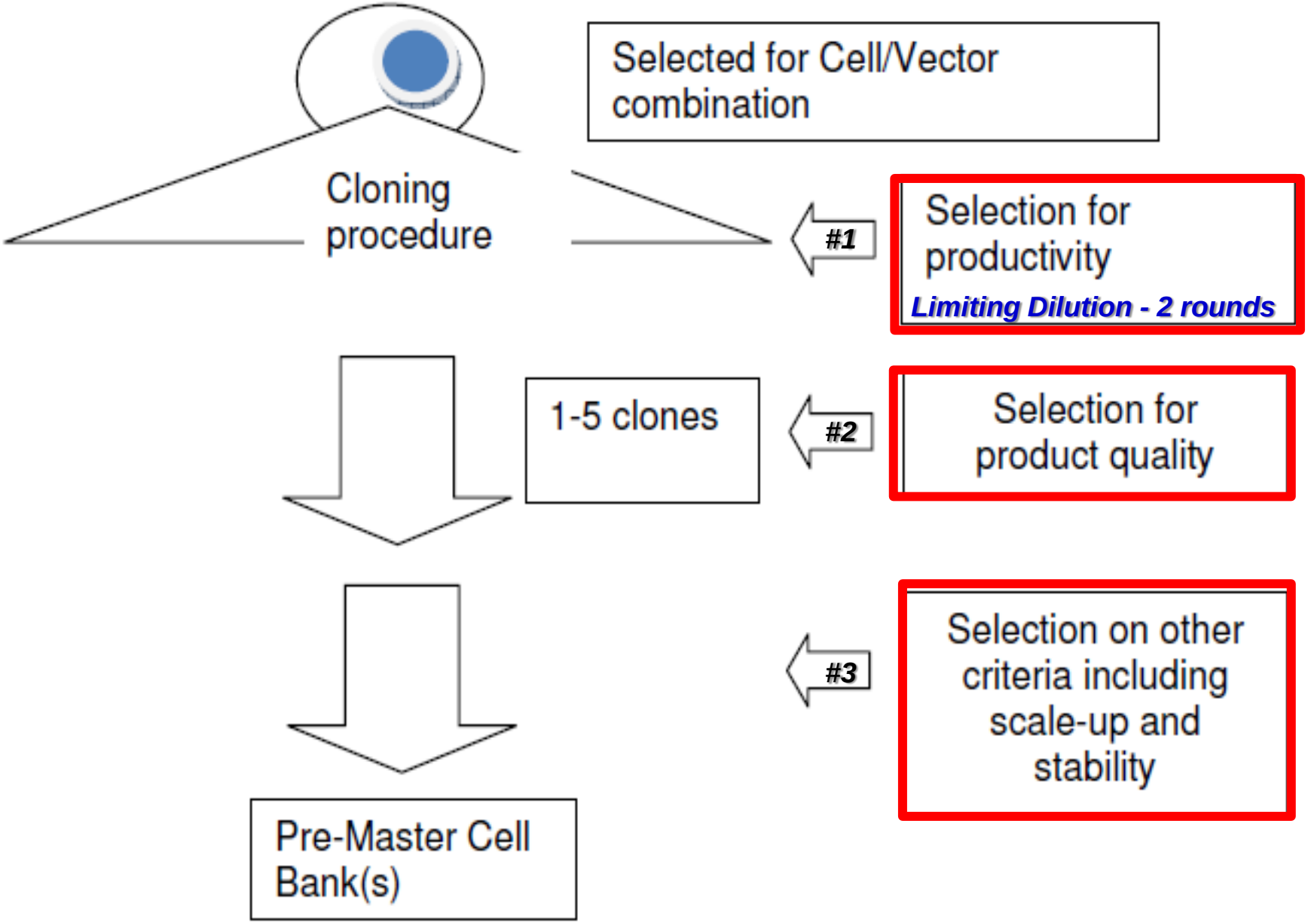
Limiting dilution cloning (LDC) is a procedure whereby cells are plated at a low density, ideally <0.5 cells/well in a 96-wellplate, with the aim of obtaining only 1 cell in a well from which progeny can grow. Some wells will be devoid of cells. This is achieved by preparing a set of increasingly greater dilutions of the non-clonal starting population and visually verifying the number of cells initially deposited per well.

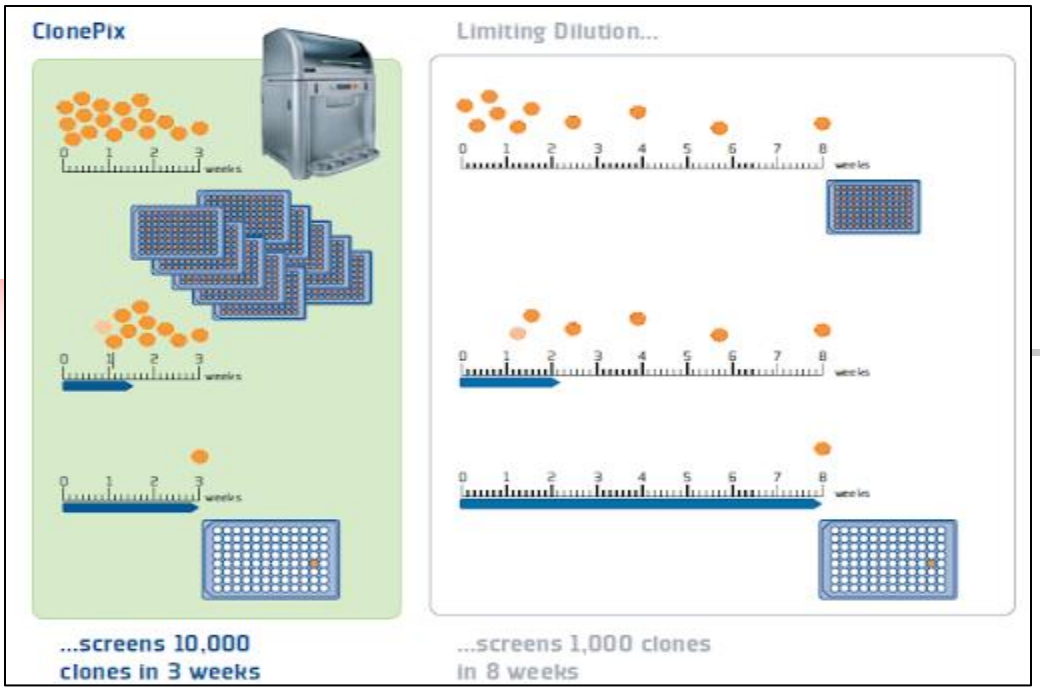
Two rounds of LDC are recommended if manufacturers want to establish a clonal cell line, particularly in the absence of additional supporting technology, to ensure monoclonality (e.g., imaging). Two rounds of LDC provide an approximately 99% probability that the cell line will be monoclonal.

However, it is a time-consuming process and can take up to 12 months to complete.

Other more modern methods (e.g., high speed image scanning, high speed laser manipulation) of confirming clonality are also discussed

WHO – illustration of three essential screens in clone selection

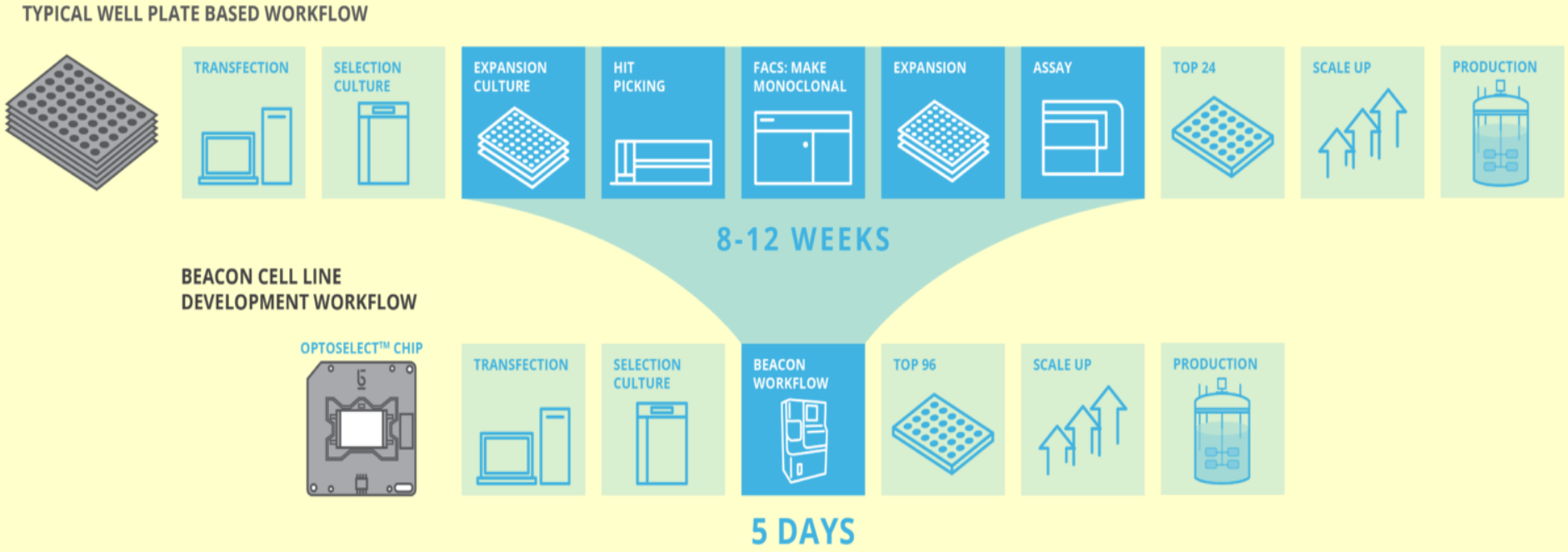




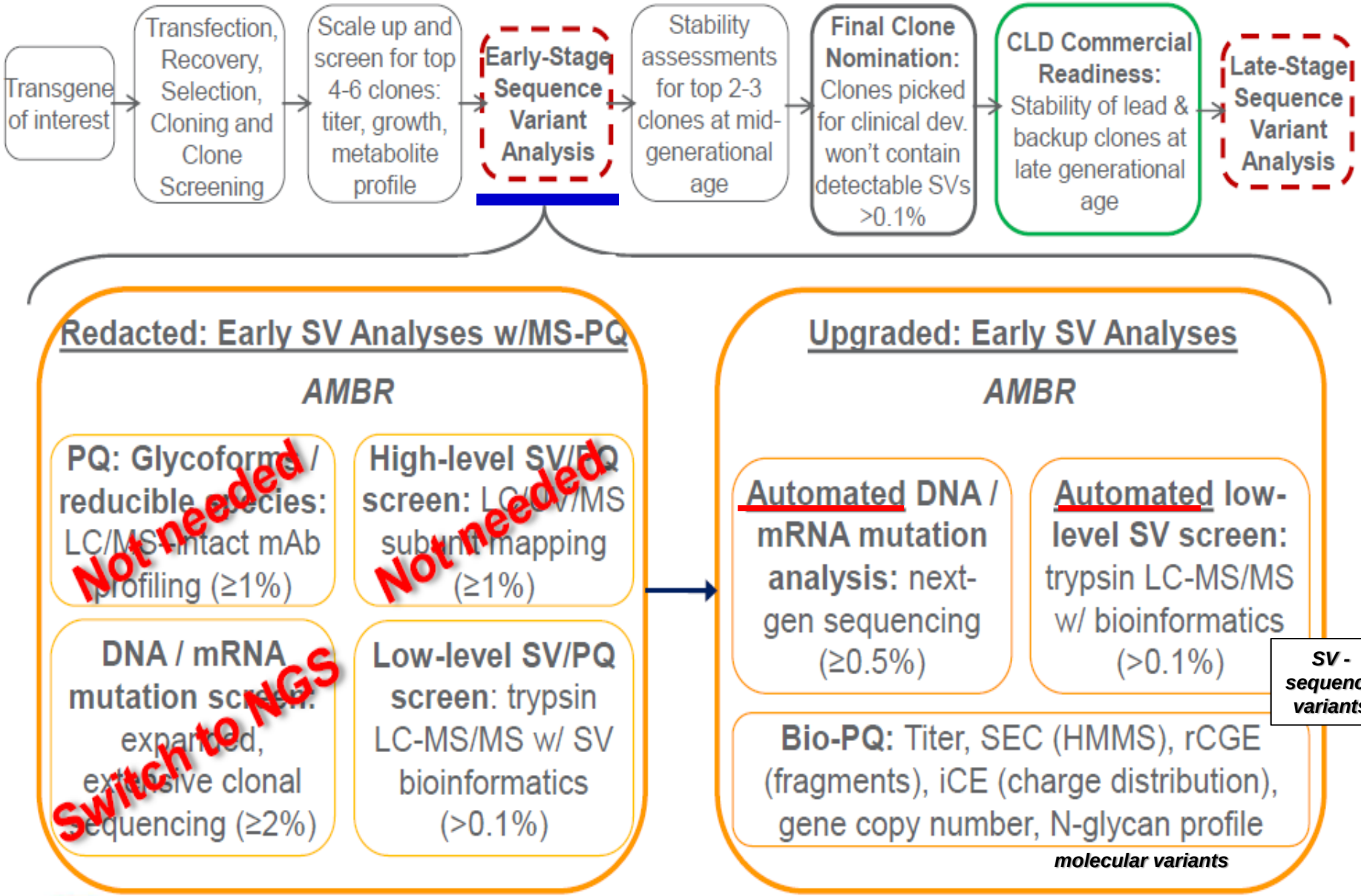
Improved speed and sensitivity, and documented cloning techniques for FIRST STEP:

selection of high producer clones

computer imaging, robotics, data archival



Improved analysis assays for SECOND STEP: evaluating clone product quality



Different CQA levels with each clone – which clone would you select for your MCB?

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

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*

Master Cell Bank – Source Material

Cloned Cell Substrate

Prepared under principles of GMP

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 batches
Prepared under cGMP

Lots of testing ($$) to safety and identity testing for the Master Cell Banks (ICH Q5A)

Sterility GMP Analysis**	*
Mycoplasmastasis	
Mycoplasma GMP Analysis	*
Identity COI sizing cytochrome c oxidase subunit I	*
Identity COI barcoding	
in vitro Adventitious Agent CHO Detector Line	*
in vitro Adventitious Agent MRC-5 Detector Line	*
in vitro Adventitious Agent Vero Detector Line	*
Optional *in vitro* Adventitious Agent 324K Detector Line	
in vivo inapparent virus	

HAP	Hamster antibody production
MAP	Mouse antibody production
TEM	Transmission electron microscopy
Bovine 9CFR	
Porcine 9CFR	
S+L- Focus Forming	
Retrovirus PERT	
Retrovirus Co-Cultivation Mus Dunni	
MMV PCR	Mouse minute virus

* **Working Cell Banks**

Genetic Characterization

Copy Number	*
Restriction Enzyme (Southern)	
Sequencing	

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***

"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

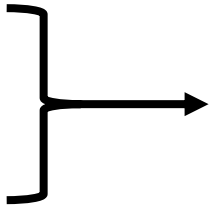
applied to development genetics and the Master Cell Bank (MCB)

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

CMC Details Required

***BRIEF* description IND/IMPD**

***DETAILED* description in BLA/MAA**



Description in IND/IMPD for clinical development

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

Description in BLA/MAA for market approval

(same development process described briefly for IND/IMPD years before)

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)

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	
brief description IND/IMPD	***detailed description in BLA/MAA***
Level of CMC Regulatory Review	
limited, single CMC reviewer	***thorough, multi CMC team reviewers***
patient safety focus	***patient safety focus + manufacturing 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….

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 (April 2013)

regulatory authority IND/IMPD CMC reviewers do not catch everything

Patient Safety is Always a Key Focus

Absence of adventitious agents of concern + …

- ***Prions – TSEs***
  - ***Prevented through risk minimization strategy in choices for raw materials used to prepare bank (e.g., avoiding animal- or human-derived materials)***
- ***Viruses – insect/animal/human cell lines***
  - ***<u>Extensive</u> viral safety testing of bank; $$$***
- ***Mycoplasmas – insect/animal/human cell lines***
  - ***28 day testing of bank***
- ***Bacteria/Fungi – all cell lines***
  - ***Culture purity testing of bank (if bacterial/yeast)***
  - ***Sterility testing of bank (if animal/human)***

ICH Q5D

Patient Safety is Always a Key Focus

… + correct identity of genetic components

- ***Gene Authentication***
  - *DNA sequencing to confirm correct nucleotide sequence*
  - *Protein sequencing to confirm correct amino acid sequence from DNA*
- ***Vector Authentication***
  - *DNA sequencing to confirm correct regulatory/control elements*
  - *Restriction enzyme mapping of vector elements*
- ***Host Authentication***
  - *DNA fingerprinting*
  - *Absence of non-host cells (documentation)*

ICH Q5B

ICH Q5D

Reviewer Considerations for Clonality at the IND stage

- 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

- 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

Regulatory authorities discover surprises in the MCB during the thorough BLA/MAA review, that were not noticed during the IND/IMPD review

Concern about clonality of MCB – absence of documented proof

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	
brief description IND/IMPD	***detailed description in BLA/MAA***
Level of CMC Regulatory Review	
limited, single CMC reviewer	***thorough, CMC team reviewers***
patient safety focus	***patient safety focus + manufacturing 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)

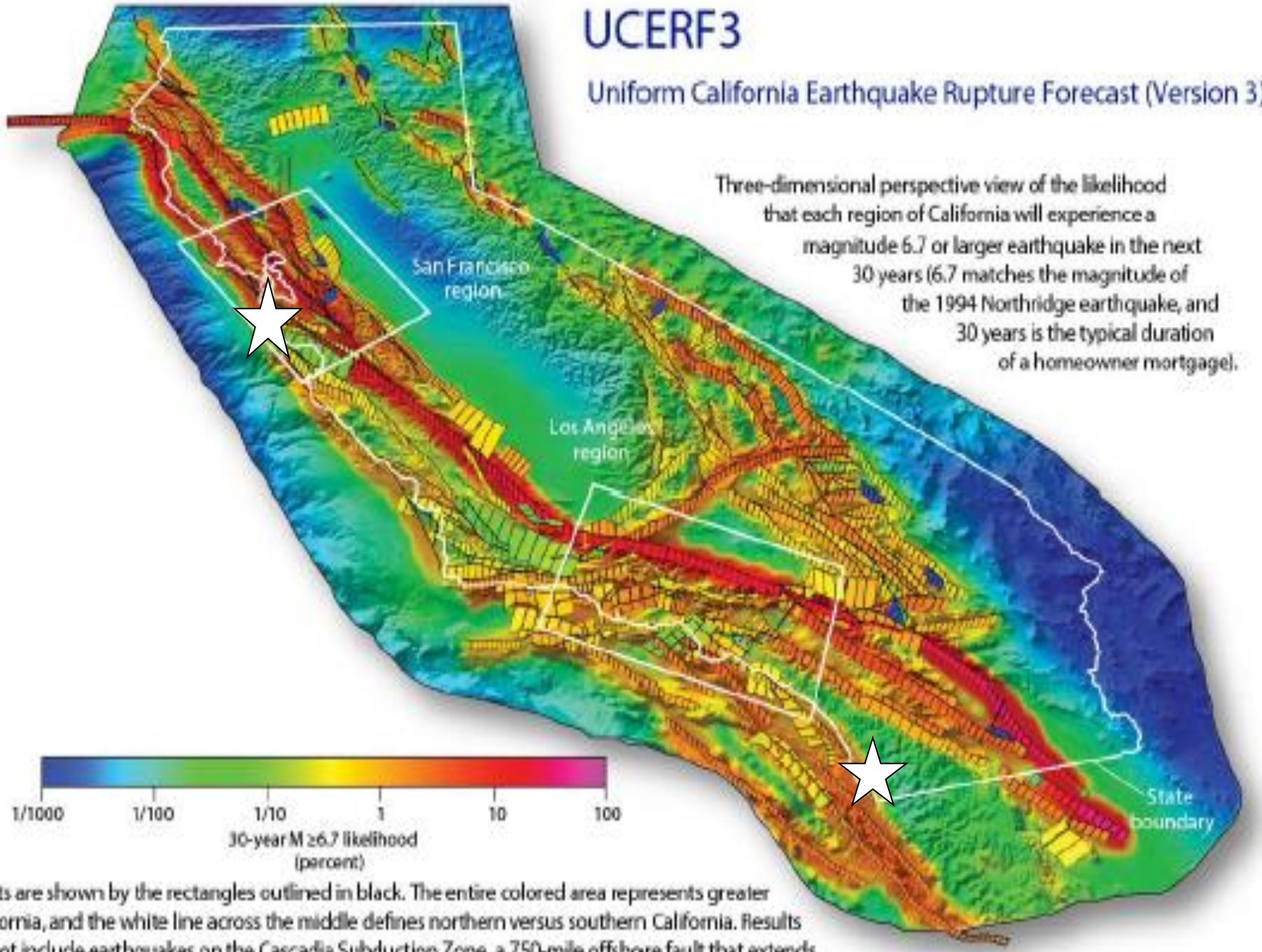
CMC requirements for commercial manufacturing

one critical GMP feature: a secure catastrophic event plan

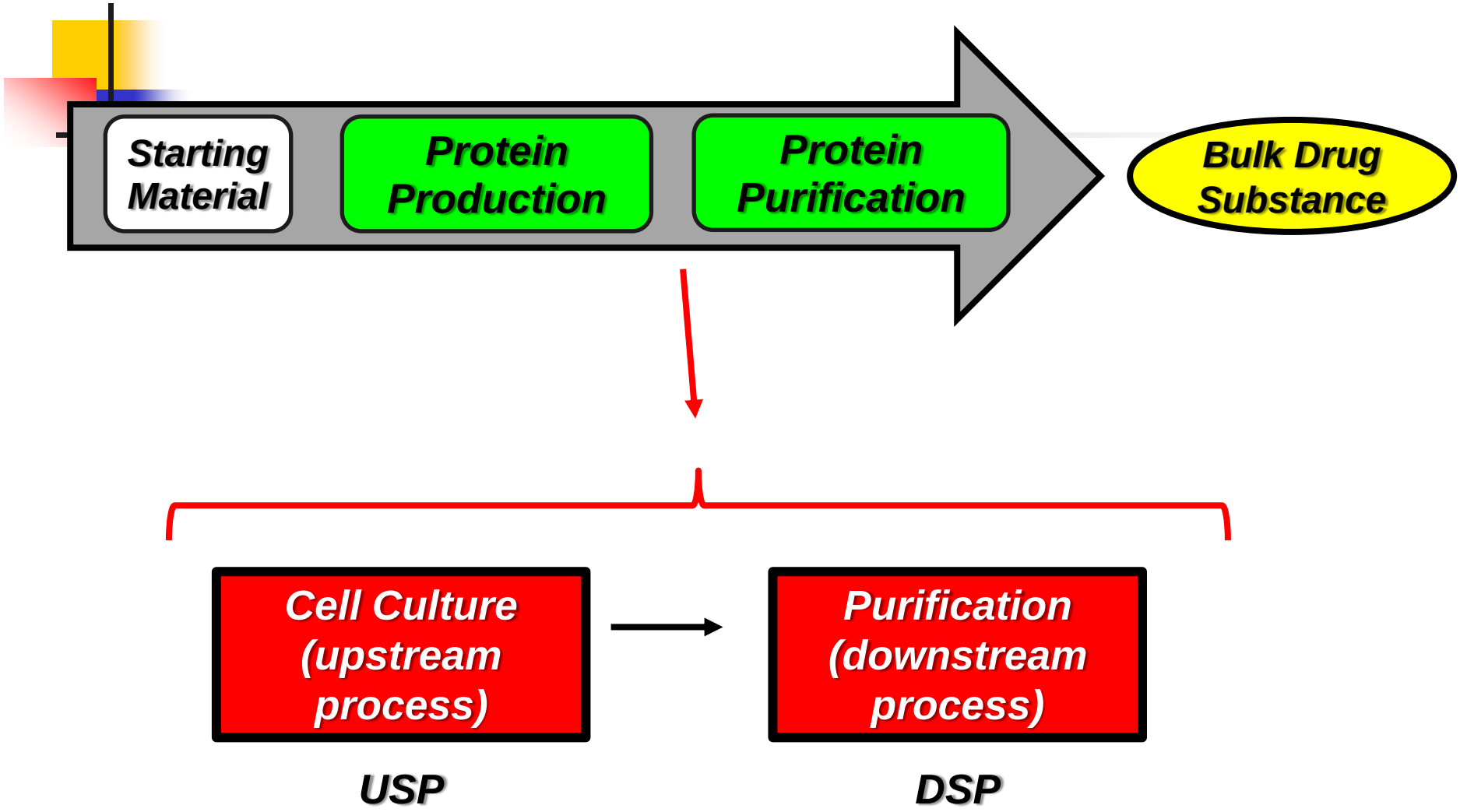
To ensure continuous, uninterrupted production of pharmaceuticals, manufacturers should carefully consider the steps that can be taken to provide for protection from catastrophic events that could render the cell bank unusable. Examples of these events include fires, power outages and human error. Manufacturers 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



Genentech video

Manufacture of Monoclonal Antibodies (Genentech) 4 min

Many Choices for the Manufacturing Cell Culture Production Process

Choice of Recombinant Host Cell

- Bacterial
- Yeast
- Insect
- Animal
- Human

glycosylation ↓

protein complexity ↓

Choice of Bioreactor Operational Mode

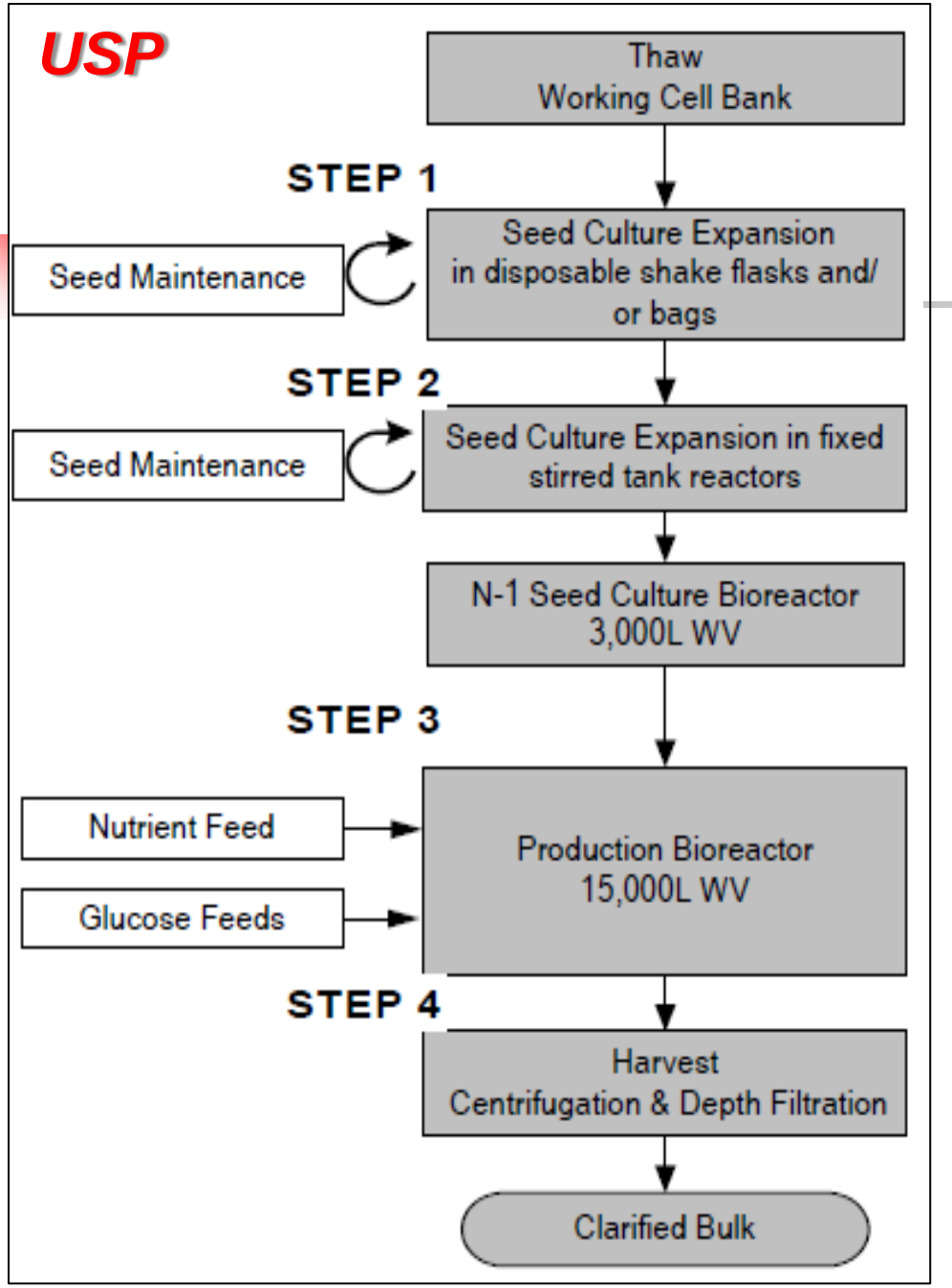
- **Fed-Batch Mode**
  fresh culture medium is added to the bioreactor in fixed volumes throughout the process, while neither cells nor medium nor product leave the bioreactor
- **Perfusion Mode (continuous)**
  fresh culture medium is continuously added to the bioreactor while removing an equivalent amount of medium (and product)

Choice of Batch Size (Liters of Bioreactor)

100L → 500L → 1000L → 2000L → 5000L → → 25,000L

Choice of Bioreactor Type

- In-place stainless steel tanks (hard-piped)
- Single-use bioreactors (SUBs; disposable)



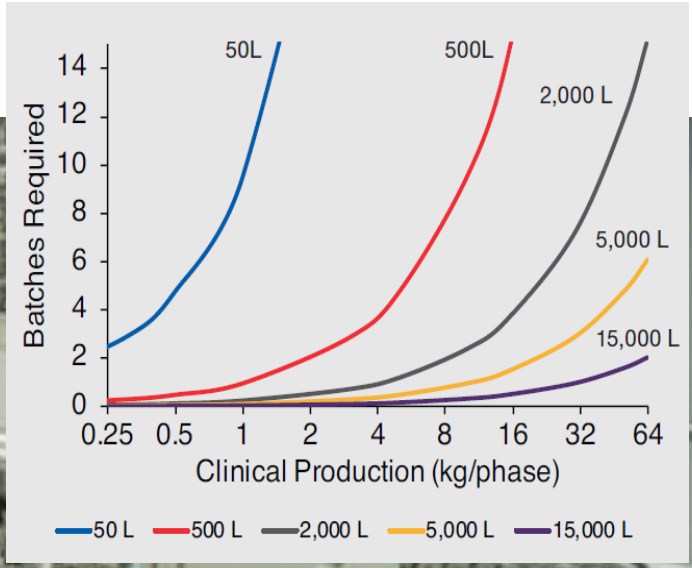
Cell culture production of monoclonal antibodies

'platform approach'

Current Production Trends

- ***~80% of bioprocessing involves mammalian cell culture (mostly CHO)***
- ***Fed-batch dominates over perfusion (continuous) bioprocessing***
- ***Production Average: ~ 4g mAb/L***
- ***Production Cost: ~$100-300/g mAb***
- ***Production Capacity:***
  - ***5+ million liters (USA)***
  - ***5+ million liters (Europe)***
  - ***2+ million liters (Asia)***

Need more rprotein or monoclonal antibody – scale up production!



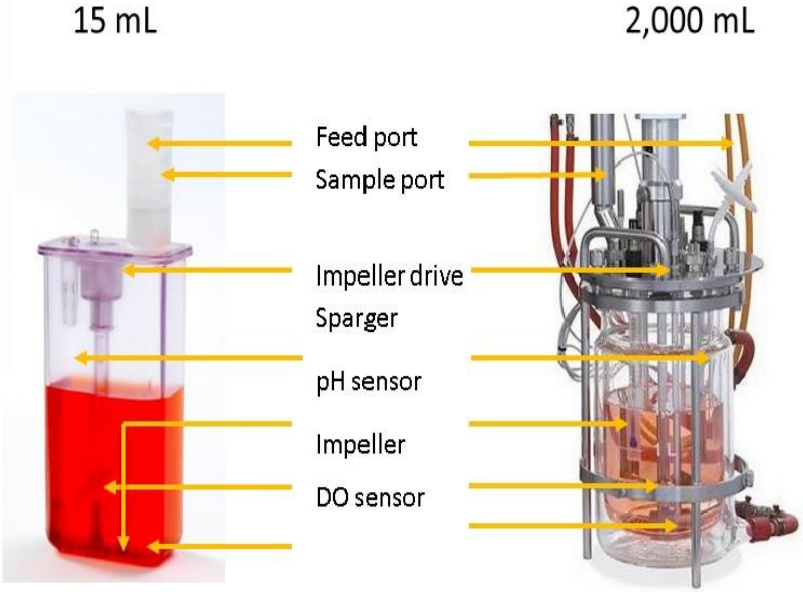
SAMSUNG BIOLOGICS

620,000 L of biomanufacturing capacity (by 2023)

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

DOE



<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, …

Commonality of Upstream Manufacturing Processes

Recombinant Protein/mAb	Gene-Based Recombinant Virus
Recombinant WCB Thaw	Host Cell WCB HEK293 Thaw
Recombinant Cell Expansion	Host Cell Expansion
Protein Induction (Temperature Shift)	Cell Transfection (Plasmid Transfection)
Protein Expression	Virus Propagation

suspension cell culture
(common for protein production)

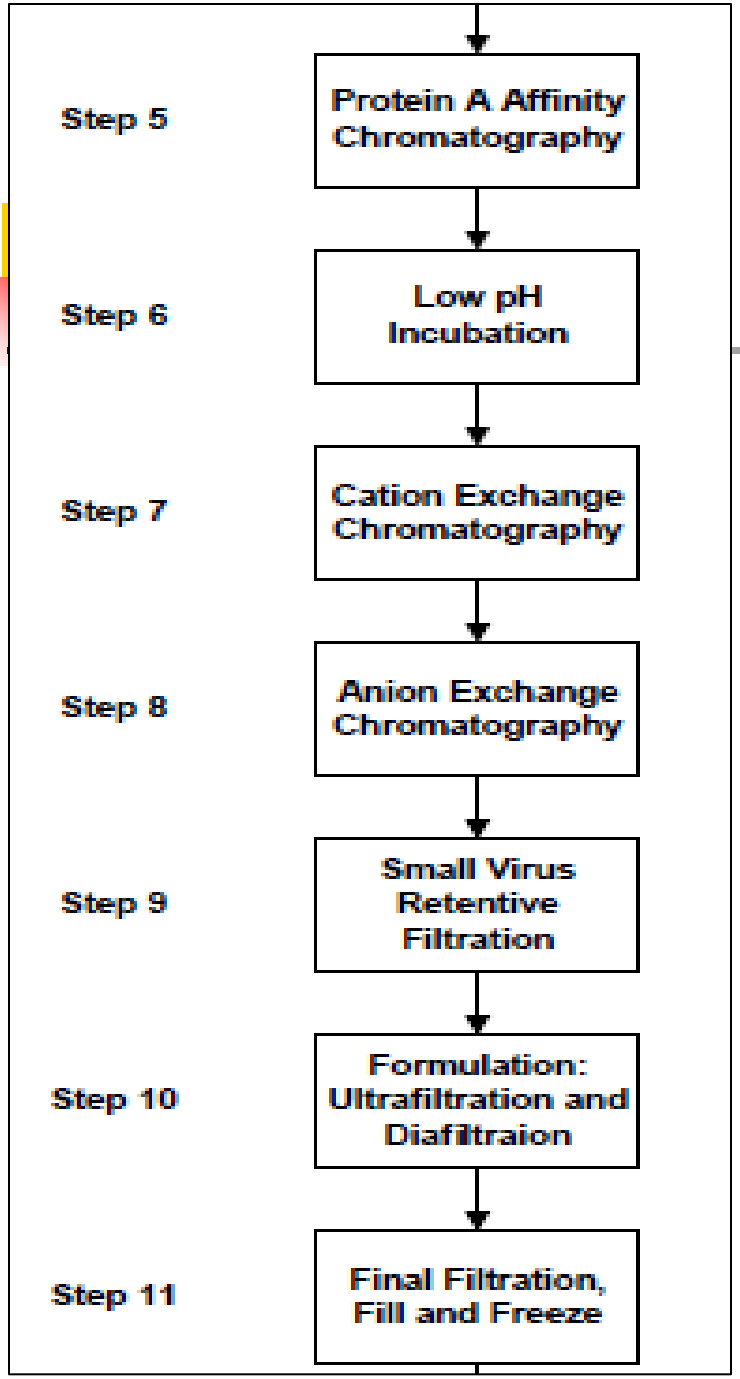
adherent cell culture
(common for virus production)

Many Choices for the Manufacturing Purification Process

Chromatography Columns

Affinity
Anion Exchange
Cation Exchange
Reversed Phase
Size Exclusion
Hydrophobic Interaction

0.2 µm Filtration (microbe removal)
0.1 µm Filtration (mycoplasma removal)
~ 20 nm Nanofiltration (virus removal)



DSP

Purification of monoclonal antibodies

'platform approach'

Current Purification Trends

- ***Protein A affinity chromatography remains the initial purification step***
- ***'Putative virus' protection with low pH treatment early and nanofiltration later in the purification process***
- ***Considerable adoption of single use (disposable) filter cartridges, buffer bags, and eluant collection bags in the purification process***

But, don't let the DSP 'predictability' lull you into not confirming the science for your protein purification process

Product-Related Impurities: aggregation, deamidation, oxidation, SV, …

Process-Related Impurities: HCDNA, HCP, surfactants, leachables, …

Viral Safety Clearance: putative virus

Individual purification steps

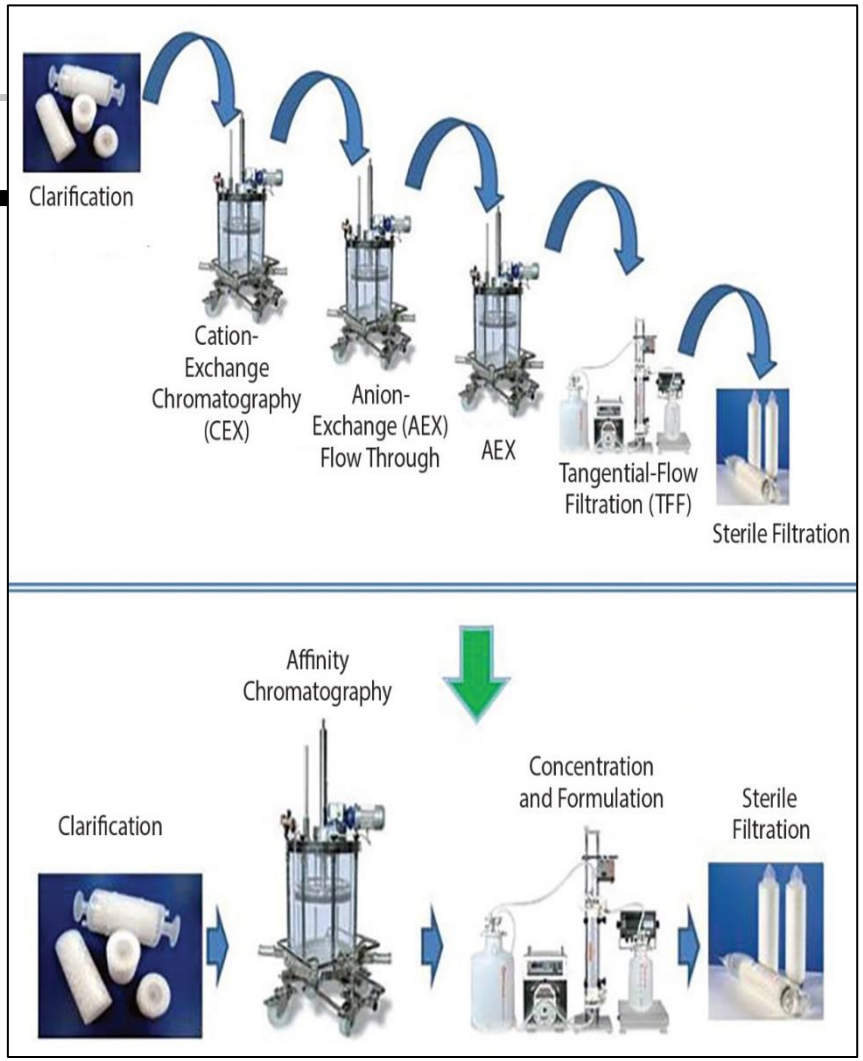
'Robust'	*≥ 4 log_{10} reduction*	*(e.g., viral clearance by low pH)*
'Polishing'	*1-3 log_{10} reduction*	*(e.g., impurities by AEX Membrane flowthrough)*

Overall residual removal

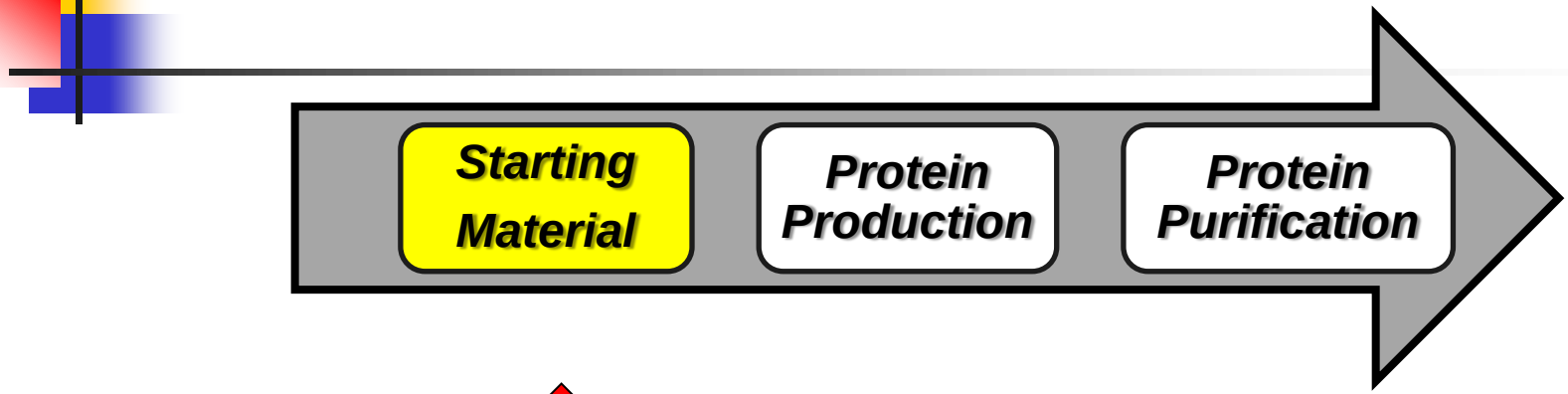
Must be below identified safety thresholds (e.g., HCDNA NMT 10 ng/dose) or regulatory informal concern levels (e.g., HCP <100 ppm)

Commonality of Downstream Manufacturing Processes

Recombinant Protein/mAb	Gene-Based Recombinant Virus
Release/Clarification (Removal of Cells/Debris)	Release/Clarification (Removal of Cells/Debris)
Multiple Purification Process Steps	Multiple Purification Process Steps
TFF (buffer exchange, concentration)	TFF (buffer exchange, concentration)
0.2µ Bioburden Filtration	0.2µ Sterile Filtration
API (Purified Protein)	API (Purified Virus)



4 Major CMC regulatory compliance issues impacting recombinant protein/mAb USP/DSP manufacturing processes



#1

MCB → WCB

"Why worry about the Working Cell Bank (WCB)?
There is no reason it can cause any manufacturing problems."

Regulatory authorities express concern about the WCB even at the clinical development stage

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.

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

Heightened regulatory authority concern at the commercial stage

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>

WCB problem discovered during BLA PLI

WCB not homogeneous; inconsistent viability upon thaw

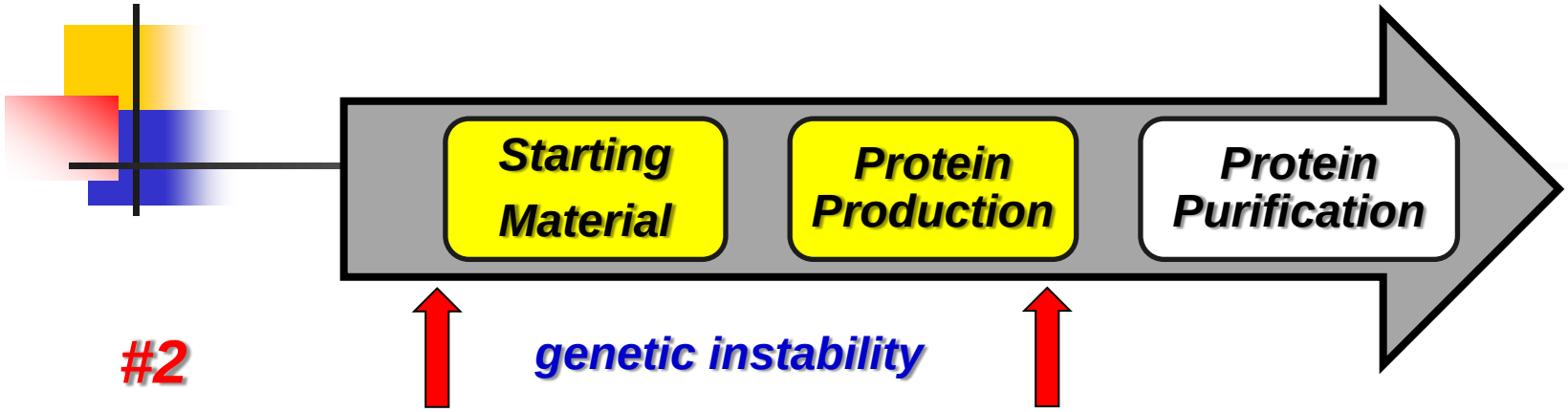
CHO cell line producing a mAb ***Genentech***

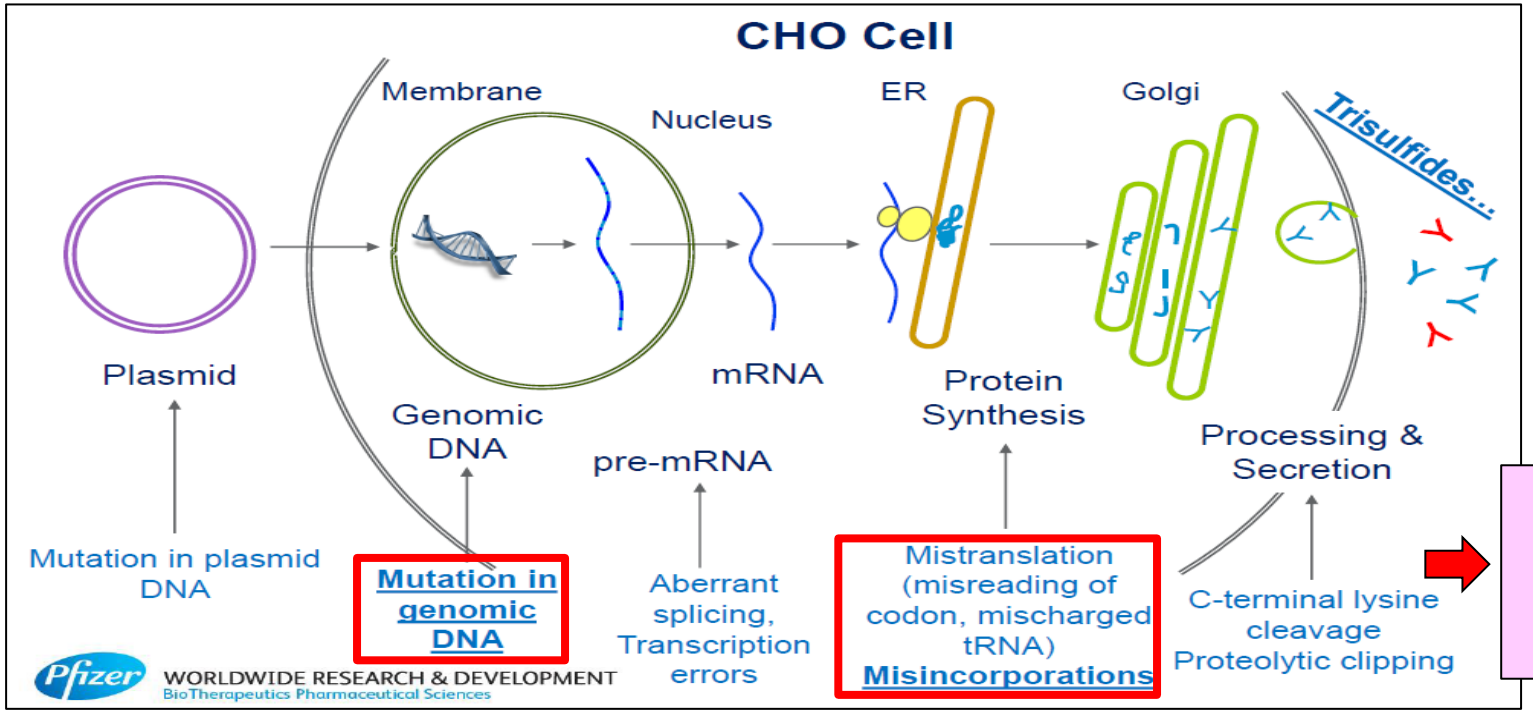
In addition, while inspecting the facility,
we discovered that the Sponsor was experiencing serious issues with the thaw and subsequent propagation of cells from WCB__ used to manufacture pertuzumab.
At the time of inspection, the root cause investigation was ongoing and no root cause had been identified, although data suggested instability of WCB … 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 Drugs – Search Drugs@FDA: FDA Approved Drug Products: Perjeta (Pertuzumab) – Approval History, Letters, Reviews and Related Documents – Chemistry Review – Product Quality Review Data Sheet (May 31, 2012)

more on this story when we get to process validation

4 Major CMC regulatory compliance issues impacting recombinant protein/mAb USP/DSP manufacturing processes





Genetic changes happen more often than one might expect!

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

According to the industry survey →

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 Example

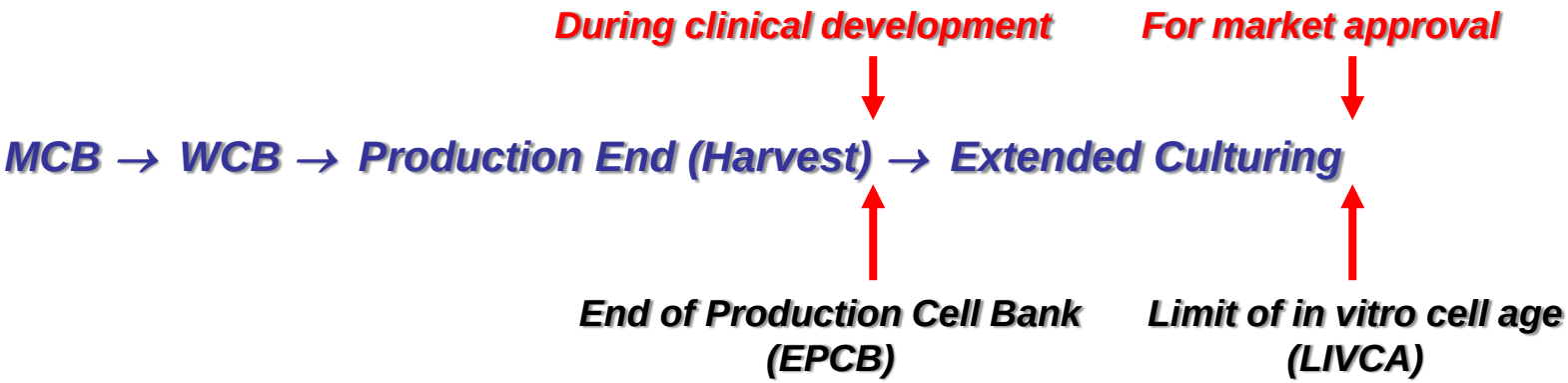
Aybintio bevacizumab **EPAR** 25 June 2020 EMA/380645/2020

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.

Samsung Biosimilar to Avastin (Genentech)

Evaluation of genetic stability

Required for clinical development: from MCB → EPCB
Required for market approval: from MCB → EPCB → → Extended culturing (LIVCA)



- ***Identification of any change in the amino acid sequence of the expressed protein***
- ***Identification of any change in the nucleic acid sequence of the cells DNA/RNA***
- ***Confirmation of absence of latent virus induction (insect/mammalian/human cells)***

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

ICH Q5B/Q5D

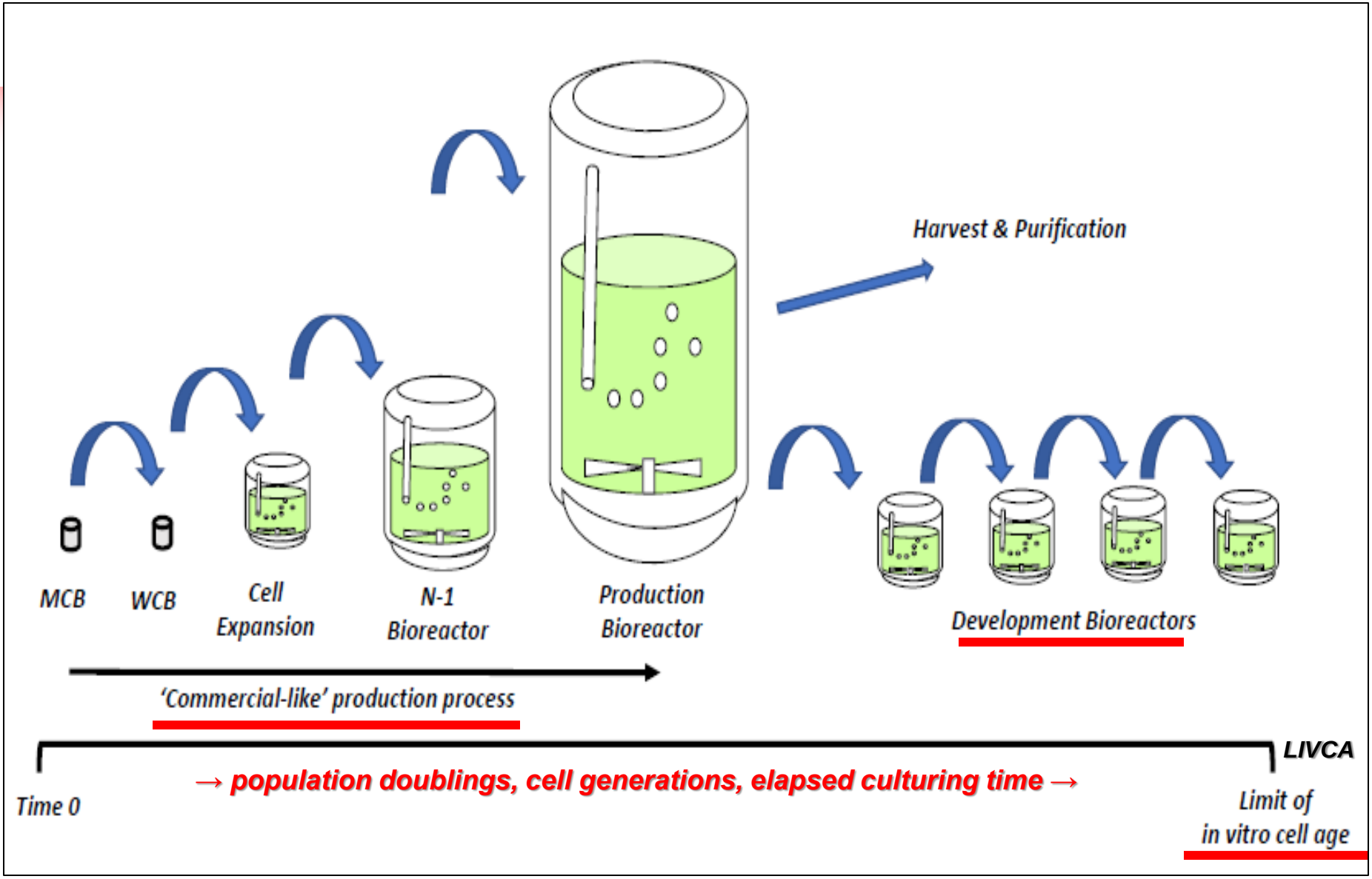
USP <1042> Cell Banking

LIVCA for inclusion in BLA/MAA submission

5.1 Genetic Characterization

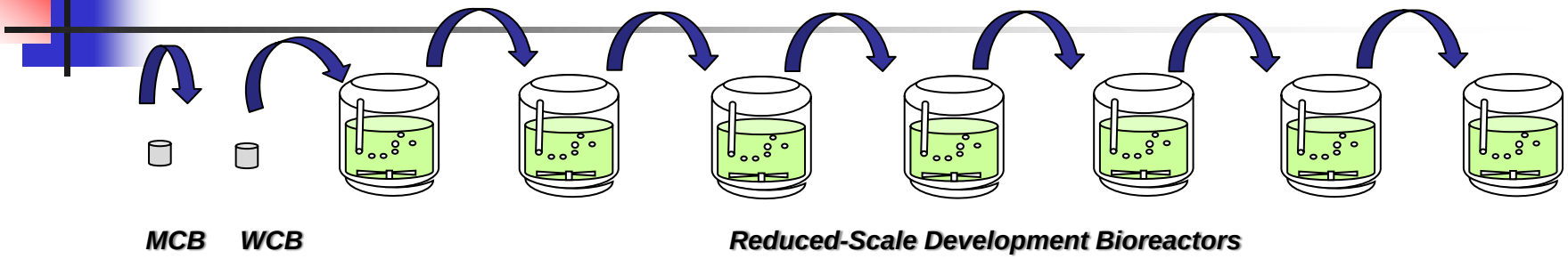
Genetic characterization to support the use of the production cell line at MCB, WCB, and end of production cells (EOP) is essential for any development program and is expected for regulatory adherence as per ICH Q5B and Q5D guidelines. Its purpose is to demonstrate the integrity of the expression construct carrying the GOI throughout the intended commercial manufacturing. The manufacturing cell culture duration starts from the cell banks (MCB and/or WCB) and continues to the proposed limit of in vitro cell age (LIVCA) for the DS production. It is recommended that LIVCA be determined based on the cell age of the EOP cells by a defined duration beyond the routine commercial DS manufacturing process. At a minimum, LIVCA should have 10 population doubling levels (PDLs) beyond the typical manufacturing window as per EMA guideline 3AB4A (9). The additional generations are added to allow for future changes to the manufacturing process and to ensure that the LIVCA is not exceeded in future manufacturing operations. The EOP cells should be harvested from a representative commercial process, either at a pilot scale or a commercial scale.

***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]

Genetic instability is observed in commercial mAbs!

Case Example

Copy number loss

Inflectra MAb (Infliximab Biosimilar) EPAR Hospira 2013

Sp2/0 murine cells

Cells at the limit of *in vitro* cell age were characterised from the EPCB and acceptable testing results for the EPCB are provided. Retrovirus particles have been identified, as expected for this cell line. Genetic stability testing for the EPCB compared with the MCB indicated a significant reduction in gene copy number, but although this affects productivity, the quality of CT-P13 from the EPCB was shown to be acceptable. Evaluation using a scale-down model showed similar growth profiles from the MCB to the EPCB, but clear differences in the cumulative product titre were demonstrated. Product quality was

CQAs → no impact
KPIs → yield lowered

KPI – key process indicator

Case Example

Chromosomal gene translocation ('jumping genes')

Merck Serono SA

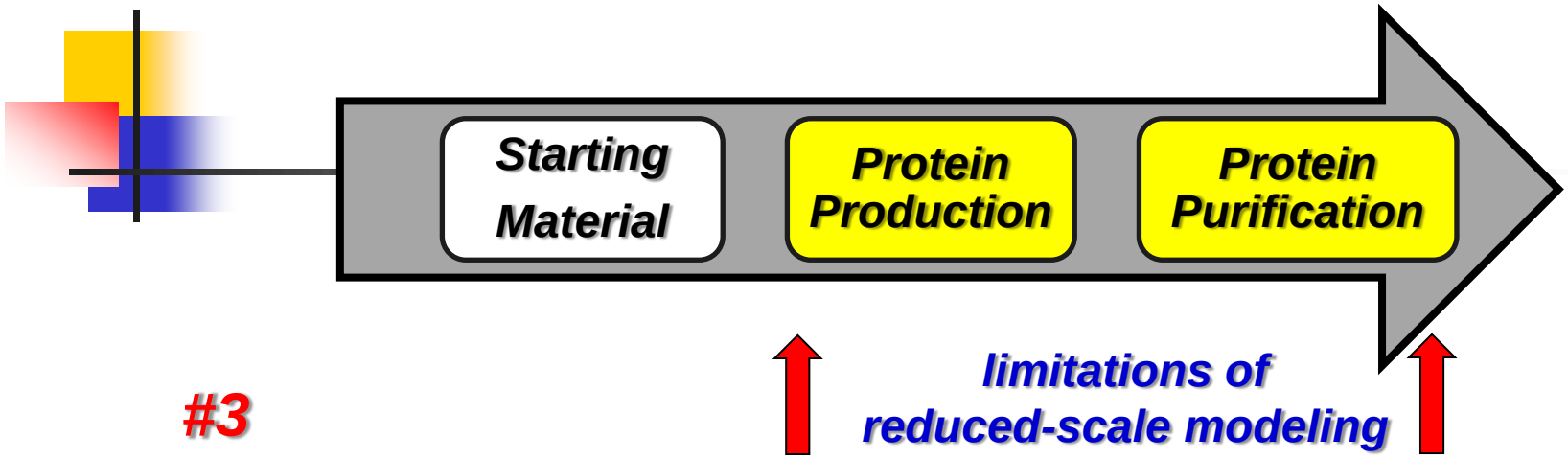
ABSTRACT: During the validation of an additional working cell bank derived from a validated master cell bank to support the commercial production continuum of a recombinant protein, we observed an unexpected chromosomal location of the gene of interest in some end-of-production cells. This event—identified 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.

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

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

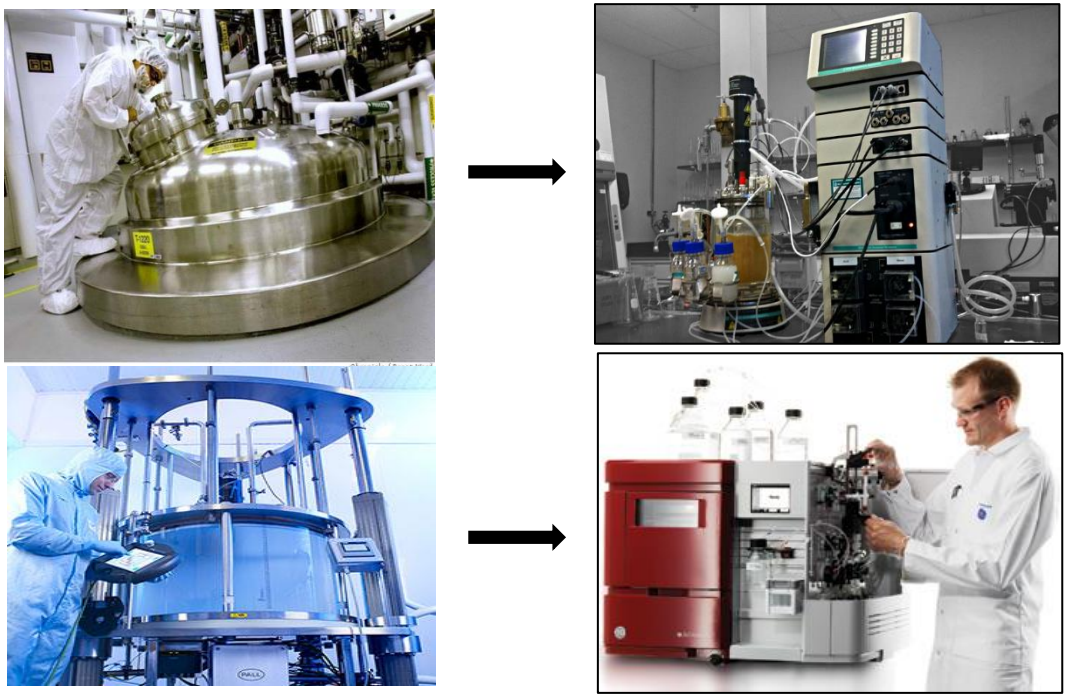
CQAs → no impact
KPIs → no yield impact

4 Major CMC regulatory compliance issues impacting recombinant protein/mAb USP/DSP manufacturing processes



#3

Not always easy to VISUALIZE the connection between full scale and scaled-down!



Scaled-down models are absolutely necessary for biopharmaceuticals!

due to the limitations of full-scale studies

- ***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, scaled-down models 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."*

British mathematician and statistician George E P Box

parsimonious – frugal, stingy

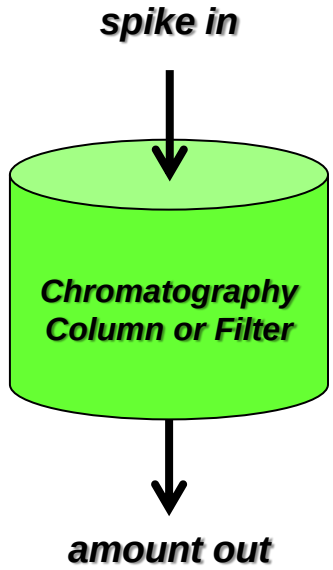
Scaled-down models are used throughout the biopharmaceutical manufacturing process!

UPSTREAM PROCESS (UPS)

- *Cell culture media optimization, and identification of critical raw material attributes*
- *Identification of cell culture CPPs (DOE)*
- *Genetic stability (limit in-vitro cell age)*

DOWNSTREAM PROCESS (DSP)

- *Identification of purification CPPs (DOE)*
- *Process hold times*
- *Clearance studies*
  - *Putative virus safety (low pH, chromatography, nanofiltration)*
  - *Process-related impurities (host cell DNA and proteins, Protein A leachables)*
  - *Product-related molecular variants (oxidation, deamidation, aggregates)*
- *Chromatographic resin use life*



Regulatory authorities expect justification of scaled-down studies compared to the commercial scale 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 demonstration of the suitability of the small-scale model can enable manufacturers to propose process validation with reduced dependence on testing of commercial-scale batches. Data derived from commercial-scale batches should confirm results obtained from small-scale studies used to generate data in support of process validation. Scientific grounds, or reference to guidelines which do not require or specifically exclude such studies, can be an appropriate justification to conduct certain studies only at small-scale (e.g., viral removal).

ICH Q11

scaled-down studies need to be confirmed at commercial scale (if possible)

Important – make sure to include all relevant CQAs at the process step being evaluated in the scale-down study

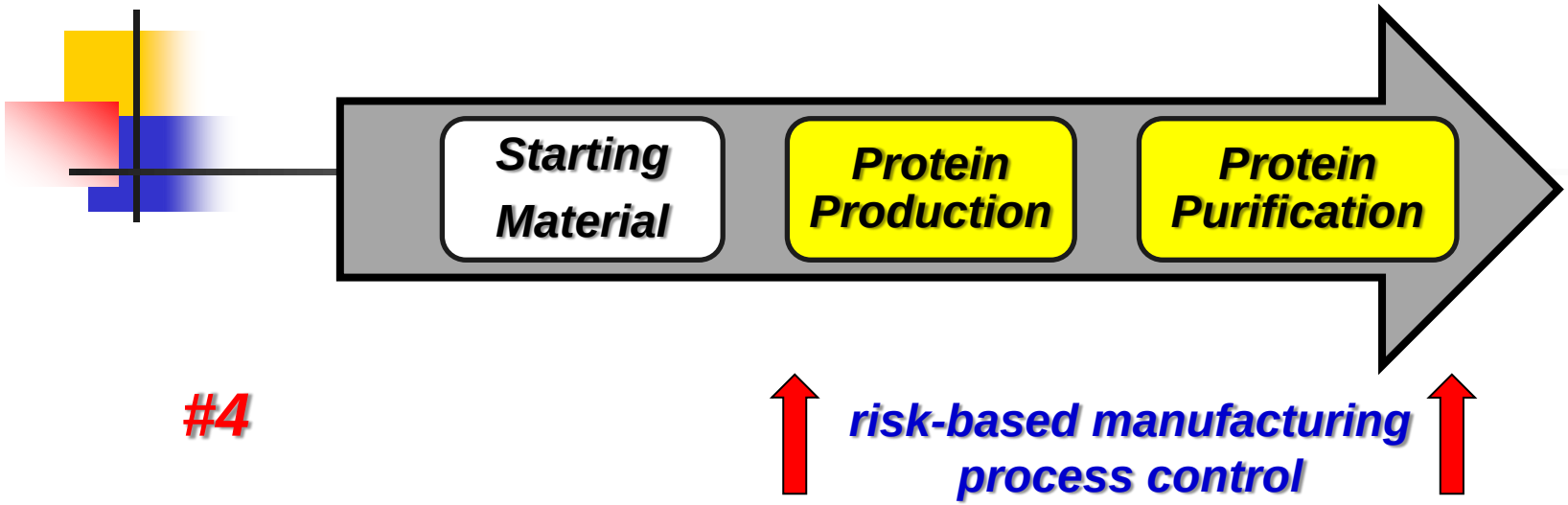
expect that regulatory authorities will review and challenge the design

Case Example: Trulicity (dulaglutide; rGLP-1-Fc) Eli Lilly

Process characterization studies used to determine the regulatory commitments in the BLA, including the process parameters and in-process controls were inadequate. These studies relied upon the use of small scale models that were not appropriately qualified. For example, the qualifications did not include all CQAs relevant to the unit operations, and the criteria used to evaluate the models were not sufficient. In addition, the process characterization studies themselves were not adequate. For example, all relevant CQAs were not included, and the process parameter ranges studied were, in some cases, too narrow. To address this issue, at the request of the Agency, the sponsor updated sections 3.2.S.2.2, 3.2.S.2.4, 3.2.P.3.3, and 3.2.S.P.3.4 of the BLA with additional regulatory commitments.

FDA Chem Review of BLA (May 30, 2014)

4 Major CMC regulatory compliance issues impacting recombinant protein/mAb USP/DSP manufacturing processes



'adequate and appropriate' risk-based control

- Stage 1 — ESTABLISHING process control
- Stage 2 — CONFIRMING process control
- Stage 3 — MAINTAINING process control

MINIMUM* CMC Regulatory Compliance *CONTINUUM

Regulatory authorities have a common concern about control of the DS manufacturing process during clinical development

Adequate and Appropriate Risk-Based Process Control

	FDA	***EMA***
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

Adequate & Appropriate Risk-Based Process Control ***at Stage 1***

S.2.5. Process validation

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

validation required for viral clearance and for sterilizing process steps

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

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

Adequate and Appropriate Risk-Based Process Control

	FDA	EMA
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)

	FDA	EMA
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 product of the desired quality (Process Performance Qualification – PPQ – batches)

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 and Appropriate Risk-Based Process Control at Stage 2

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.

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, frequently attaches to the meeting minutes, a "hot topic" list of frequently encountered PV deficiencies

Meeting Type: B
Meeting Category: Pre-BLA

Nexviazyme (avalglucosidase alfa-ngpt)

Meeting Date and Time: June 30, 2020; 11:15 AM – 12:15 PM ET
Meeting Location: Teleconference

Genzyme

www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761194Orig1s000AdminCorres.pdf

FDA Comments for Drug Substance Process Validation 3.2.S.2.5
Bioburden and endotoxin data obtained during manufacture of 3 process qualification (PPQ) lots
Bioburden and endotoxin data (before and after maximum hold time) from 3 successful product intermediate hold time validation runs at manufacturing scale
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
Information and summary results from the shipping validation studies
FDA Comments for Drug Product Process Validation 3.2.P.3.5
Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the 3 validation studies and describe the equipment and component revalidation program
Bioburden and endotoxin data (before and after maximum hold time) from 3 successful product intermediate hold time validation runs at manufacturing scale
3 successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs
Information and summary results from the shipping validation studies

why '3'? →

Number of Process Validation Replicates That Keep Coming UP

The '3 Run' Rule

Entrenched Industry Standard

3 successful, consecutive manufactured batches of drug substance / drug product representative of the commercial scale

Where did the '3 run' rule originate?

Statistical value of 3 runs?

→ ***Monty Python***

Monty Python – ‘Quest for the Holy Grail’ – Bridge of Death 3 min

The '3 Run' 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? How comprehensive is the control strategy?	Are all CQAs identified? How robust is the product stability profile?	Level of batch-to-batch variation? Process capability knowledge?

Determine overall residual risk level

Translate into number of PPQ batches to run

QUESTION: So how many PPQ batches will you run?

The dostarlimab active substance manufacturing process has been validated. The approach taken to validate dostarlimab manufacturing process is based on an enhanced approach, where the process is demonstrated to perform consistently and dostarlimab meets all the biochemical, functional and microbiological acceptance criteria.

Four active substance batches were successfully processed through upstream process and three consecutive batches were fully executed through the downstream process and were successfully processed to active substance. One batch was terminated due to a non-process related contamination in the harvest tank (root cause established). Thus, consistency in production has been shown on three consecutive full-scale commercial batches. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces dostarlimab active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

The dostarlimab active substance process has adequately demonstrated the removal of process related impurities (e.g. host cell proteins (HCP), host cell DNA, media components) at acceptably low levels. Additional impurities risk assessments and spiking studies have been provided.

Concurrent at scale validation protocols have been provided for chromatography resin lifetimes, UF/DF membranes lifetimes and reprocessing for viral filtration and final filtration prior bulk fill. Small scale resin lifetime studies and reprocessing studies have been included. Ongoing process verification will be used to monitor the validated commercial dostarlimab manufacturing process.

Biologic process validation missteps unfortunately occur!

Case Example

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)

FDA meeting minutes Complete Response Letter discussion

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. T his 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)

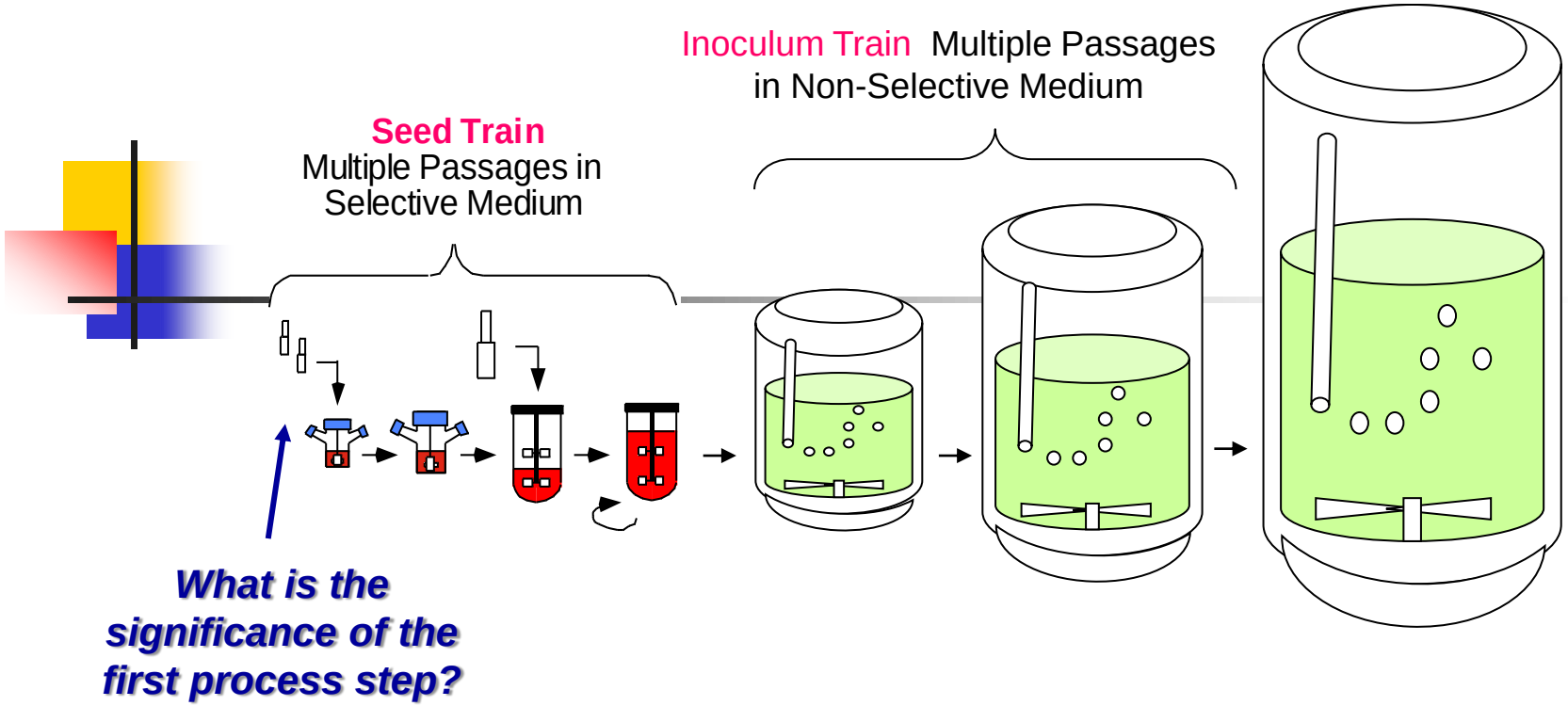
Biologic process validation missteps unfortunately occur!

Case Example

Genentech
Perjeta (pertuzumab)

BLA filed with FDA; during the Pre-Approval Inspection (PAI), FDA inspectors raised the alarm that the manufacturing process is not validated

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



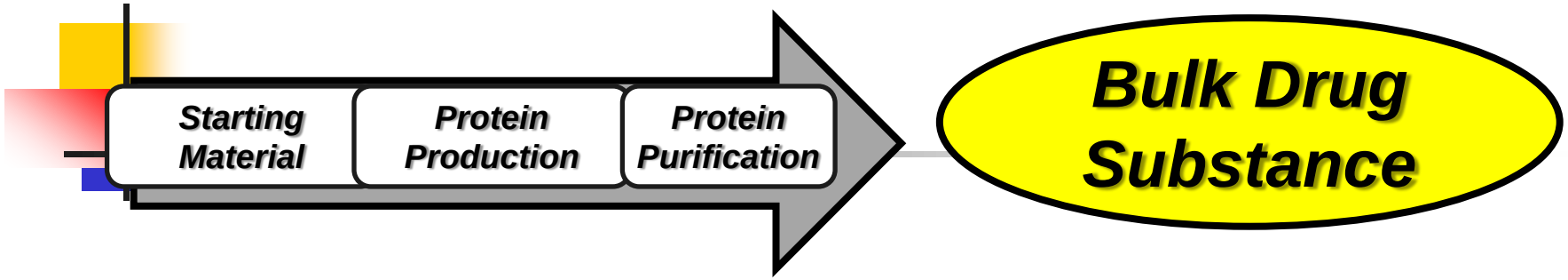
Summary Review for Regulatory Action

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.

Applied Risk-Management Across the Manufacturing Process



During Clinical Development

- *Molecular Characterization*
- *Impurity Profile*
- *In-Process Controls (IPCs)*
- *DS Specifications (CQAs)*
- *DS Stability*

- ***Molecular Characterization***

Characterisation of a biotechnological or biological substance (which includes the determination of physico-chemical properties, biological activity, immuno-chemical properties, purity and impurities) by appropriate techniques is necessary to allow a suitable specification to be established. Reference to literature data only is not acceptable, unless otherwise justified by prior knowledge from similar molecules for modifications where there is no safety concern (e.g. C-terminal lysine for monoclonal antibodies). Adequate characterisation should be performed in the development phase prior to phase I and, where necessary, following significant process changes.

All relevant information available on the primary, secondary and higher-order structure including post-translational (e.g. glycoforms) and other modifications of the active substance should be provided. Details should be provided on the biological activity (i.e. the specific ability or capacity of a product to achieve a defined biological effect). 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.

EUROPEAN MEDICINES AGENCY

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

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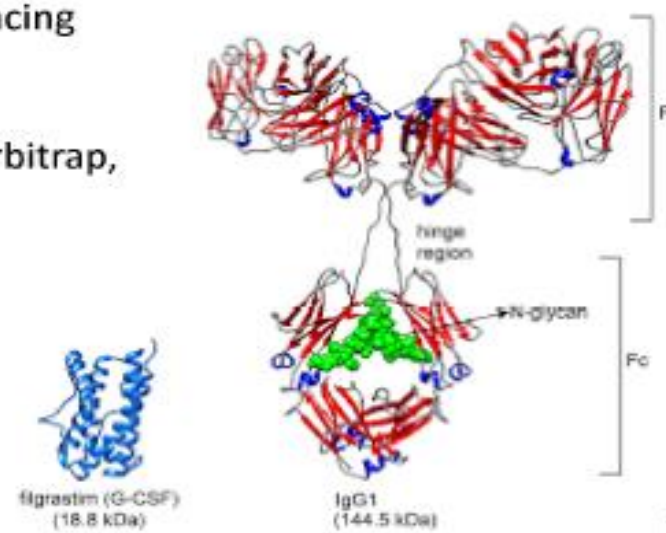
***Mature* testing tool box for characterization of mAbs**

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



Japelj et al Sci Reports 2016

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

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

- ***Impurity Profile*** ***(comparison)***

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

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.

Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials

27 January 2022
EMA/CHMP/QWP/545525/2017 Rev. 2

In cases where reference to a pharmacopoeial monograph listed above cannot be made, impurities (e.g. degradation products, residual solvents) deriving from the manufacturing process or starting materials relevant to the drug substance used for the clinical trial, should be stated.

Discussion on (potential) mutagenic impurities according to ICH M7 should be provided (structure, origin, limit justification). The level of detail necessary depends on the phase of the clinical trial.

Absence of routine control for solvents/catalysts used in the manufacturing process should be justified.

Biopharmaceutical impurity limits are proprietary, EXCEPT for commercial vaccine recombinant proteins (FDA Package Insert)

VBI Vaccines

PREHEVBRIO
Hepatitis B Vaccine (Recombinant)

BLA APPROVAL
November 30, 2021

PREHEVBRIO contains the small (S), middle (pre-S2) and large (pre-S1) hepatitis B surface antigens, co-purified from genetically modified CHO (Chinese Hamster Ovary) cells cultured in growth medium containing vitamins, amino acids, minerals, and fetal bovine serum.

The hepatitis B surface antigens are co-purified from the supernatant of CHO cells by a series of physicochemical steps as virus-like particles containing CHO cell membrane lipids.

Each 1.0 mL dose is formulated to contain 10 mcg hepatitis B surface antigens (S, pre-S1 and pre-S2) adsorbed on aluminum hydroxide [$Al(OH)_3$] as an adjuvant (aluminum content of 0.5 mg/mL).

Each 1.0 mL dose of PREHEVBRIO also contains sodium chloride (NaCl) (8.45 mg/dose), potassium chloride (KCl) (0.02 mg/dose), disodium hydrogen phosphate dodecahydrate ($Na_2HPO_4.12H_2O$) (0.38 mg/dose), potassium dihydrogen phosphate anhydrous (KH_2PO_4) (0.02 mg/dose) and water for injections (WFI). Each dose may contain residual amounts of CHO cell proteins (up to 2.5 ng/dose), CHO cell DNA (up to 10 pg/dose), Bovine Serum Albumin (up to 2.5 ng/dose) and Formaldehyde (up to 500 ng/dose) from the manufacturing process.

Host Cell Protein (CHO HCP)	***≤ 250 ng/mg***
Host Cellular DNA	***≤ 1 ng/mg***

Fetal Bovine Serum (FBS)	***≤ 250 ng/mg***
Formaldehyde	***≤ 50 µg/mg***

But note, only 3 x 10 µg doses total!

Vaccines want to be immunogenic!

- ***In-Process Controls (IPCs)***

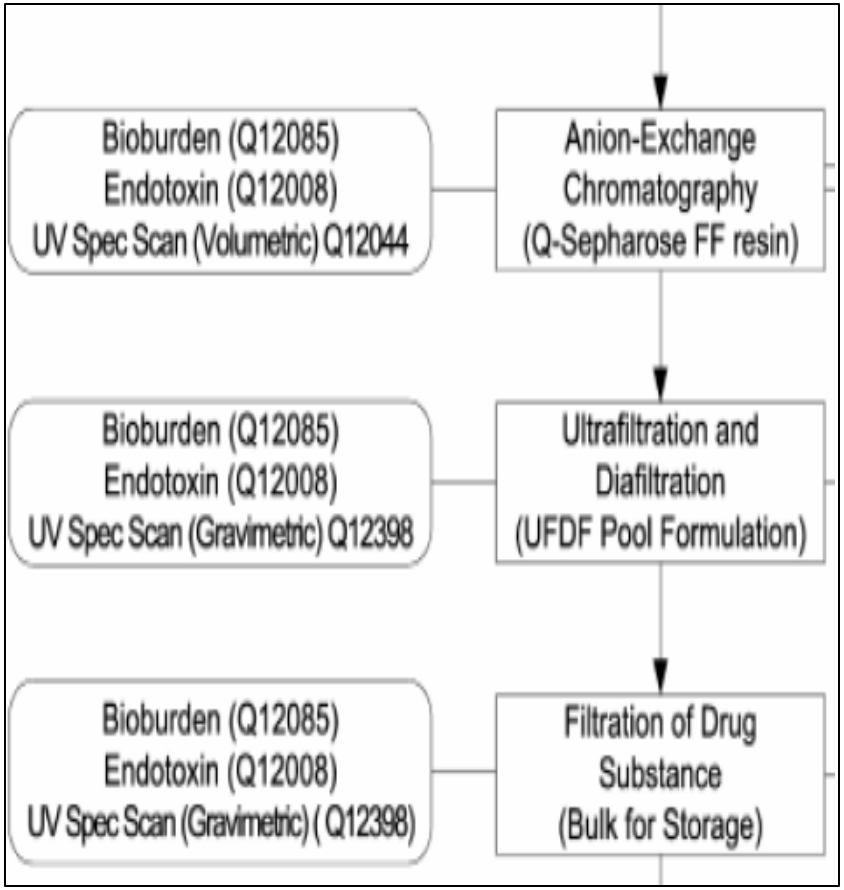
For each purification process step – to be developed during clinical development

MINIMUM

Microbial Control

Bacterial Endotoxin

Protein Content
(for step yield calculation)



- ***DS Specifications (CQAs)***

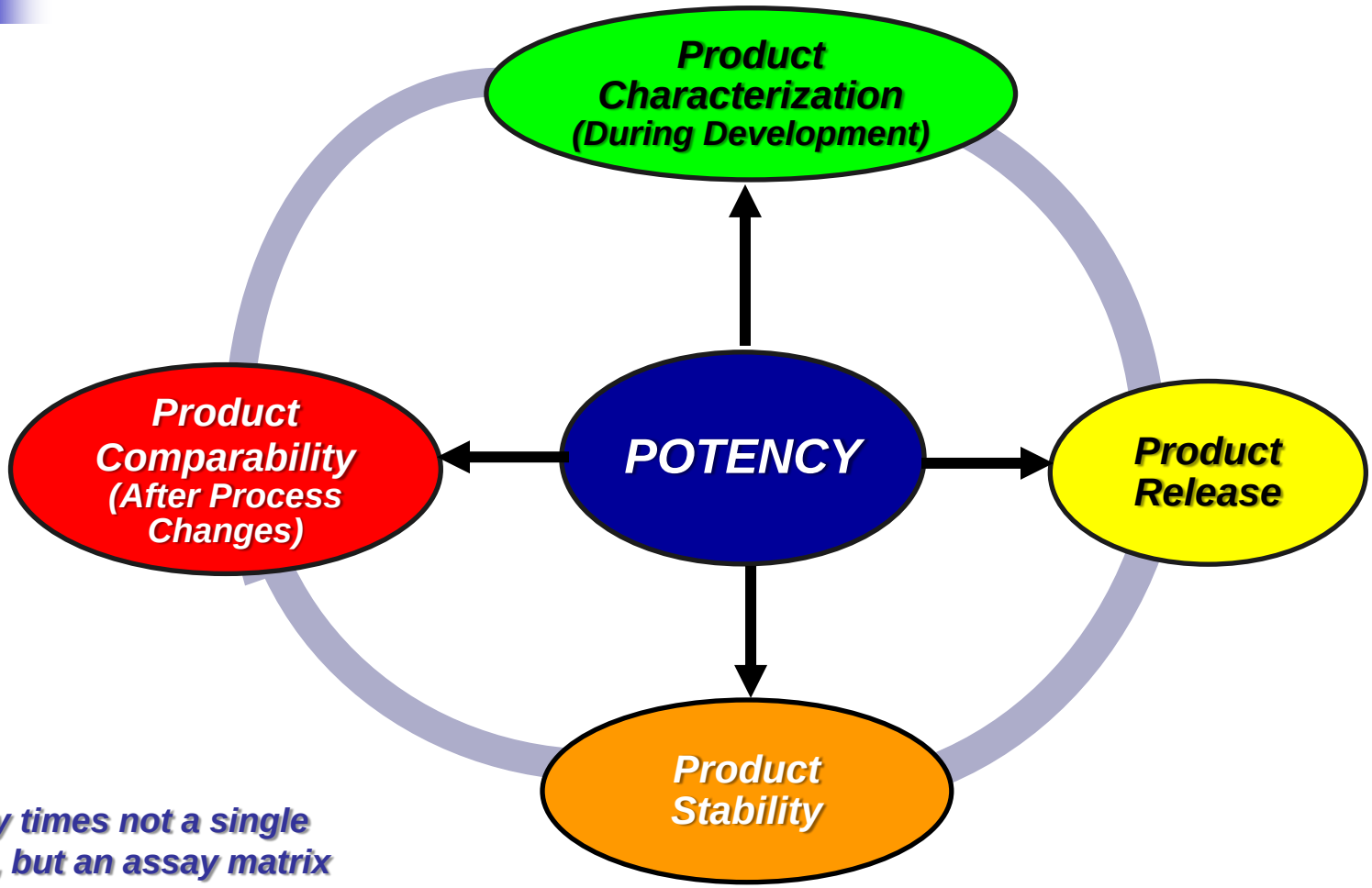
The specification for the batch(es) of active substance to be used in the clinical trial should define acceptance criteria together with the tests used to exert sufficient control of the quality of the active substance. Tests and defined acceptance criteria are mandatory for quantity, identity and purity 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).

POTENCY CQA – the center of a strong control strategy

need in place sooner than later!



many times not a single assay, but an assay matrix

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

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%)		
Purity by NR-CE-SDS[a]		
Main Peak (%CPA)	*molecular size variants*	
Sum of LMW Forms (%CPA)		
Purity by IE-HPLC		
Main Peak (area%)		
Acidic Region (area%)	*molecular charge variants*	
Acidic Peak 2 (area%)		
Basic Region (area%)		
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??

• 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.

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

Roche 2 min

What are ADCs?

Purified mAb

Antibody-Drug Conjugate (ADC)

making a pure complex mAb even more complex

ADCETRIS (brentuximab vedotin)

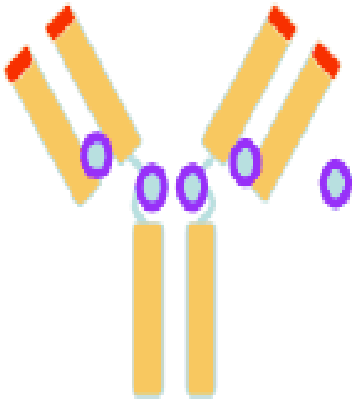
Antibody | **Chemical Linker** | **Cytotoxic Drug**

cAC10 anti-CD30 antibody

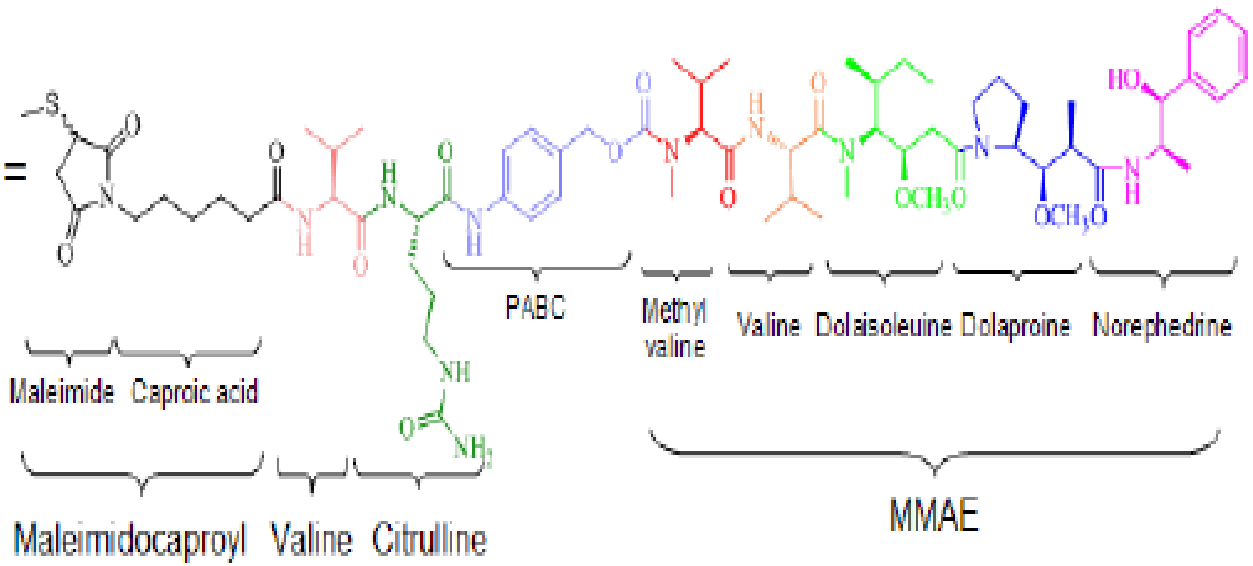
Attachment group

Protease-cleavable linker

MMAE cytotoxic drug



~ 4 MMAE molecules linked to a mAb molecule



The Multi-Step Manufacturing Challenges of ADCs

1st part, all of the manufacturing challenges of the mAb

as previously discussed

MONOCLONAL ANTIBODY (mAb) Intermediate		
Process Stage	***CMC Regulatory Compliance Concerns (FDA/EMA)***	***Biologic mAb***
Source Material (MCB/WCB)	**Absence of Adventitious Agents** **Clonality** **Stability** **Inventory**	✓ ✓ ✓ ✓
Cell Culture Expansion & Production	**Absence of Adventitious Agents** **Consistency of Bioreactor Production** **Critical Process Parameters (CPPs)** **Acceptable Productivity**	✓ ✓ ✓ ✓
Purification	**Consistency of Purification** **Impurity Profile (e.g., HCP, DNA)** **Product Recovery (Overall Yield)**	✓ ✓ ✓
mAb Intermediate	**Consistency of mAb Batches** **Characterization of mAb** **Critical Quality Attributes (CQAs)** **Stability of mAb**	✓ ✓ ✓ ✓

The Multi-Step Manufacturing Challenges of ADCs

2nd part, the manufacturing challenges of the chemical linker + cytotoxic drug

enter the world of chemical drug manufacturing process control

LINKER-DRUG Intermediate			
Process Stage	***CMC Regulatory Compliance Concerns (FDA/EMA)***	***Chemical Linker***	***Chemical Toxin***
Chemical Synthesis	**Starting Material** **Consistency of Manufacturing** **Critical Process Parameters (CPPs)** **Impurity Profile** **(Organic Solvents, Elements, Mutagenic)** **Stability** **Safety of Manufacturing/QA Staff**	✓ ✓ ✓ ✓ ✓	✓ ✓ ✓ ✓ ✓ ✓
Linker-Toxin Intermediate	**Chemical Reaction of Linker + Toxin** **Characterization of Linker-Toxin** **Critical Quality Attributes (CQAs)** **Stability of Linker-Toxin** **Safety of Manufacturing/QA/QC Staff**	✓ ✓ ✓ ✓ ✓	

The Multi-Step Manufacturing Challenges of ADCs

3rd part, the manufacturing challenges of the ADC

chemical reaction of biologic with linker-chemical drug

ANTIBODY DRUG CONJUGATE Drug Substance		
Process Stage	**CMC Regulatory Compliance Concerns (FDA/EMA)**	**ADC**
Chemical Reaction	**Chemical Reaction of Linker-Toxin with mAb** **Consistency of Manufacturing** **Critical Process Parameters (CPPs)** **Impurity Profile** **(Unbound toxin)** **Acceptable Yield** **Safety of Manufacturing/QA Staff**	✓ ✓ ✓ ✓ ✓ ✓
ADC Drug Substance	**Characterization of ADC** **Critical Quality Attributes (CQAs)** **Stability of ADC**	✓ ✓ ✓

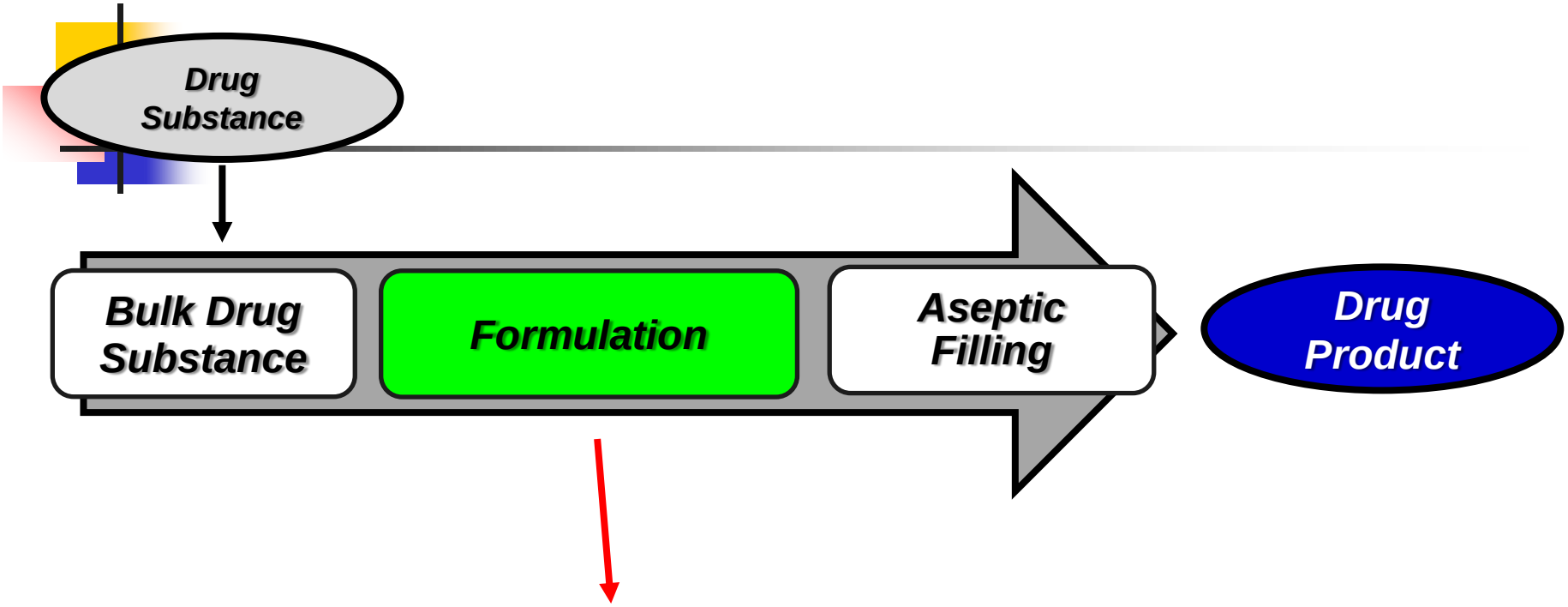
DAR →

video

What DAR do you need?

Waters DAR 6 min

Applied Risk-Management Across the Manufacturing Process



Biologic proteins need to be formulated with excipients

(but each excipient present, and its level, needs to be justified!)

(note, sometimes the final formulation is present at the bulk drug substance stage}

Recombinant protein/mAb drug products are formulated with excipients

For market approval, the excipients present and their assigned level will need to be justified: 3.2.P.2.1.2

Function of Excipients

- ***Stability of bioactivity/functionality (HOS)***
- ***Solubility of biologic product***
- ***Minimization of molecular variant formation***
- ***Bulking agent for protection during protein lyophilization***
- ***Antimicrobial preservative for multi-use delivery***

Common excipients used with mAbs

- ***Polysorbate 80****
- ***Sodium chloride***
- ***Sucrose***
- ***Histidine***
- ***Sodium phosphate***

*** Can be unstable forming peroxides (due to oxidative degradation) or releasing free fatty acids (due to residual HCP lipases)***

Case Example

Formulation development documented in BLA/MAA

Formulation development **3.2.P.2.2**

An acceptable overview of the formulation development is provided, including satisfactory data supporting the proposed composition of the commercial finished product. The rationale used to select the final composition/formulation has been described in the dossier. A formulation robustness DoE study was performed identifying the solution pH to significantly impact the Sum of HMW Forms, Acidic Region 1, and Basic Region 2. Based on these results the pH acceptance criterion was tightened to 5.8-6.2 to improve control of stability of the commercial formulation.

A low number of translucent to white visible particles (VP) has been observed during stability studies. Extended characterisation studies were performed to identify the observed particles. The results show that the particles are composed of protein and/or silicone oil and do not dissolve at room temperature, i.e. the particle formation is irreversible. VPs are routinely controlled at release and shelf life. This is acceptable.

Roche	**Enspryng** satralizumab	22 April 2021 EMA/CHMP/265568/2021	EPAR

Formulation changes are frequently necessary due to a move to 'user friendly' administrations – IV → SC

(which requires increasing protein concentrations)

Roche Rituxan/MabThera (commercial mAb)

IV admin	→	***SC admin***
10 mg/mL		***120 mg/mL***
Sodium chloride		***Histidine HCl***
Sodium citrate		***Trehalose***
Polysorbate 80		***Polysorbate 80***
		L-methionine
		Recombinant human hyaluronidase

Formulation changes even occur with biosimilars

(remember the innovator's formulation is typically 15-20 years old)

Humira (adalimumab)				
INNOVATOR	**BIOSIMILAR**			
Abbvie Humira (FDA, 2002)	Coherus Yusimry (FDA, 2021)	Samsung Hadlima (FDA, 2019)	Pfizer Abrilada (FDA, 2019)	Mylan Hulio (FDA, 2020)
Expression System CHO				
Strength: 50 mg/mL Pre-filled syringe				
Formulation				
Mannitol Polysorbate 80 Sodium phosphate Sodium citrate Sodium chloride	Polysorbate 80 Sodium chloride L-histidine Glycine	Sorbitol Polysorbate 20 Sodium citrate L-histidine	Sucrose Polysorbate 80 L-histidine L-methionine EDTA	Sorbitol Polysorbate 80 Sodium glutamate L-methionine

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, biologic formulation changes are considered '<u>high risk</u>'

(formulation components can alter the protein effect in the human body)

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

<u>Well Known Case Example (1998)</u>

- *J&J changed their pre-filled syringe formulation for its anemia drug erythropoietin – desired to remove a human-derived excipient - HSA*
- *The formulation was changed – polysorbate 80 was added to replace HSA*
- *After ~2 years on the market, a new adverse event appeared – PRCA – pure red cell aplasia – (severe anemia)*
- *MOST LIKELY CAUSE: Polysorbate 80 (a detergent) was dissolving the rubber septum in the pre-filled syringe – the leachables were associated with the risk in PRCA*

<u>Another Case Example</u> → ***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 trsnsfer?***
- ***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***

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

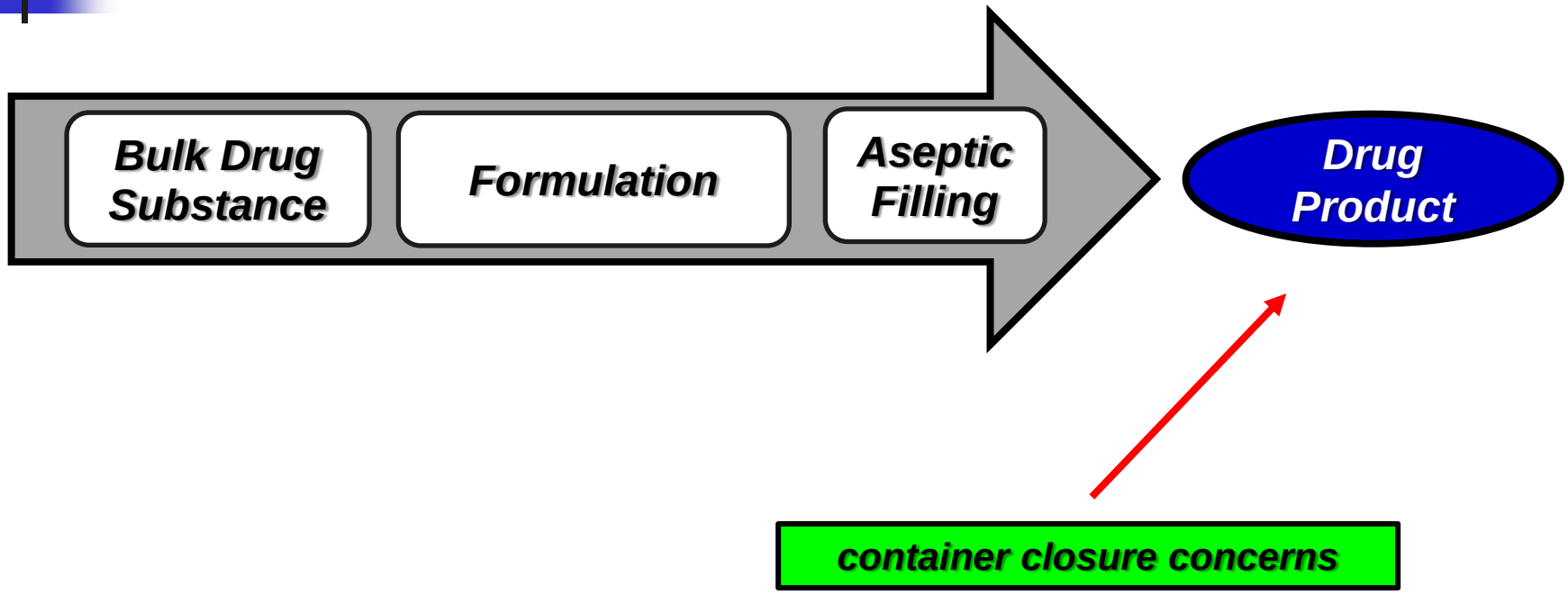
- ***"The addition of EDTA appears to increase the absorption rate of GM-CSF, the active ingredient in Leukine, and may result in a temporary increase in plasma concentration of GM-CSF shortly after administration"***
- ***Sudden protein burst caused body to go into defense mode***
- ***Fainting is part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

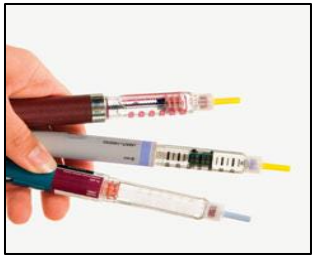


Container Closures for Biopharmaceuticals

heightened concern at all product-contact surfaces

Injection ('Parenteral') – IV, IM, SC

- ***Glass vial with rubber stopper***
- ***Pre-filled syringe***



Inhalation

- ***Aerosol nebulizer (Pulmozyme, recombinant human DNase)***
- ***Dry powder inhaler (Afrezza, recombinant human insulin)***

Topical

- ***Transdermal gel in tube (Regranex, recombinant human PD growth factor)***
- ***Eye drop adapter (Oxervate, recombinant human nerve growth factor)***

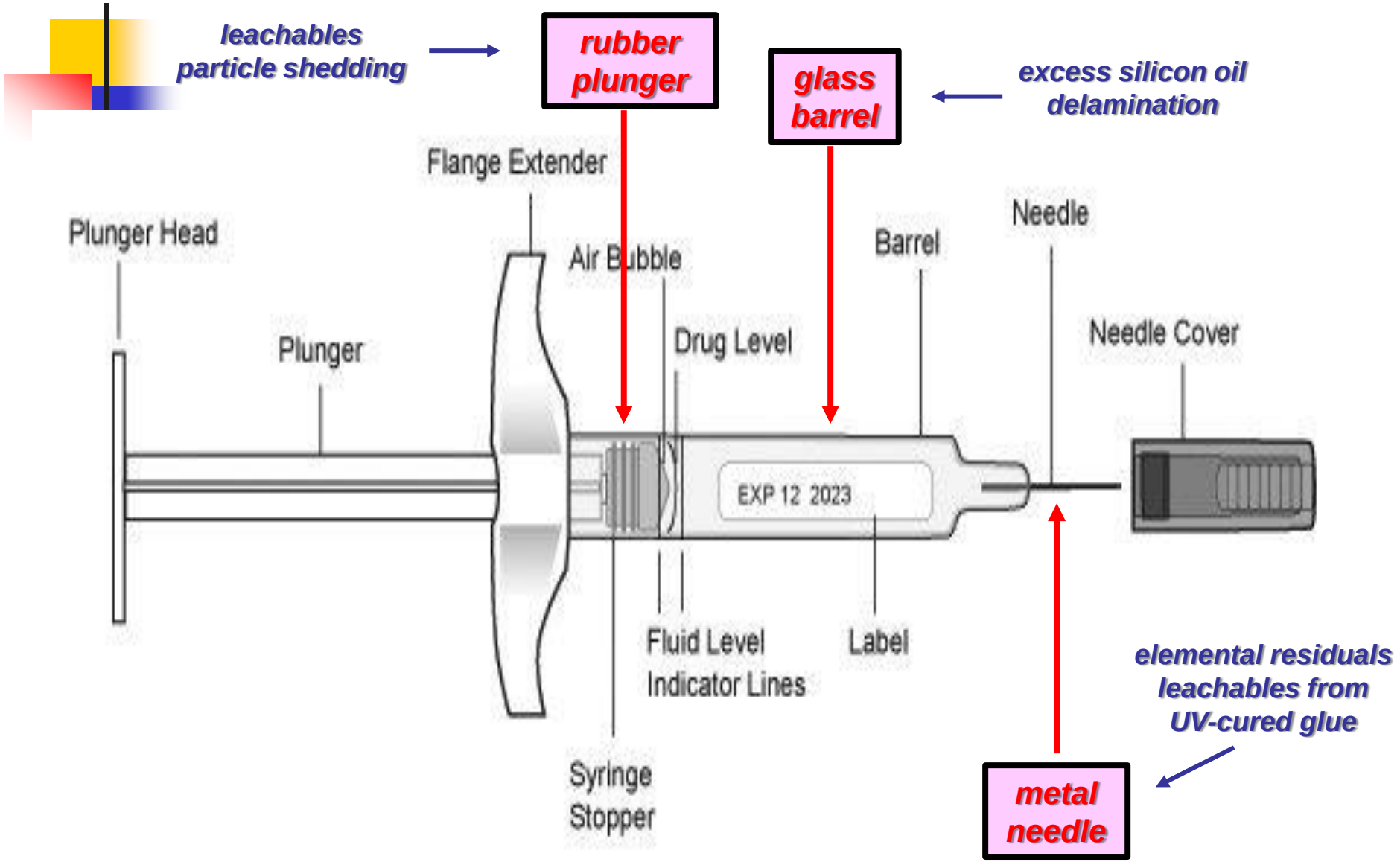
Rectal

Vaginal

Oral

- ***Tablet – Blister Pack (Rybelsus, GLP-1 peptide, recombinant)***

Product-contact surfaces of the container closures

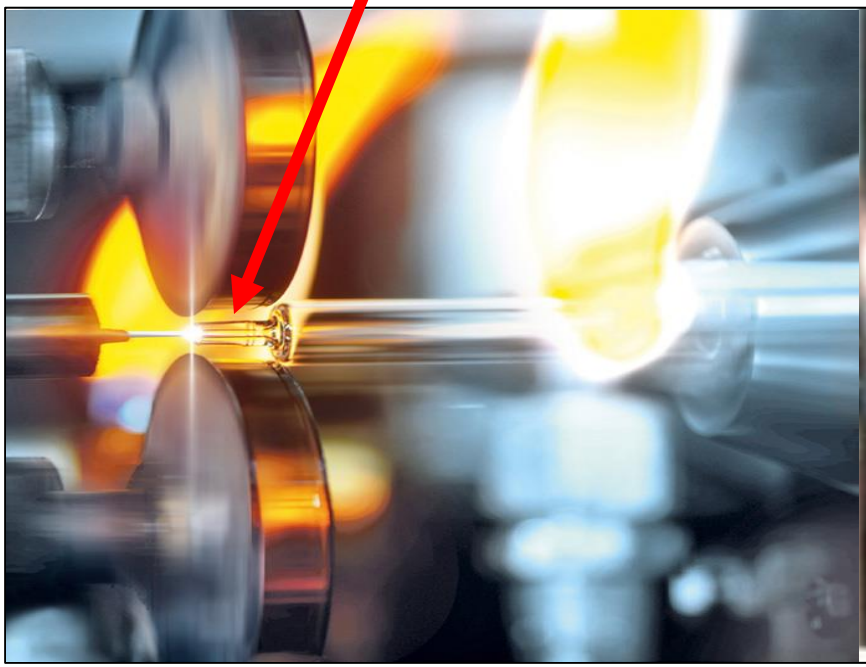


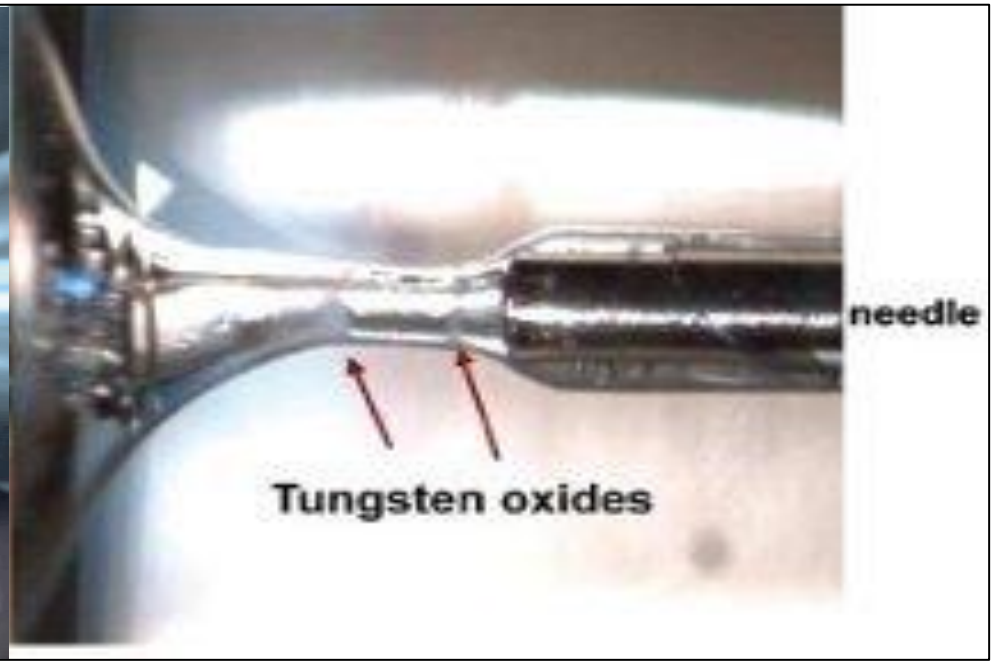
Impact of container closure on biologic!

Pre-filled 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 biologic on container closure!

Glass Vials – discovery of protein solutions causing glass delamination

Micro-Flow Imaging (MFI)

(counting and photographing each type of particle present)

Discovered glass shards in solution in 2010

Amgen: delamination has occurred in potentially <u>every</u> glass vial of Epogen manufactured <u>since 1982</u>!

<u>Patient safety concern</u>
glass shards could cut capillaries

AMGEN **Recall** **September 2, 2010** **Epogen (epoetin alfa)**

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

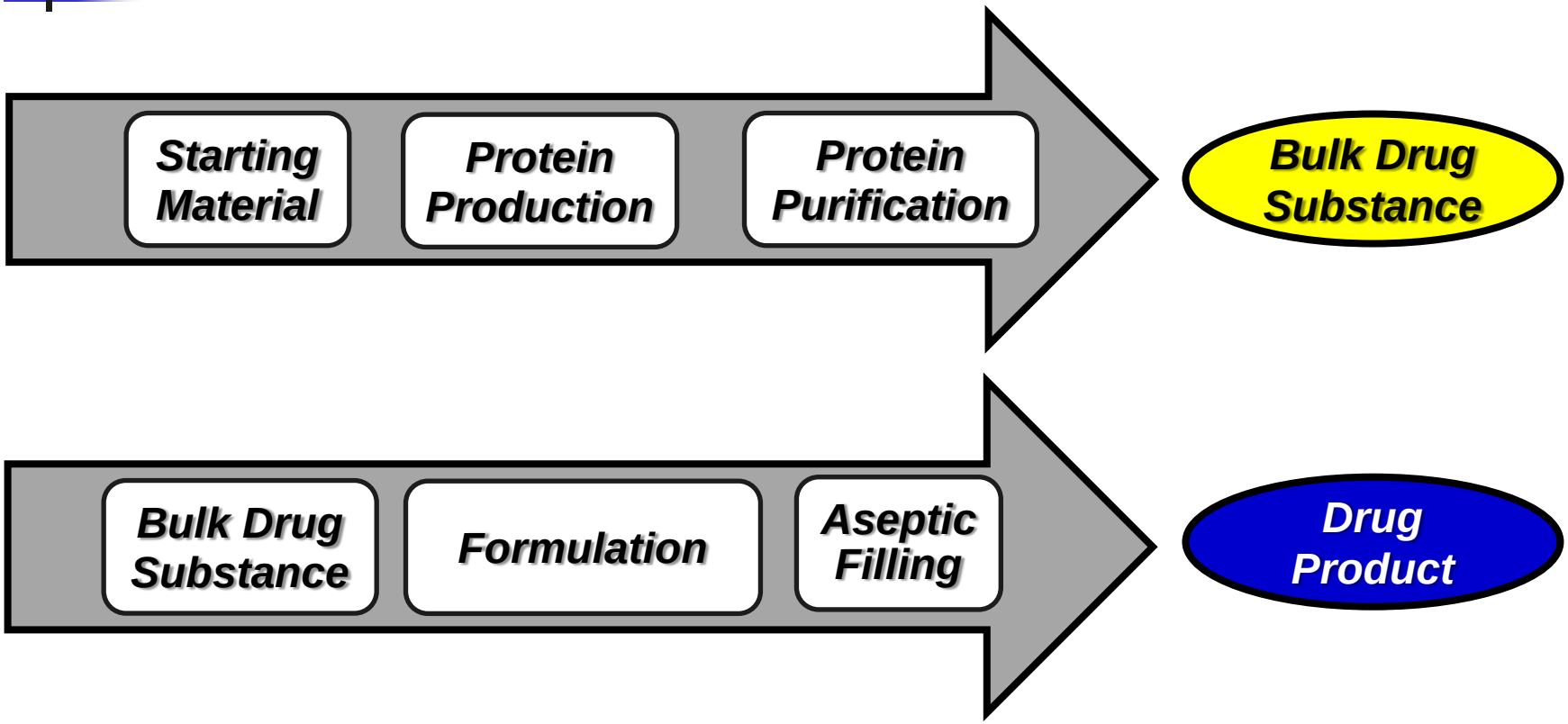
2011 Advisory to Drug Manufacturers – Glass Delamination

- ***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***

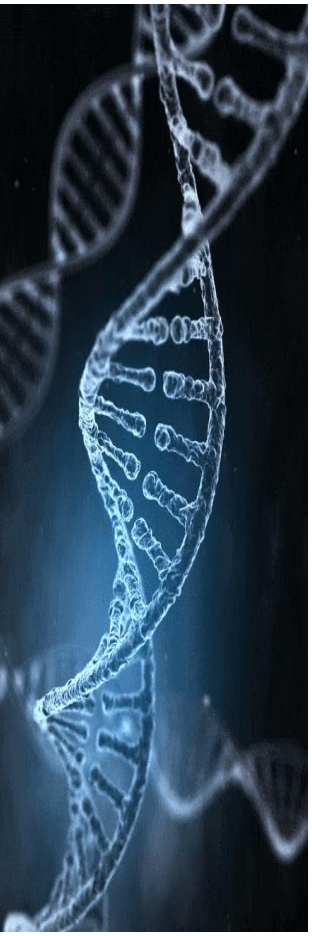
Happens with chemical drugs also!

Gilead receives NDA Complete Response Letter for lenacapavir due to delamination of glass vials March 08, 2022

Applied Risk-Management Across the Manufacturing Process



Questions??



Course Outline

4. Demonstrating Comparability After Manufacturing Process Changes

- *Defining 'Highly Similar'*
- *3 key design elements of an effective risk-managed comparability exercise*
- *Comparability 'contracts' with regulatory authorities*


TO IMPROVE IS TO
CHANGE
TO BE PERFECT IS TO
CHANGE
OFTEN
~ Winston Churchill ~
to change
Resistance is futile.

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

- *Cell line change (e.g., switch to a higher productivity cell line)*
- *Change in chromatography conditions to further reduce residual impurities*
- *Scaleup to larger bioreactor capacity*
- *Manufacturing site change (e.g., switch from clinical cGMP to commercial cGMP facility)*
- *Improvements in the potency assay (e.g., switch from early clinical-stage binding assay to late clinical-stage cell-based bioassay)*

CMC Regulatory Guidance on Assessing Product Comparability

For recombinant proteins and monoclonal antibodies

ICH HARMONISED TRIPARTITE GUIDELINE

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

Q5E 2004

Also is adaptable to the gene-based biopharmaceuticals

Questions and answers

Comparability considerations for Advanced Therapy Medicinal Products

6 December 2019
EMA/CAT/499821/2019

Q2: How does ICH Q5E guideline that addresses comparability of biological/biotechnological medicinal products, apply to ATMPs?

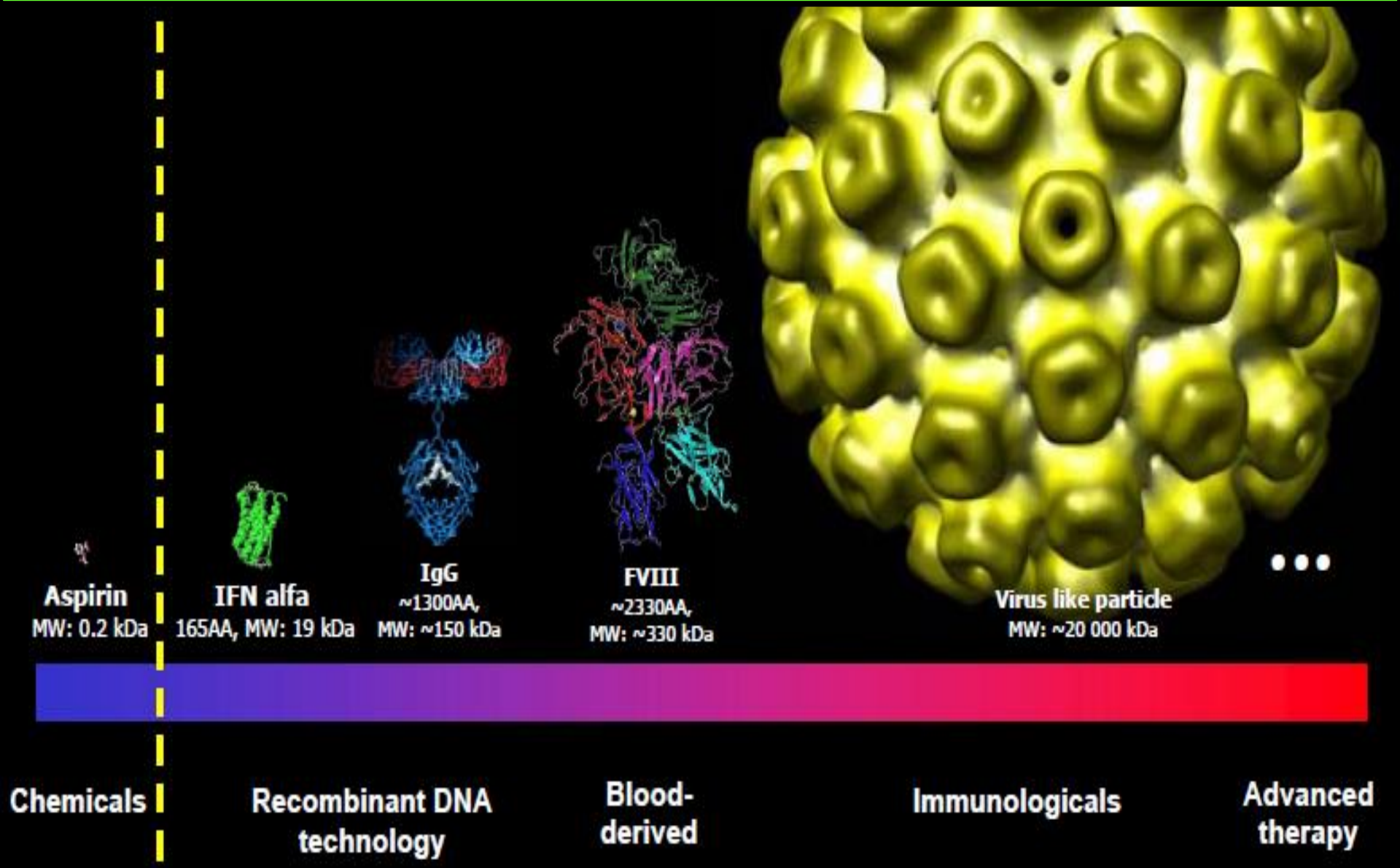
ATMPs are outside the scope of ICH Q5E guideline.

Overall, the general principles of ICH Q5E can be applied to ATMPs

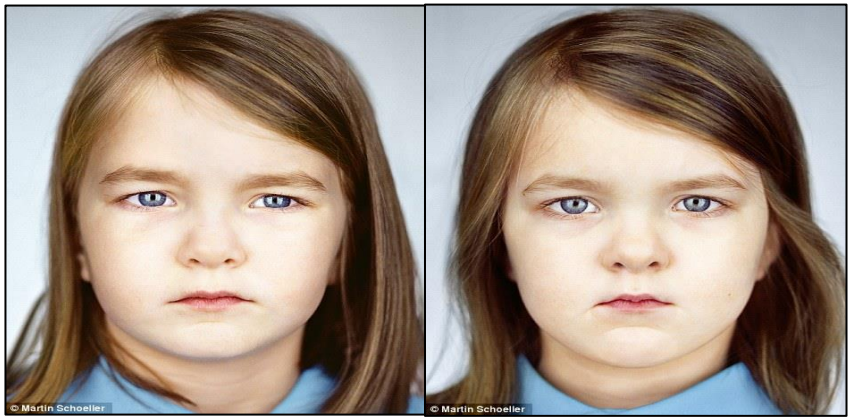
STANDARD TO BE MET FOR CONFIRMING PRODUCT COMPARABILITY

equivalent ***'highly similar'***

→ ***increasing molecular complexity, increasing limitations in testing methods***



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/properties/characteristics are compared

(primary structure vs product-related impurities)

depends upon who is evaluating

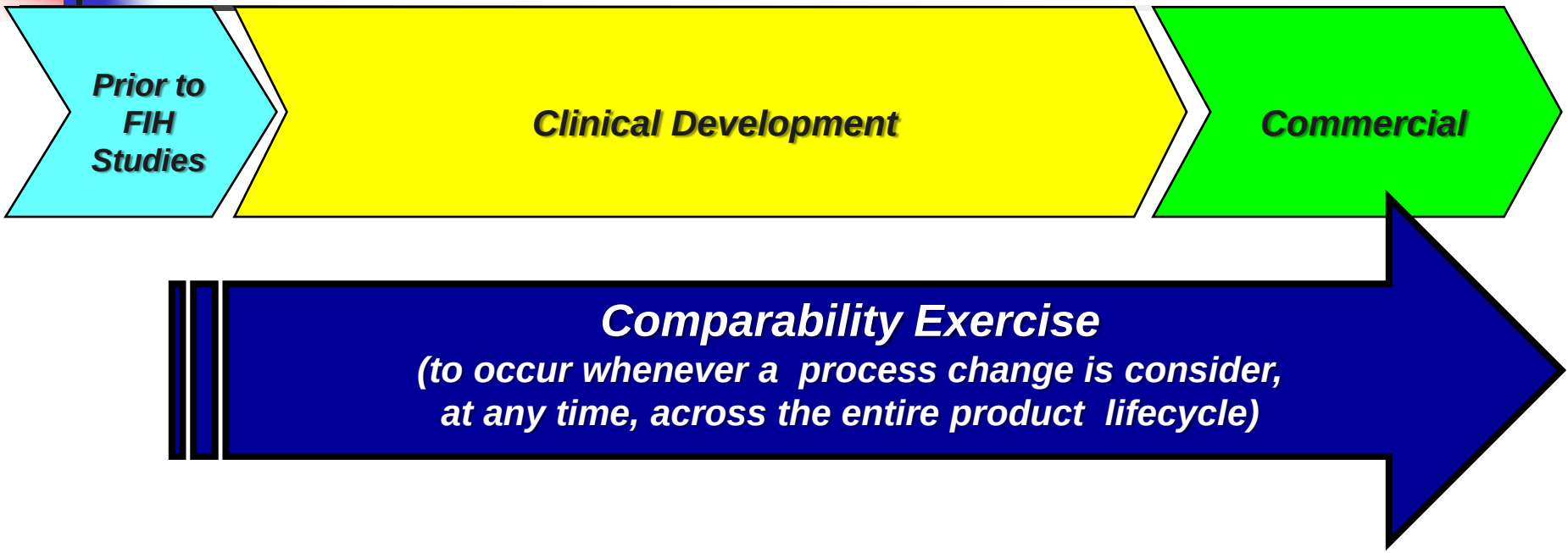
(you, CMC team, Executive Mgmt, or FDA/EMA)

but same standard applied

'Highly Similar' applies to innovator manufacturers

'Highly Similar' applies to biosimilar manufacturers

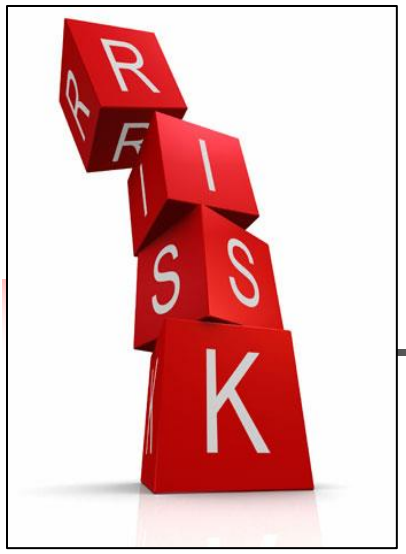
'Highly Similar' is confirmed by means of a 'comparability exercise'



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

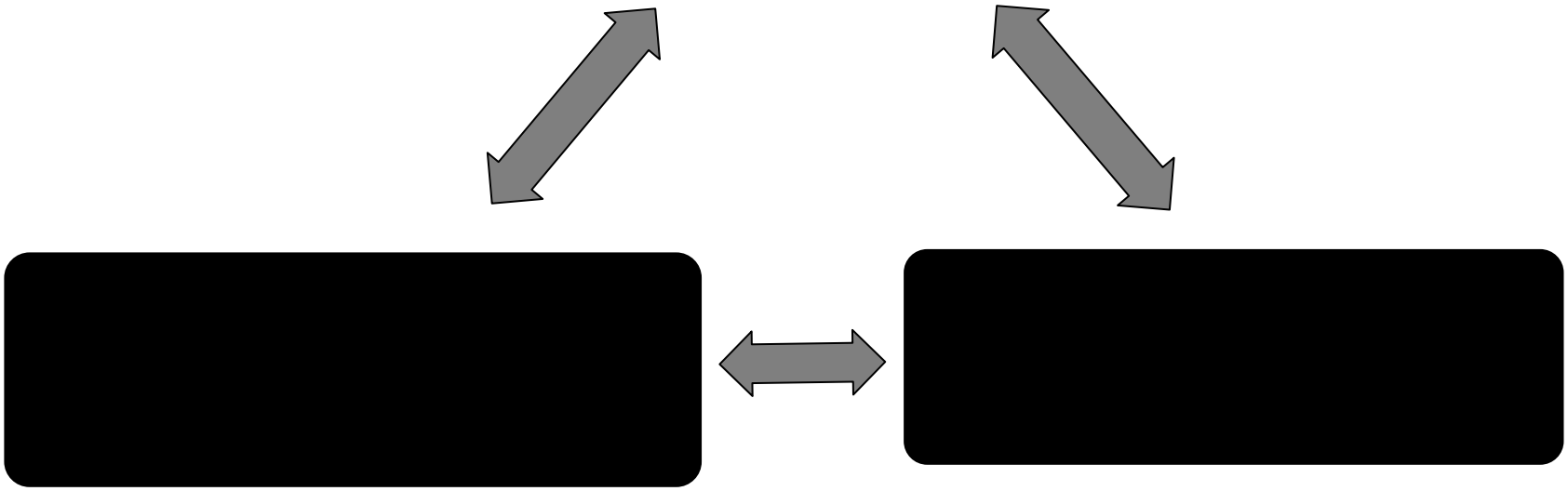
Q5E
2004

"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 key design elements of an effective risk-managed comparability exercise

Assess the risk associated with the **STAGE** of development

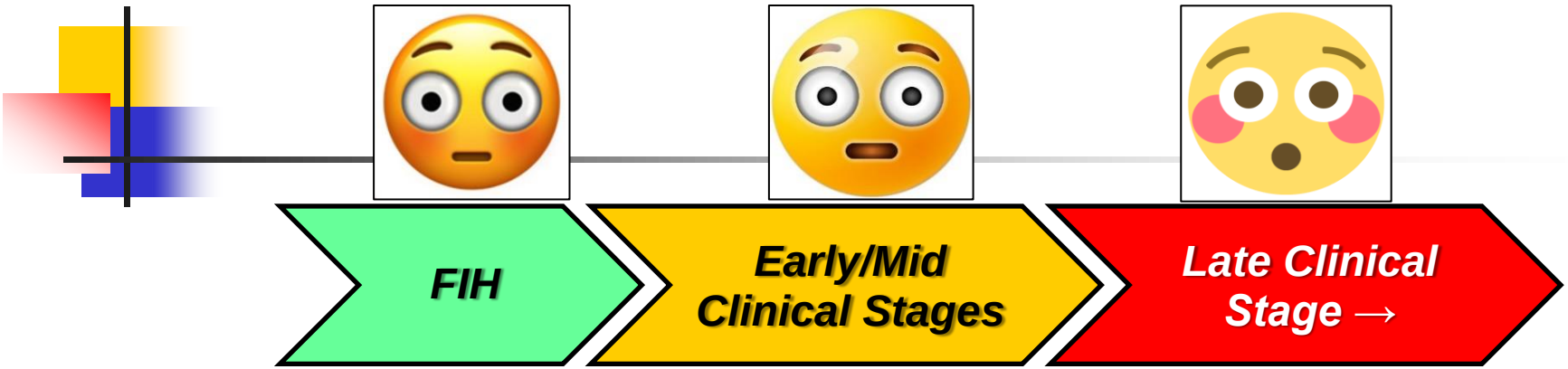


Comparability exercise goal at different stages of development

ICH Q5E

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. During early phases of nonclinical and clinical studies, comparability testing is generally not as extensive as for an approved product. As knowledge and information accumulate, and the analytical tools develop, the comparability exercise should utilise available information and will generally become more comprehensive. 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.

Assess the risk associated with the STAGE of development

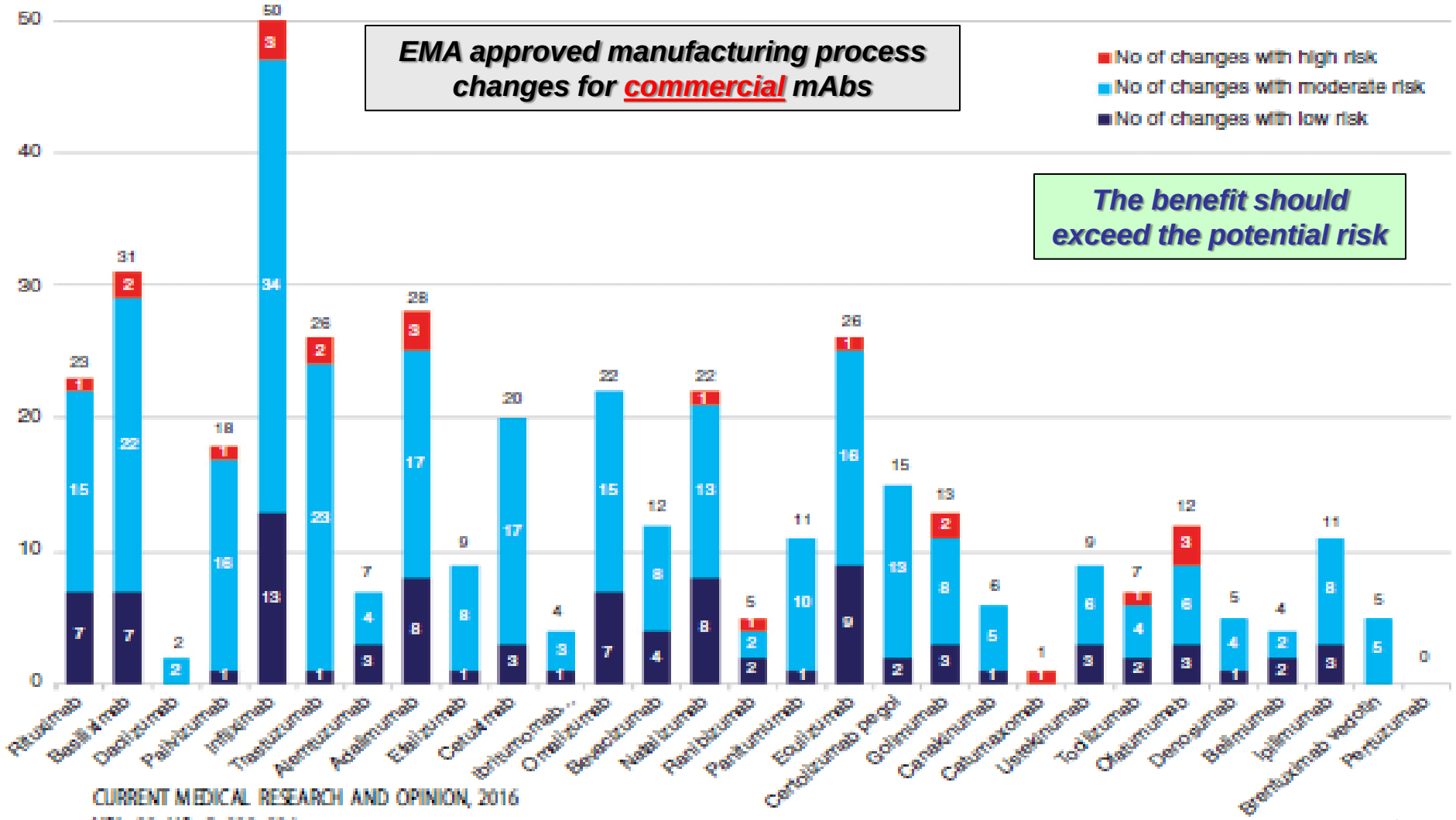


ICH Q5E: Product Comparability Testing by Clinical Stage	
Prior to Clinical	not required
Early Clinical Stage	not as extensive
Mid Clinical Stage	more comprehensive
Late Clinical Stage *	comprehensive & thorough
Commercial *	comprehensive & thorough

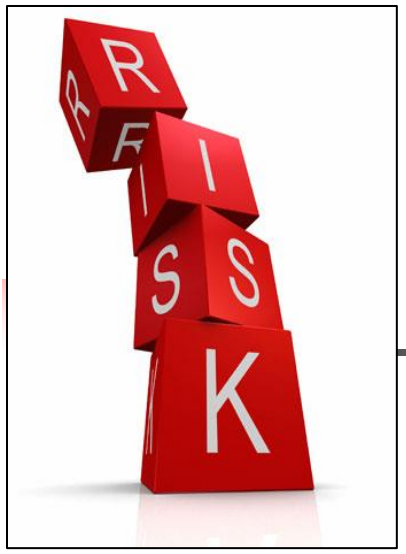
* Change can impact statistical efficacy or safety

'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 potential risk!



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



3 key design elements of an effective risk-managed comparability exercise

Assess the risk associated with the STAGE of development

[redacted]

Assess the risk associated with the TYPE of the manufacturing process change

Assessment of risk due to the proposed change

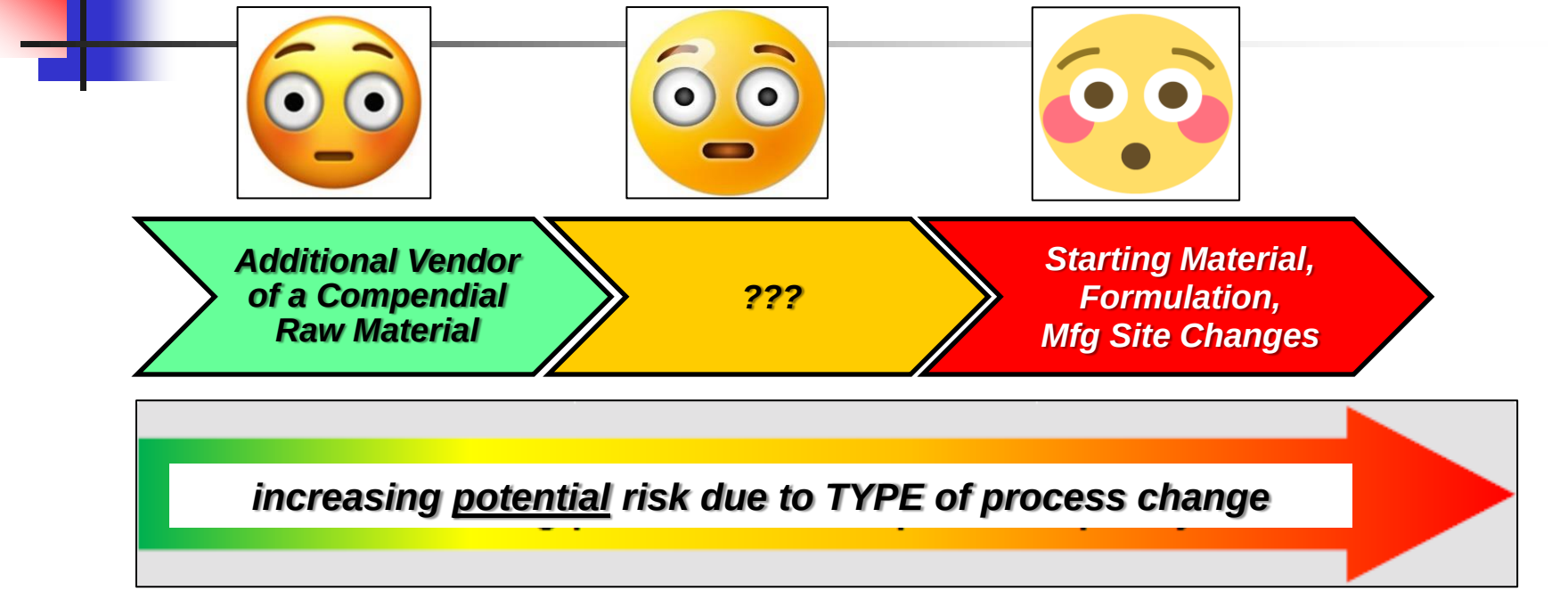
ICH Q5E

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.

Assess potential risk due to:

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

Assess the risk associated with the NATURE (type and extent) of the change



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

Available regulatory guidance on assessing the level of risk associated with TYPES of manufacturing process changes for biopharmaceuticals

Change in Master Cell Bank (MCB)
Introduction of new Working Cell Bank (WCB)
Change in DS manufacturing site with same CMO
Scale-up in bioreactor size (100L → 500L)
Change from a stainless steel bioreactor to a single use bioreactor (SUB)
Increase in working volume of 1000L bioreactor (500 → 900L)
Removal of a chromatography column step due to redundancy of mode of separation
Scale-up of filling process (1000 → 5000 vials)
Increase in fill volume of final 5cc DP vial (2 mL → 4 mL fill)
Change in DP glass vial vendor
Widening of pH DP specification
Tightening of the potency DP specification
Reduction in DP shelf life

- ***During Clinical Development***
  - ***EMA*** →
- ***Post-Market Approval***
  - ***ICH (established conditions)***
  - ***EMA (variations)***
  - ***FDA*** →

If in doubt of risk level, don't be afraid to ask FDA/EMA!

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

REFERENCE 1 (pp 22 → 29)

Risk-level assignment of manufacturing process changes DURING CLINICAL DEVELOPMENT

EMA Guidance on Manufacturing Process Changes During Clinical Development (√ level of risk box) →		EMA's Perception of Risk (page number listed)	
		Substantial	Non-Substantial
Source Material	Change in Master Cell Bank (MCB)	22	
	Introduction of new Working Cell Bank (WCB)	22	
DS	Change in DS manufacturing site with same CMO	22	
	Scale-up in bioreactor size (100L → 500L)	22	
	Change from a stainless steel bioreactor to a single use bioreactor (SUB)	22	
	Increase in working volume of 1000L bioreactor (500 → 900L)	√	
	Removal of a chromatography column step due to redundancy of mode of separation	22	
DP	Scale-up of filling process (1000 → 5000 vials)		26 (if media fill)
	Increase in fill volume of final 5cc DP vial (2 mL → 4 mL fill)	√	
	Change in DP glass vial vendor	28	28 (if same comp & specs)
	Widening of pH DP specification	26	
	Tightening of the potency DP specification	26 (if safety)	26 (not safety)
	Reduction in DP shelf life	28 (if safety)	28 (not safety)

Risk-level assignment of manufacturing process changes
POST-MARKET APPROVAL

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

FDA has issued numerous guidances on level of risk for post-approval process changes –
BUT they have limitations by biological 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	Exclusion
BLAs rproteins mAbs biosimilars	all other BLAs

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	Exclusion
BLAs rproteins mAbs biosimilars	all other BLAs

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	Exclusion
NDAs ANDAs	all BLAs

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	Exclusion
BLAs Advanced Therapy Vaccines	BLAs rproteins mAbs biosimilars

Risk-level assignment of manufacturing process changes
POST-MARKET APPROVAL

FDA Guidance on Post-Market Approval Manufacturing Process Changes (√ level of risk box) →		FDA's Perception of Risk (page number listed)		
		Major (PAS)	Moderate (CBE30)	Minor (AR)
Source Material	Change in Master Cell Bank (MCB)	√		
	Introduction of new Working Cell Bank (WCB)	(if no SOP on file in BLA)		p6 (SOP on file)
DS	Change in DS manufacturing site with same CMO	p4		2.3 (in BLA)
	Scale-up in bioreactor size (100L → 500L)	p4		
	Change from a stainless steel bioreactor to a single use bioreactor (SUB)	√		
	Increase in working volume of 500L bioreactor (200→500L)		[p5 →]	3.2
	Removal of a chromatography column step due to redundancy of mode of separation	√	[← p4]	
DP	Scale-up of filling process (1000 → 5000 vials)			p6
	Increase in fill volume of final 5cc DP vial (2 → 4 mL fill)	√		
	Change in DP glass vial vendor	(if different comp & specs)		5.1 (if same comp & specs)
	Widening of pH DP specification	p3		
	Tightening of the potency DP specification			4.7
	Reduction in DP shelf life	√		

Additional EMA guidance on risk-levels for commercial process changes

7.2.7. How should I submit a new working cell bank (WCB)? (Classification category B.I.a.2 a) ***New Jun 2017***

If a new WCB is introduced using the limits/conditions as detailed in an approved qualification protocol, the new WCB is covered by the existing quality assurance system and there is no need to submit a variation.

If the documentation of the WCB in the dossier does not include an approved qualification protocol for introducing new WCBs, the MAH should file a variation B.I.a.2 a type IB (as condition 5 is not met).

To introduce a qualification protocol for preparation of a new WCB, the MAH should file a variation type II B.I.a.2.c. The addition of the new WCB can be covered as part of this single variation type II.

Changes to an approved standard procedure (protocol) should be filed using a variation type IB B.I.a.2.a, or a variation type II B.I.a.2.c, as relevant depending on the complexity of the change. The addition of a new WCB can be covered as part of this single variation.

7.2.8. How should I submit a new reference standard for a biological medicinal product? ***New Jun 2017***

If a new reference standard is introduced using the limits/conditions as detailed in an approved qualification protocol, the new reference standard is covered by the existing quality assurance system and there is no need to file a variation.

If no qualification protocol has been approved and the old material is still available and the MAH is able to provide comparability test results using both reference standards, the MAH should file a type IB variation either under B.I.b.2.e for Active Substance or under B.II.d.2.d for Finished Product.

If no qualification protocol has been approved and the old material is not available anymore and therefore no direct comparison new/old material is possible the MAH should file a type II variation either under B.I.b.2.d for Active Substance or under B.II.d.2.c for Finished Product.

Don't get the post-approval assigned risk level wrong!

Dr. Roger J. Hinton
Managing Director
Porton Biopharma, Limited

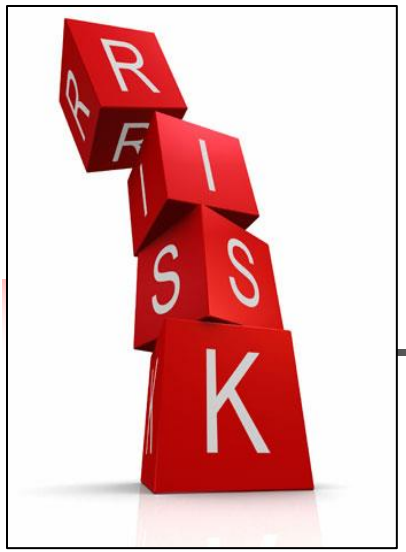
FDA Warning Letter
January 2017

Erwinaze
(Asparaginase)

and drug product batches. You failed to ensure sufficient change control oversight to assure the **(b)(4)** new working cell banks were acceptable for use in the commercial operation.

You manufacture Erwinaze® under contract on behalf of Jazz Pharmaceuticals, which holds the Biologics License Application for Erwinaze®. The process changes discussed above were not approved by FDA before you manufactured, or your customer, Jazz, distributed, Erwinaze®. Specifically, working cell banks **(b)(4)** were used in commercial production prior to approval. These working cell banks were not reviewed and approved by the Agency

ask 3 consultants, get 3 different answers

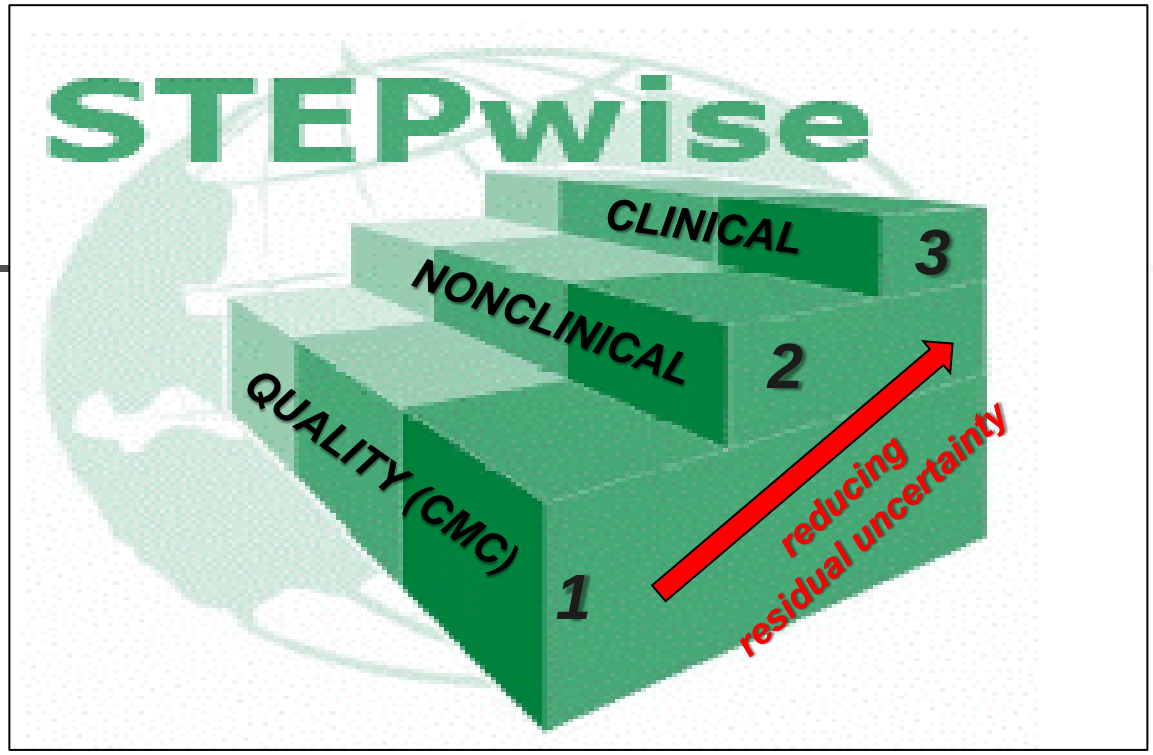


3 key design elements of an effective risk-managed comparability exercise

Assess the risk associated with the STAGE of development

Assess the risk associated with the TYPE of the manufacturing process change

Address the risk associated with the remaining RESIDUAL UNCERTAINTY in the gathered comparability results



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

Step 1

QUALITY (CMC)

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)

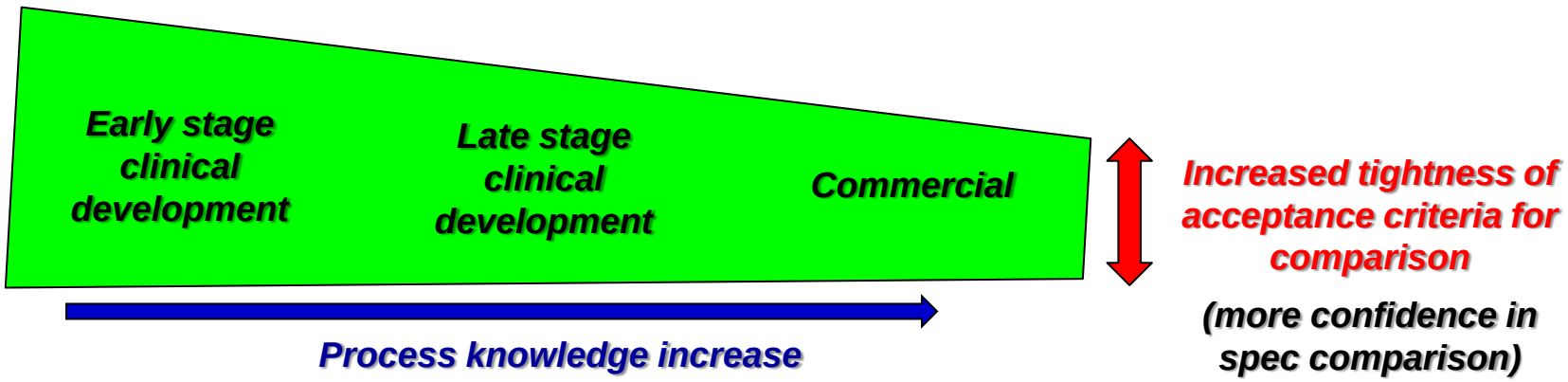
b) Relevant, comprehensive physicochemical, biological and functional assay characterization (head-to-head testing preferred)

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)

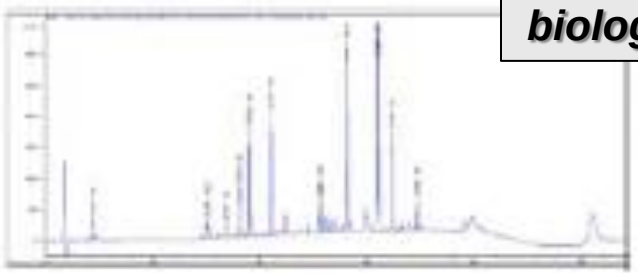
- *Acceptance criteria should be established and justified based on data obtained from lots used in preclinical and/or clinical studies, data from lots used for demonstration of manufacturing consistency and data from stability studies, and relevant development data* ICH Q6B
- *Specifications … should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



Fingerprinting

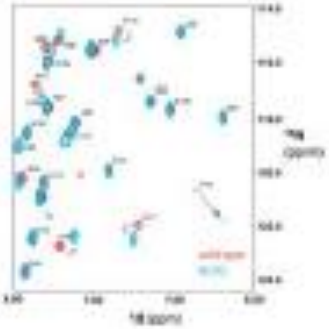
U.S. Food and Drug Administration
Protecting and Promoting Public Health

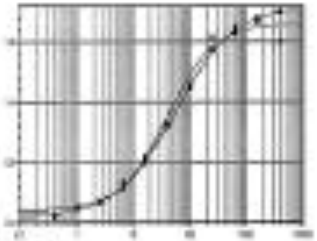
#1b Relevant, comprehensive physicochemical, biological and functional assay characterization



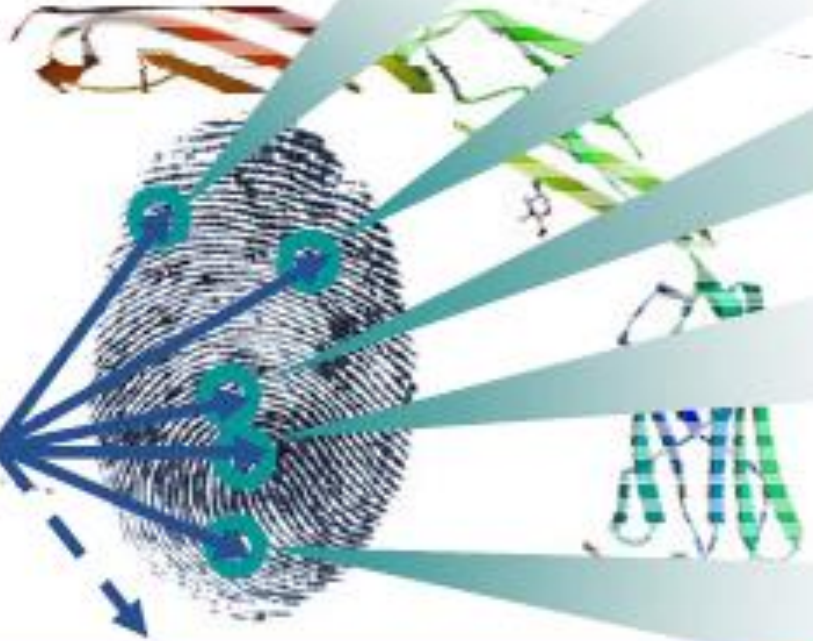
Sequence & Modifications

Higher Order Structure

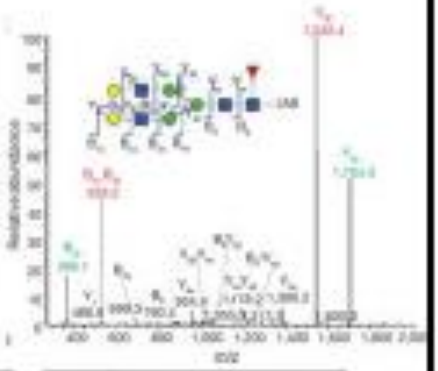




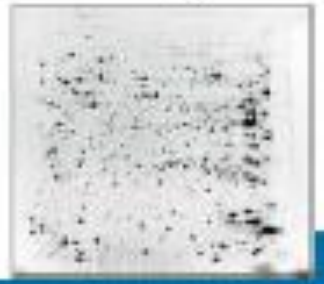
Bioactivity



Glycoforms



Impurity Profile



video – power of LC/MS – characterization comparison of biosimilar mAb to innovator mAb

Characterization by LC/MS Monoclonal Antibody 8 min

Waters

Statistical considerations for Step 1 analytical comparability

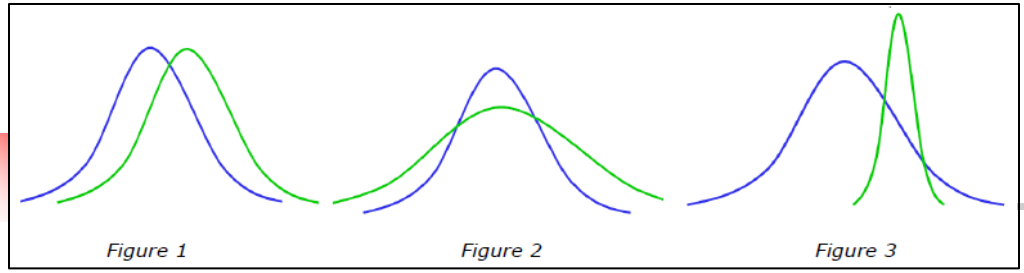


Figure 1 Figure 2 Figure 3

"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

Statistical Methods for Evaluation ...

1. *Tier 1 (Equivalence Test) .....*
2. *Tier 2 (Quality Range Approach) .*
3. *Tier 3 (Visual Displays) .....*

FDA U.S. FOOD & DRUG ADMINISTRATION

Statistical Approaches to Evaluate Analytical Similarity

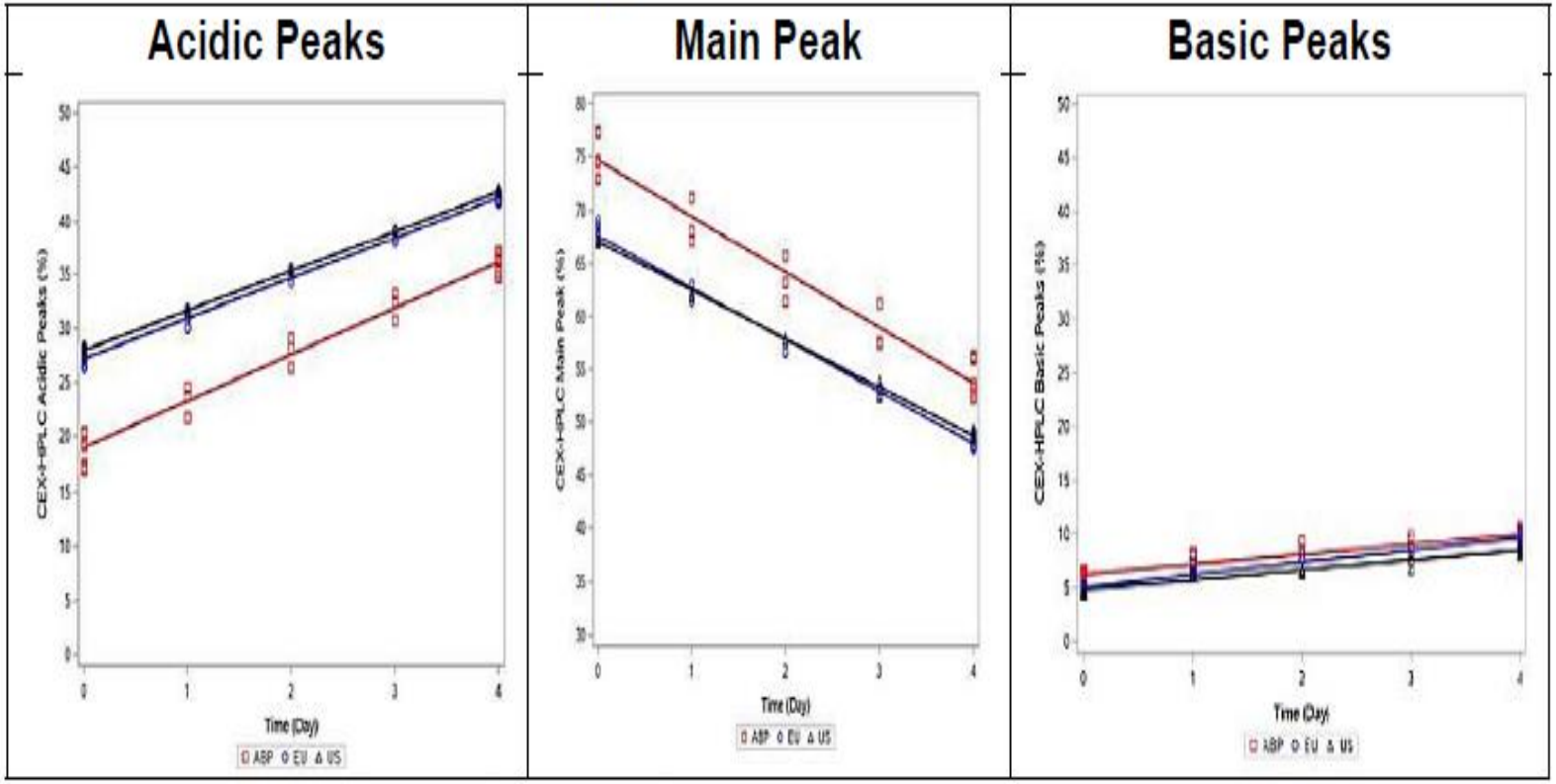
(withdrawn in 2018, but still available Google)

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 2017

#1c Accelerated and stress stability
rate of degradation slope comparison (rate of molecular variant change)

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: Concerns raised during EMA MAA Review

Step #1a alone insufficient to confirm comparability!

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

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.

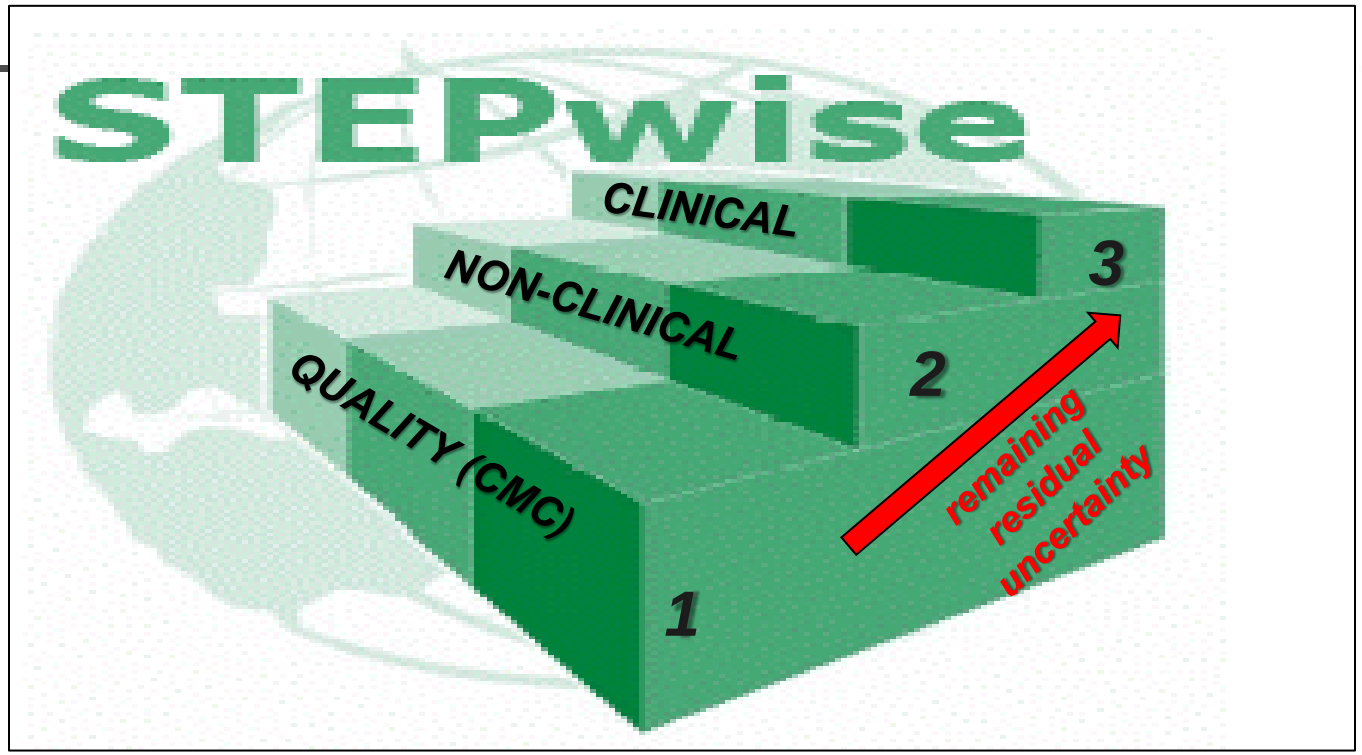
Takhzyro (lanadelumab)

CHO-based

18 October 2018
EMA/794314/2018

Shire

Steps 2 and/or 3 are necessary for comparability if 'RESIDUAL UNCERTAINTY'



Innovator Biologic — ***<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 Manufacturer

addressing residual uncertainty – clinical product vs commercial product

Step 1 + Human pK (Step 3)

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.

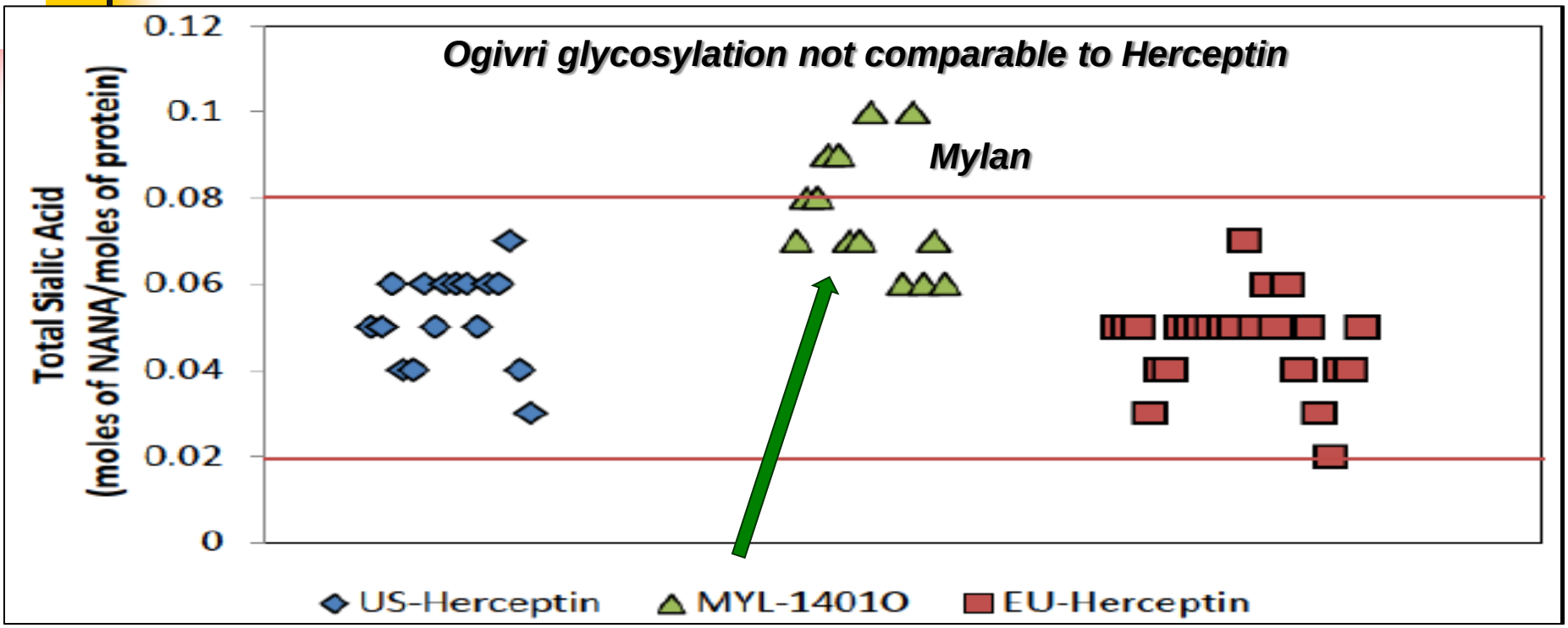
To support comparability between the different manufacturing processes two formal ICHQ5E compliant comparability evaluations were performed. An initial comparability assessed early (C1) to late phase (C2) processes and a commercial comparability, which assessed late phase (C2) to commercial phase process (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

Case Example: Biosimilar Manufacturer

residual uncertainly about glycosylation differences

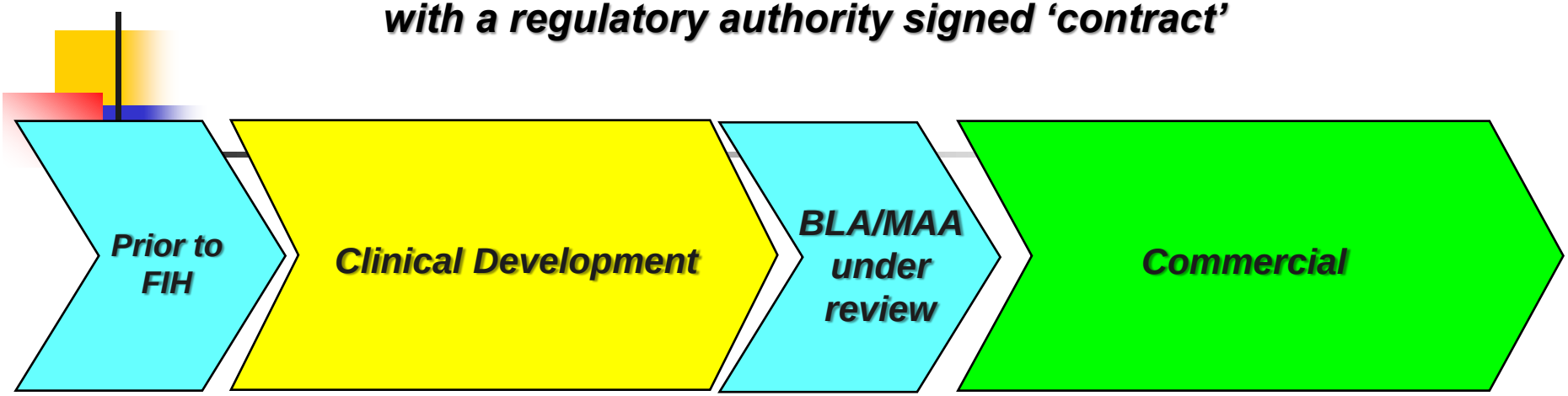
Step 1 + Human pK (Step 3)

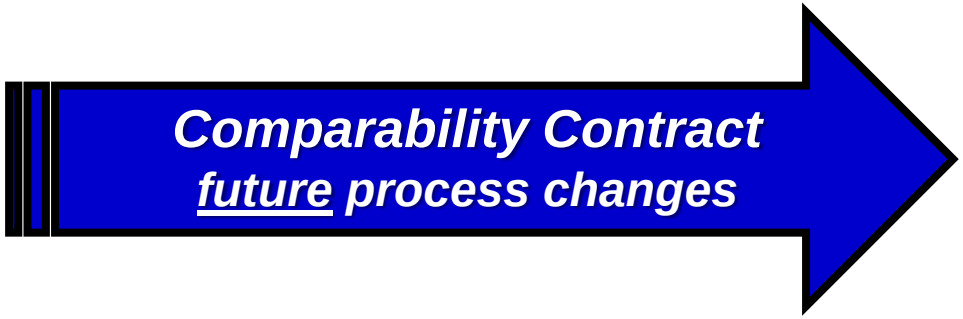


mol/mol). MYL-1401O lots with minor differences in glycosylation with respect to the US-Herceptin lots were included among those used in clinical studies. Residual uncertainty about biosimilarity that resulted from the differences in high mannose and sialylated glycans is adequately addressed by data that showed no impact of these differences on PK. These

2017 FDA Advisory Committee Meeting

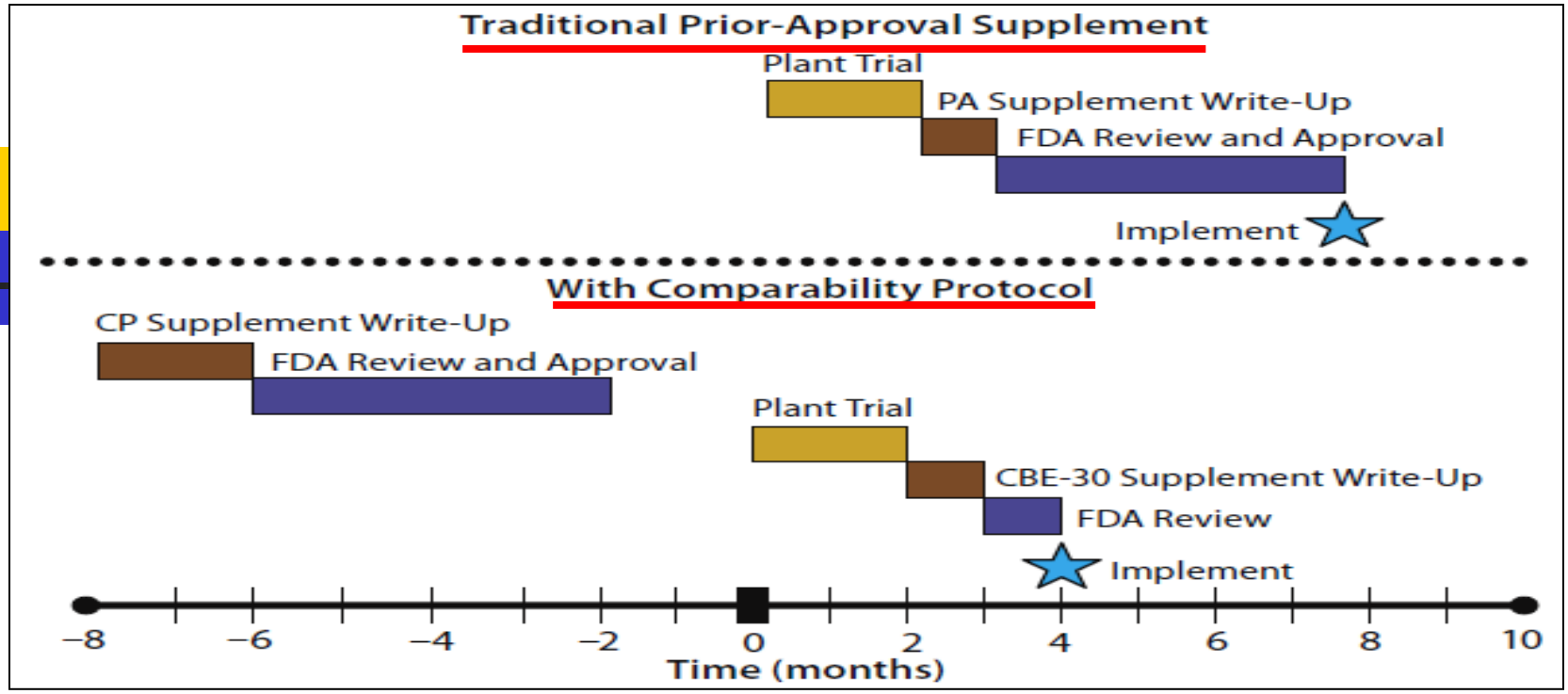
*Preparing for **FUTURE** manufacturing process changes with a regulatory authority signed 'contract'*





EMA, ICH: post approval change management protocol (PACMP)

FDA: comparability protocol (CP) = PACMP



Note, <u>total elapsed time</u> sometimes is longer with the contract route, but time to implement a process change after completion is shorter!

Benefits of a regulatory authority contract

(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* requested comparability contracts submitted in a BLA/MAA**

examples below

RYLAZE

asparaginase erwinia chrysanthemi (recombinant)-rywn)

Jazz Pharmaceuticals

FDA BLA CMC Review 06/18/2021

Drug Substance:

i. Protocols approved:

1. MCB and WCB long term stability monitoring protocols (3.2.S.2.3)
2. Concurrent release protocol for chromatography resin lifetime (3.2.S.2.5)
3. Requalification of reference standards protocol (3.2.S.5)
4. Qualification of new working reference standards protocol (3.2.S.5)
5. Post-approval annual stability protocol (3.2.S.7.2)

Replacement of new Working Cell Bank is also typically included

Note, if it is not in writing from the regulatory authority,
it is not an approved future manufacturing process change protocol!

Contract for new DS manufacturing site → tough

Contract for new DP manufacturing site → doable

Case Example: EMA review of a proposed PACMP

future additional manufacturing DP site for a mAb

Assessment report

Jemperli
dostarlimab

GlaxoSmithKline

25 February 2021
EMA/176464/2021

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.

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 Biopharmaceuticals

Summary of Course

- ✓ **CMC Regulatory Compliance is Challenging for Biopharmaceuticals**

  Due to the increasing diversity of biopharmaceuticals, the regulatory authorities have developed review systems to effectively control them

- ✓ **Risk-Managed Biopharamceutical CMC Regulatory Compliance Strategy**

  The 'minimum CMC regulatory compliance continuum' is a risk-based, clinical stage-appropriate, flexible strategy to effectively protect patients during clinical development

- ✓ **Applied Risk-Managed CMC Regulatory Compliance Strategy**

  QbD/QRM risk-based strategy applied across the manufacturing process from raw materials → starting materials → protein production → protein purification → bulk drug substance

- ✓ **Demonstrating Comparability After Manufacturing Process Changes**

  Applying the 3 key design elements ensures comparability after manufacturing process changes; and comparability contracts are possible with regulatory authorities

Thank you!

Deficient CLINICAL PLAN causes TERMINATIONS

Only if time

Explains why senior management spends so much focus on the Clinical Plan, but …

Deficient CMC Regulatory Compliance strategy causes DELAYS

… but delays are costly also to a manufacturer!

Classroom Work Problem

REFERENCE 2

Value of meeting with FDA to discuss your CMC regulatory compliance strategy

MEMORANDUM OF MEETING MINUTES

Tepezza (teprotumumab-trbw)

Meeting Type:	B
Meeting Category:	End of Phase 2
Meeting Date and Time:	August 19, 2016 from 9:30AM – 10:30AM (EST)
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1309 Silver Spring, Maryland 20903
Application Number:	112952
Product Name:	RV001 (teprotumumab for injection) **(Tepezza)**
Indication:	treatment of moderate to severe thyroid eye disease (TED)
Sponsor/Applicant Name:	River Vision Development Corporation **(Horizon)**

How did FDA response to the CMC regulatory compliance strategy proposed by this company?

read & fill-in table

TEAM DISCUSS

Classroom Work Problem

Value of Meeting with FDA

(20 minutes to read/scan)
(10 minutes to team discuss)

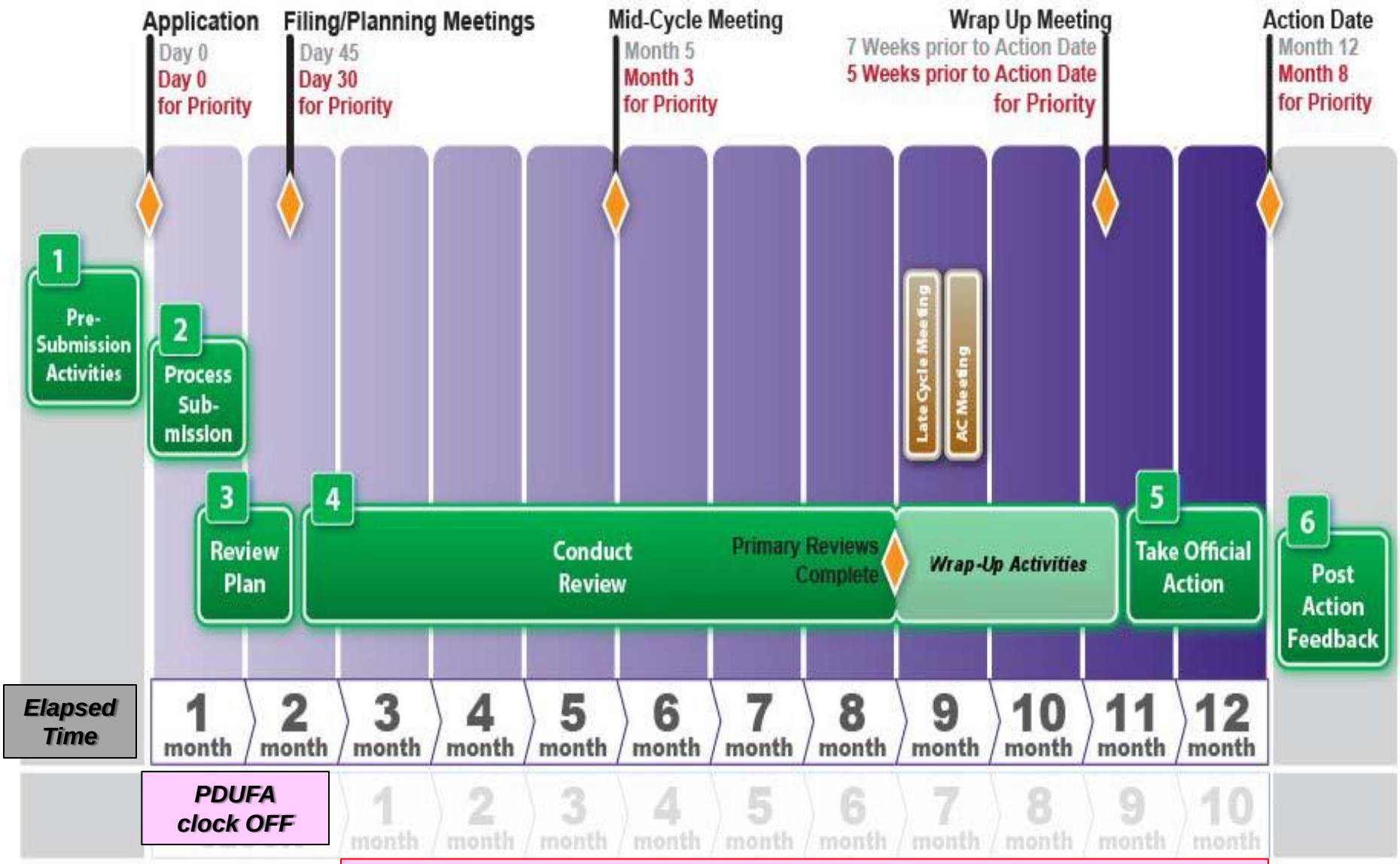
REFERENCE 2 Horizon Therapeutics Tepezza (teprotumumab-trbw)

Proposed CMC Regulatory Compliance Strategy (see pp 7-16)	FDA Response to CMC Regulatory Compliance Strategy	
	FDA Reaction (No, Yes but, …)	FDA comments on proposed CMC Strategy
Preamble: The quality of the meeting package provided to the FDA		
9. Proposed program to confirm product comparability after changing manufacturing sites for both DS and DP		
10. Proposed control strategy (justification of CQAs)		
11. Bioassay bridging strategy		
12. Proposed HCP test strategy		
13. Proposed process validation strategy		
14. Proposed shelf life determination		

How valuable was this meeting with the FDA?

(FDA market approved January 2020)

FDA review of submitted BLAs



Standard review 10 months Priority review 6 months

Classroom Work Problem

Trazimera (trastuzumab-qyyp) 04/20/2018

COMPLETE RESPONSE

We have completed our review of this application and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

Biosimilar to Herceptin

REFERENCE 3

The CRL lists 14 Critical (pp 1-5) and 8 Major CMC (pp 6-8) issues

(even after the FDA worked with the company for 10 months to resolve the issues)

What specific CRITICAL CMC issues did the FDA have with this submitted BLA?

read & fill-in table

TEAM DISCUSS

Classroom Work Problem

REFERENCE 3

Trazimera (trastuzumab-qyyp)

Biosimilar to Herceptin

(20 minutes to read/scan)
(10 minutes to team discuss)

	CRITICAL CMC Concern	FDA's comments in the CRL
1	MCB/WCB Stability	
2	Drug Product Filling	
3	DP Shipping Validation	
4	Additional Specs	
5	Spec Justification	
6	DP Storage Conditions	
7	Method Transfer Validation	
8	PPQ Criteria	
9	Media Fill Validation	
10	Hold Times	
11	DP Capping	
12	DP Vial Washing	
13	DP Bioburden	
14	Low Endotoxin Recovery	

FDA market approved March 2019 – 1 year CMC delay