CMC Regulatory Compliance Strategy For Biopharmaceuticals

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October 2020

CMC Regulatory Compliance Strategy For Biopharmaceuticals

Course Outline

1. CMC Regulatory Compliance is Challenging for Biopharmaceuticals
2. Risk-Managed CMC Regulatory Compliance Strategy
3. Applied Risk-Managed CMC Regulatory Compliance Strategy
4. Demonstrating Comparability After Manufacturing Process Changes

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

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

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CMC Regulatory Compliance Strategy For Biopharmaceuticals

Course Outline

1. ***CMC Regulatory Compliance is Challenging For Biopharmaceuticals***
   - ✓ ***Ever increasing diversity of biopharmaceuticals***
   - ✓ ***Regulatory authority systems in place to control these evolving manufacturing processes and products***

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Biologic/Biological: Consensus Definition

(EMA, FDA, HC, WHO, …)

Definition of biological medicinal product

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

3 components

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

Immune Serums (diphtheria)
Vaccines (polio)
Plasma-derived proteins (Factor 8)
Animal-derived hormones (pig insulin)

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Biopharmaceutical: No consensus definition today

3 components

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

Publications: "bio-health medicine" (including chemically synthesized HIV antivirals, iRNA, hepatitis C, …)

FDA/EMA: biotech drug product, recombinant DNA-derived drug

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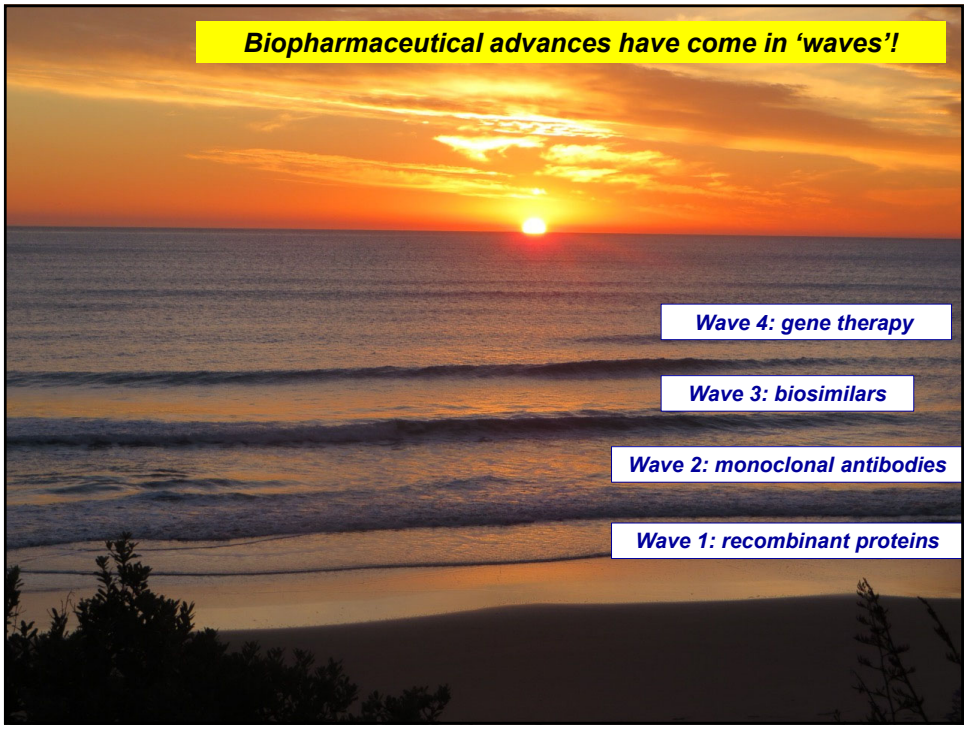
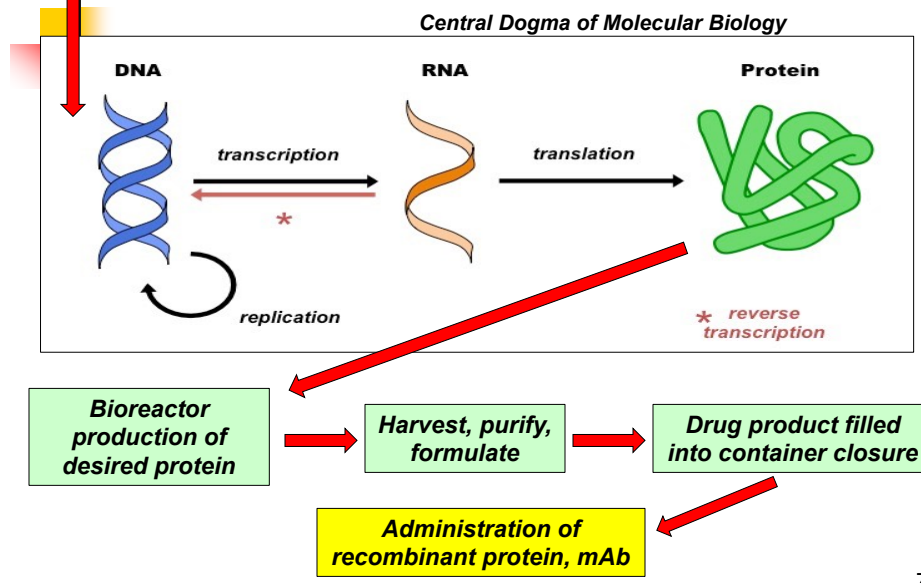


DNA inserted into a living microorganism
(e.g., E. coli, CHO), to produce a protein medicine

WAVES 1, 2, 3



Bioreactor production of desired protein → **Harvest, purify, formulate** → **Drug product filled into container closure** → **Administration of recombinant protein, mAb**

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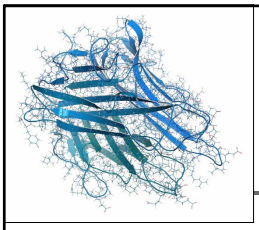


WAVE 1
Recombinant Proteins

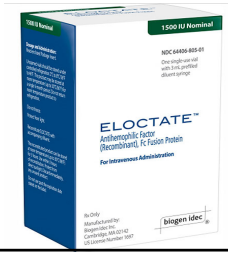
1982 1st recombinant protein

Global human insulin market: > $30 billion

TODAY

- **100+ recombinant proteins market approved by FDA/EMA**
- **Recombinant proteins are vaccines and plasma-derived proteins**

Shingles



Factor VIII

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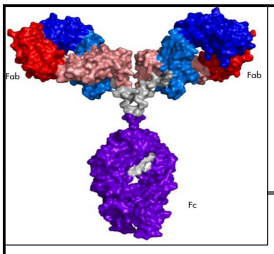

WAVE 2
Monoclonal Antibodies

recombinant immunoglobulin protein – specific single binding site

1986 1st mAb (murine)

1997 1st commercially successful monoclonal antibody (chimeric)

TODAY

- ***100+ monoclonal antibody market approved by FDA/EMA***
- ***Humira (adalimumab) best selling drug in the world: > $20 billion***

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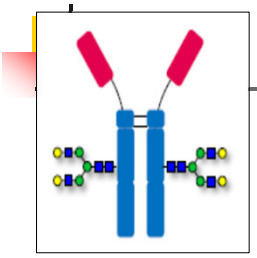
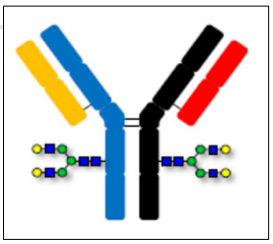
Re-engineered Antibodies



Fc-Fusion Protein

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

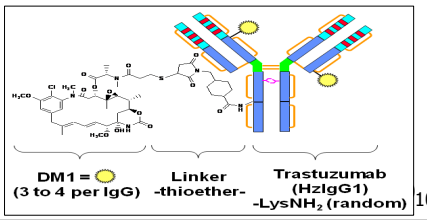
Bispecific Antibody



Blincyto	*Binds to CD19*	*Binds to CD3*
Hemlibra	*Binds to Factor IX*	*Binds to Factor Xa*

Antibody Drug Conjugate (ADC)

Besponsa	*calicheamicin*	*DAR 6*
Kadcycla	*maytansine*	*DAR 4*
Adcetris	*auristatin*	*DAR 4*
Enhertu	*topoisomerase inhib*	*DAR 8*



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WAVE 3
Biosimilars

INNOVATOR → **commercial biopharmaceutical**

*Must prove **STATISTICAL** safety & efficacy* *'medical benefit'*

BIOSIMILAR → ~~→~~ **blocked by innovator's marketing exclusivity or patent coverage**

→ **commercial biosimilar**

*Must prove **COMPARATIVE** safety & efficacy* *'highly similar'*

	Market Approved Biosimilar of Innovator's Biopharmaceutical	Europe	USA
Among the top 10 best selling medicines in the world	Adalimumab (Humira)	√	√
	TNF-α/Fc Fusion Protein (Enbrel)	√	√
	Trastuzumab (Herceptin)	√	√
	Bevacizumab (Avastin)	√	√
	Rituximab (Rituxin/MabThera)	√	√

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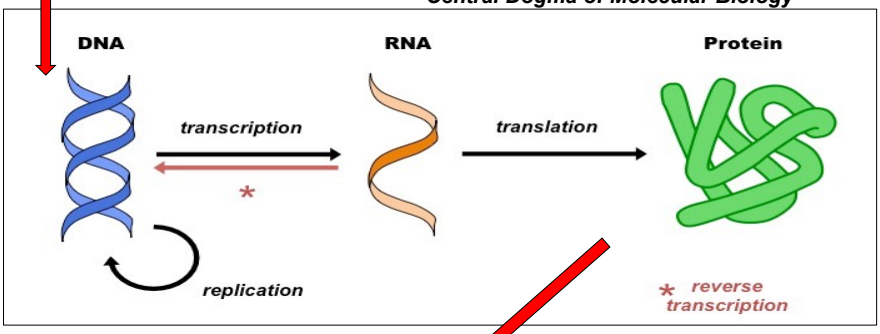
WAVE 4
advanced therapies

*Fixing defective genetic capability or adding new genetic capability to a patient's **living human cells***

Central Dogma of Molecular Biology



***The patients, themselves,** produce the desired gene product (protein), in situ*

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These advance therapies are starting to hit the market!

2017/2018	***market approved***
• *Kymriah (CANCER – CAR T-cell gene therapy)*	*FDA/EMA*
• *Yescarta (CANCER – CAR T-cell gene therapy)*	*FDA/EMA*
• *Luxturna (VISION – RPE-65 protein restoration – virus gene therapy)*	*FDA/EMA*
• *Alofisel (FISTULAS – allogeneic somatic adipose stem cell therapy)*	*EMA*
2019/2020	***market approved***
• *Zolgensma (SPINAL MUSCULAR ATROPHY - SMN, survival motor neuron, protein restoration – virus gene therapy)*	*FDA/EMA*
• *Zynteglo (β-THALASSAEMIA – β-globin protein restoration – hematopoietic stem cell gene therapy)*	*[FDA]/EMA*
• *Tecartus (CANCER – CAR T-cell gene therapy)*	*FDA/[EMA]*
• *Roctavian (HEMOPHILIA A – clotting factor VIII restoration – virus gene therapy)*	*[FDA]/[EMA]*
• *Liso-Cel (CANCER – CAR T-cell gene therapy)*	*[FDA]*
• *Ide-Cel (CANCER – CAR T-cell gene therapy)*	*[FDA]*

[under regulatory authority review for market approval]

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The amplitude of wave 4 is predicted to grow significantly!

Assessing the current pipeline and trends in incoming INDs, FDA views this as an inflection point in cell and gene therapy technology and innovation. As such, FDA attempts to project the volume of cell-based or directly administered gene therapy products in development and gaining approval in coming years:

- Currently 800+ active INDs
- Anticipate receipt of 200+ new INDs per year by 2020
- Predict approval of 10-12 cell and gene therapy products per year by 2025

Drawing an analogy to the platforms for humanizing antibodies that accelerated the mainstreaming of human monoclonal antibody drugs in the late 1990's, FDA credits the advent of safe and effective vectors (e.g., AAV vectors) for the delivery of gene therapy products as enabling this progress.

To accommodate these increases, CBER is expanding its review group dedicated to reviewing these applications, with the hope of adding about 50 additional clinical reviewers to the CBER Office of Tissues and Advanced Therapies (OTAT).

Statement from FDA Commissioner Scott Gottlieb, M.D. and Peter Marks, M.D., Ph.D., Director of the Center for Biologics Evaluation and Research on new policies to advance development of safe and effective cell and gene therapies *January 15, 2019*

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Large biopharmaceutical companies now jumping in, by acquisition!

GILEAD	*Yescarta*	Kite	*~$12 billion*
NOVARTIS	*Kymriah*	*Zolgensma*	*~$9 billion*
Bristol-Myers Squibb		JUNO THERAPEUTICS	*~$9 billion*
Roche	*Luxturna*	Spark THERAPEUTICS	*~$5 billion*
Bristol-Myers Squibb / Celgene	*Zynteglo*	bluebirdbio	*~$74 billion*

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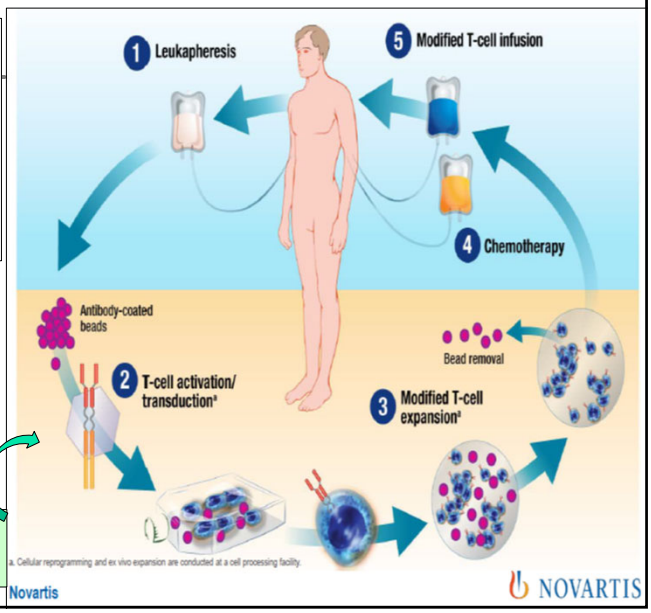
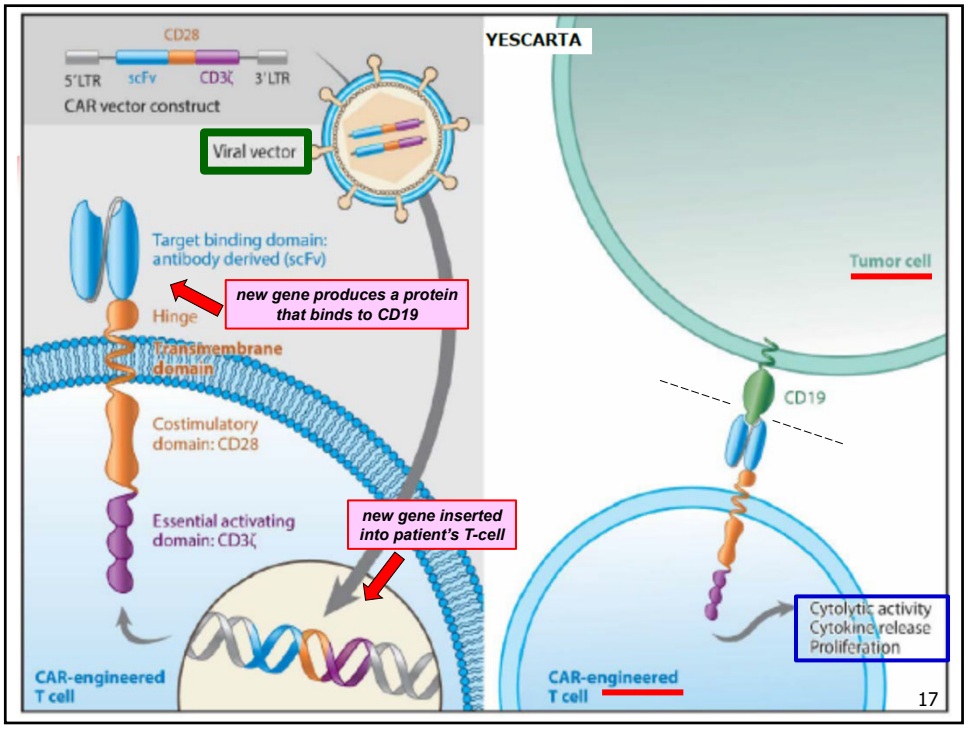
Gene Therapy Medicine: Genetically Engineered Living Cells (gene addition)

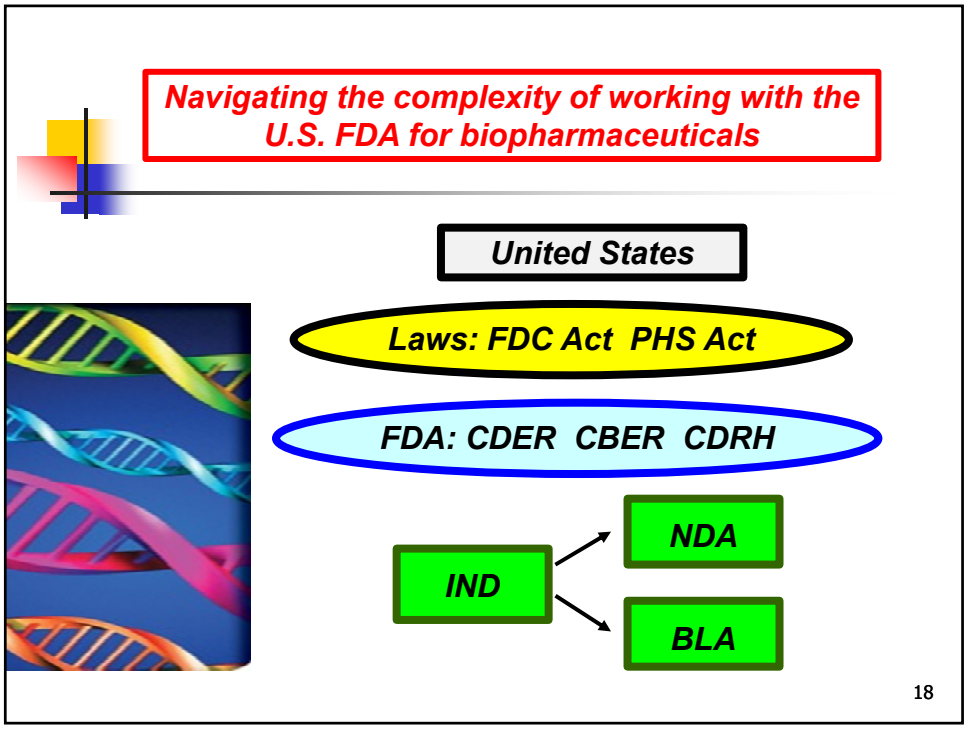
Novartis KYMRIAH
Kite YESCARTA

autologous genetically modified T-cells (CAR – chimeric antigen receptor) to bind/kill CD19-containing leukemia cells

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




CD28
5'LTR
scFv
CD3ζ
3'LTR
CAR vector construct
YESCARTA
Viral vector
Target binding domain: antibody derived (scFv)
new gene produces a protein that binds to CD19
Hinge
Transmembrane domain
Costimulatory domain: CD28
Essential activating domain: CD3ζ
new gene inserted into patient's T-cell
Tumor cell
CD19
Cytolytic activity
Cytokine release
Proliferation
CAR-engineered T cell
CAR-engineered T cell
17


Navigating the complexity of working with the U.S. FDA for biopharmaceuticals
United States
Laws: FDC Act PHS Act
FDA: CDER CBER CDRH
IND
NDA
BLA
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United States Pharmaceutical Laws

2 separate laws – yet linked

U.S. Congress passes/amends a pharmaceutical law

1938: Food, Drug & Cosmetics (FD&C) Act
1944: Public Health Service (PHS) Act

FDA, in the Executive Branch, interprets the intent of the law

↓

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

↙ ↓

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

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

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1938 Food Drug & Cosmetics (FD&C) Act

Drug (legal definition): 'an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease'

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

Investigational New Drug (IND)	→	*New Drug Application (NDA)*
21 CFR 312		*21 CFR 314*
[human clinical studies]		*[marketed products]*

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Many, many amendments since 1938

Major amendment to FD&C Act in 1984
allowing abbreviated pathways to the marketplace

(Drug Price Competition and Patent Restoration Act)

New Drug Application [505(b)(1) NDA]

[innovator proves statistical efficacy and safety – "medical benefit"]

New Drug Application [505(b)(2) NDA]

[manufacturer relies upon some efficacy and safety from others]

(past – 'Follow On Proteins')

Abbreviated New Drug Application [505(j) NDA]

[manufacturer demonstrates equivalent chemical monograph and simple bioequivalence]

Chemical Generic ANDA

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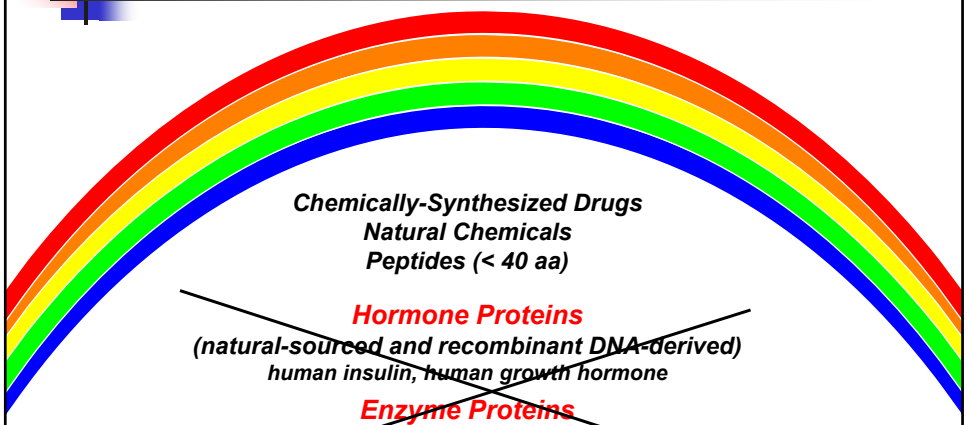
Drugs under the NDA Pathway

Regulated by the FD&C Act



Chemically-Synthesized Drugs
Natural Chemicals
Peptides (< 40 aa)

~~***Hormone Proteins***~~
~~***(natural-sourced and recombinant DNA-derived)***~~
~~***human insulin, human growth hormone***~~

~~***Enzyme Proteins***~~
~~***(natural-sourced and recombinant DNA-derived)***~~
~~***glucerases, kinases***~~

as of March 23, 2020

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1944 Public Health Service (PHS) Act

***Biological Product* (legal definition): by 'product class'**

PHS Act: Biologic License Application (BLA) Pathway

Investigational New Drug (IND)		***Biologics License Application (BLA)***
21 CFR 312	→	***21 CFR 600-680 + 21 CFR 314***
[human clinical studies]		***[marketed products]***

Note: same clinical development as FD&C Act!

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Expanding product classes under 'Biological Product' definition

- ***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)~~'***

(Advanced therapy medicines are currently under 'analogous products')

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FDA's definition 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

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Many, many amendments since 1944

Major amendment to PHS Act in 2010 allowing abbreviated pathway to the marketplace

(Biologics Price Competition and Innovation Act)

Biologic License Application [351(a) BLA]

[innovator proves statistical efficacy and safety – "medical benefit"]

Biosimilar Biologic License Application [351(k) BLA]

[manufacturer utilizes efficacy and safety from innovator; and then must demonstrate comparative quality, efficacy and safety]

Level 1: biosimilarity
Level 2: interchangeable

X

~~***Bio-Generic***~~

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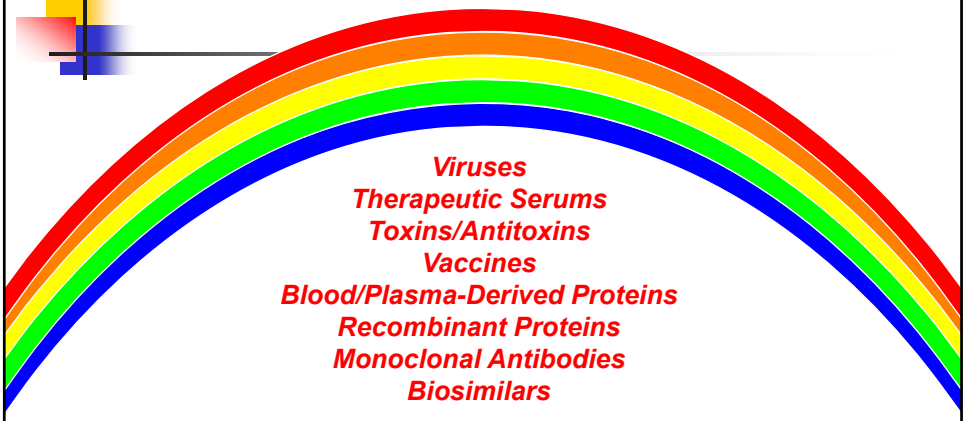
Biologics under the BLA Pathway

Regulated by the PHS Act



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

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

+ NDA Proteins (as of March 23, 2020)

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U.S. Food and Drug Administration

U.S. Department of Health and Human Services

Two primary FDA Centers involved with review and approval of PHS Act biologic products

Center for Drug Evaluation and Research (CDER)
review organized in Divisions according to medical indication

Center for Biologics Evaluation and Research (CBER)
review organized in Offices according to product type

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

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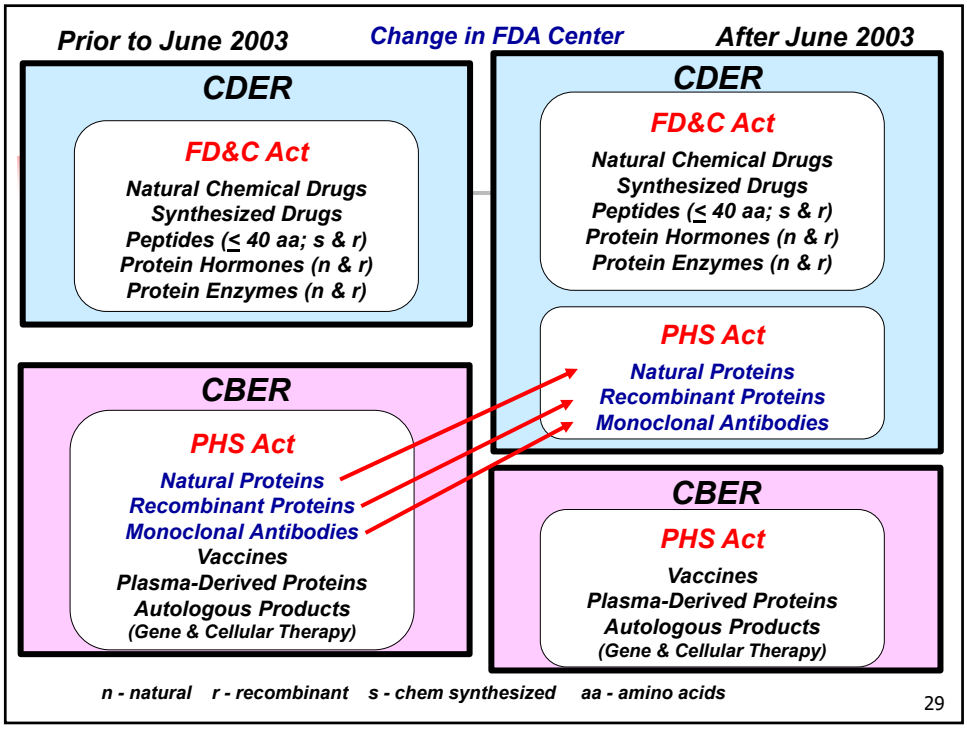
Prior to June 2003
Change in FDA Center
After June 2003
CDER
FD&C Act
Natural Chemical Drugs
Synthesized Drugs
Peptides (≤ 40 aa; s & r)
Protein Hormones (n & r)
Protein Enzymes (n & r)
CBER
PHS Act
Natural Proteins
Recombinant Proteins
Monoclonal Antibodies
Vaccines
Plasma-Derived Proteins
Autologous Products
(Gene & Cellular Therapy)
CDER
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PHS Act
Natural Proteins
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Monoclonal Antibodies
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Vaccines
Plasma-Derived Proteins
Autologous Products
(Gene & Cellular Therapy)
n - natural r - recombinant s - chem synthesized aa - amino acids
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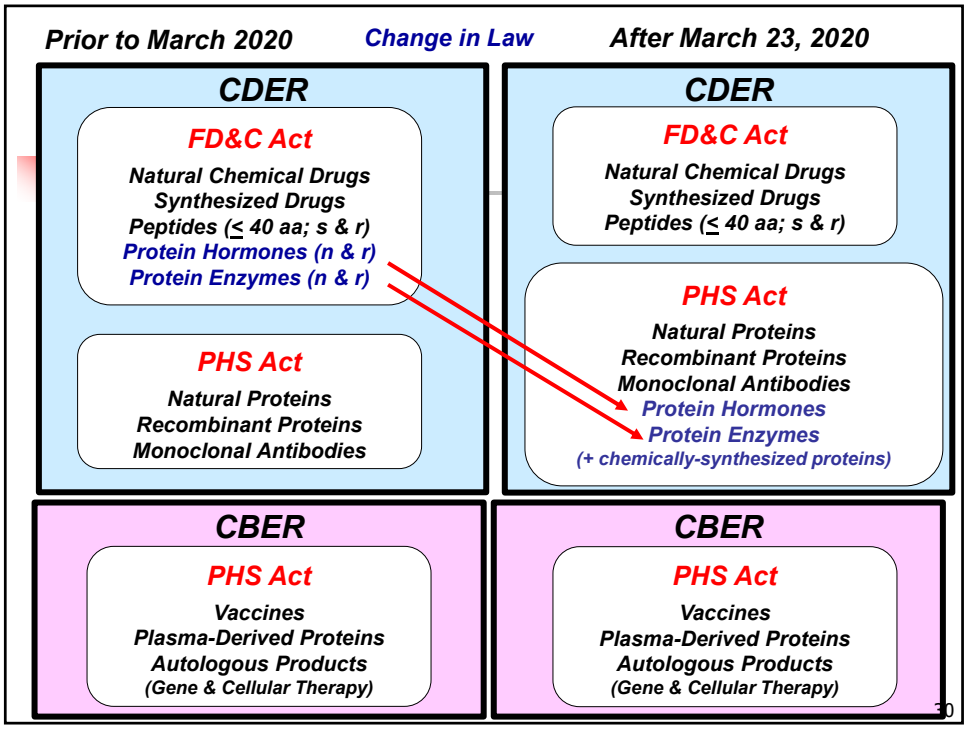
Prior to March 2020
Change in Law
After March 23, 2020
CDER
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Synthesized Drugs
Peptides (≤ 40 aa; s & r)
PHS Act
Natural Proteins
Recombinant Proteins
Monoclonal Antibodies
Protein Hormones
Protein Enzymes
(+ chemically-synthesized proteins)
CBER
PHS Act
Vaccines
Plasma-Derived Proteins
Autologous Products
(Gene & Cellular Therapy)
CBER
PHS Act
Vaccines
Plasma-Derived Proteins
Autologous Products
(Gene & Cellular Therapy)
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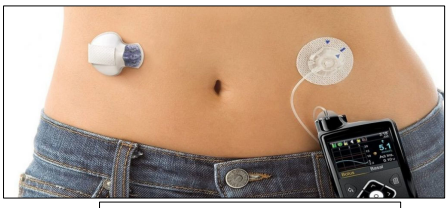
U.S. Food and Drug Administration

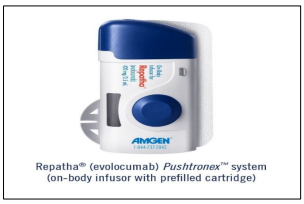
U.S. Department of Health and Human Services

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

(typically a secondary consult for CDER/CBER)

Center for Devices and Radiological Health (CDRH)





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Differences between the two laws?

PHS Act (biologics) versus FD&C Act (chemical drugs)

No! ***Administrative Regulatory***

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

No! ***CMC Regulatory Clinical Compliance***

Yes! ***CMC Regulatory Commercial Compliance***

1. *extra commercial testing requirements*
2. *may require commercial FDA pre-release*
3. *different commercial regulatory compliance procedures*
4. *different commercial marketing exclusivity rights*

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1) PHS Act has extra commercial testing requirements

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

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

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

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

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2) PHS Act can require FDA commercial pre-release

§ 610.2 Requests for samples and protocols; official release.

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

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

NOTE: FD&C Act does not require this for NDAs! Company QA solely determines release to inventory

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FDA pre-release of Vaccines required for all!

Dengvaxia – Dengue Tetravalent Vaccine, Live, Recombinant (May 01, 2019)

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).

FDA pre-release of Human Plasma-Derived Proteins required only for natural but not recombinant!

Immune Globulin Subcutaneous (Human)-hipp (December 12, 2018)

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

Andexxa – Coag Factor Xa (Recombinant) Inactivated-zhzo (May 03, 2018)

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

as stated in FDA market approval letters

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FDA pre-release of Recombinant Proteins & Monoclonal Antibodies

automatic waiver granted by FDA since 1995!

Crysvita – Burosumab-twza (April 17, 2018)

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

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

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

as stated in FDA market approval letters

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FDA pre-release of Genetic Engineered Viruses currently required for all!

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).

FDA pre-release of Genetic Engineered Cells waived on a case-by-case basis!

Yescarta – Axicabtagene Ciloleucel (October 18, 2017)

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

as stated in FDA market approval letters

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FDA team internal discussion on pre-release

TEAM MEETING SUMMARY

Application number: 125694/0 **Meeting date & time:** April 10, 2019
Product name: onasemnogene abeparvovec-xioi *genetically engineered virus*

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.

39

3) PHS Act has different commercial reporting systems

FDA requires notification if a quality defect in a commercial distributed drug product batch may present a patient safety threat:

- *Mislabeling*
- *Bacterial contamination*
- *Any significant chemical, physical, or deterioration*
- *…….*

PHS Act	FD&C Act
21 CFR 600.14	*21CFR 314.81*
Biological Product Deviation Report (BPDR)	*Field Alert Report (FAR)*
FDA Form 3486	*FDA Form 3331a*
Within 45 days of QA awareness	*Within 3 days of QA awareness*

40

4) PHS Act has different marketing exclusivity rights

"*Market Exclusivity*"

refers to certain delays and prohibitions on FDA approval of competitor drug products available under a statute that attach upon approval of the innovator drug product

PHS Act ***Blocking of Biologic Biosimilars***	***FD&C Act*** ***Blocking of Generic Chemicals***
Market Exclusivity ***12 years – new biologic entity (NBE)***	***Market Exclusivity*** ***5 years – new chemical entity (NCE)***

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Navigating the complexity of working within the European Union for biopharmaceuticals

European Union

Regulations & Directives

NCA EMA

CTA IMPD → ***MAA***

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European Union Pharmaceutical Law

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

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

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

↓

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

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

43

National Competent Authorities (NCAs) Regulate Clinical Trials For *All* Drugs and Biologics

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

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

28 Member States – each with a CMC opinion

↓ ***coming into effect 2021?***

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

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

'submitted, reviewed, authorized' – single portal entry

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EMA Regulates Marketed Products

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

of 31 March 2004

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

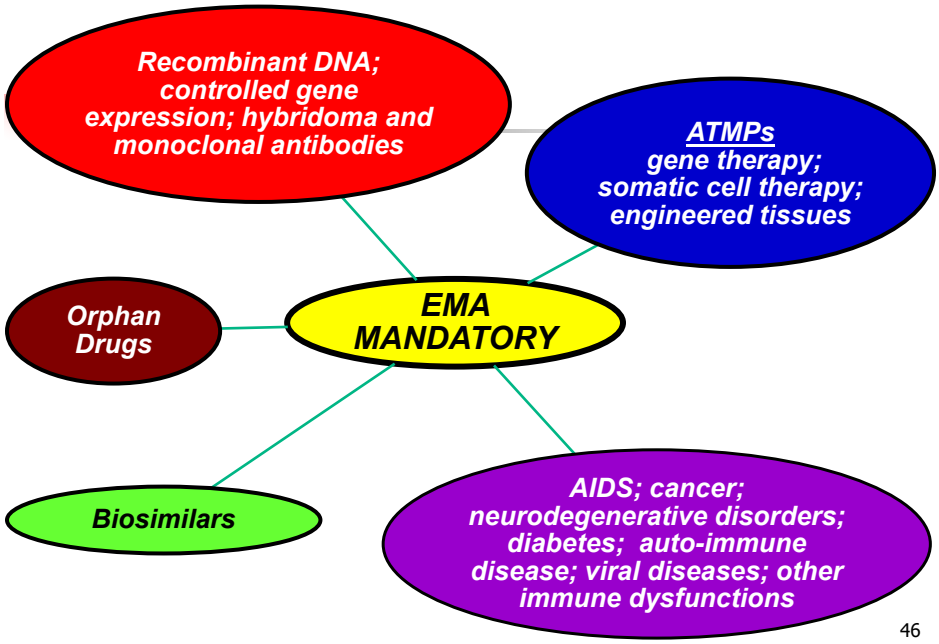
EMA Centralized Procedure

Market Authorization Application (MAA)

Mandatory for most Biologics →

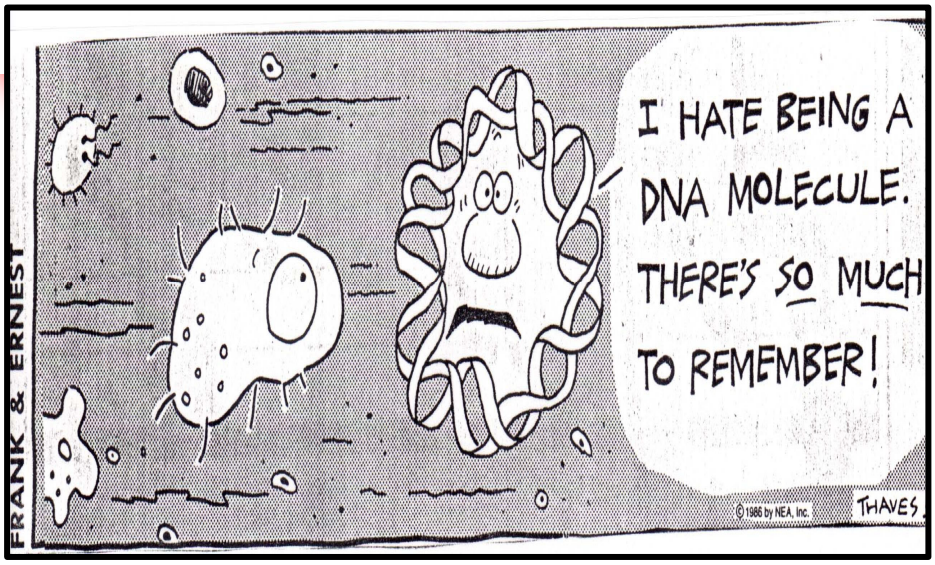
(EU still uses a national authorization and a mutual recognition procedure)

45



46

Are you confused yet?



? QUESTIONS ?

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CMC Regulatory Compliance Strategy For Biopharmaceuticals

Course Outline

2. Risk-Managed CMC Regulatory Compliance Strategy

- ✓ *Five (5) key design elements for an effective CMC strategy*
- ✓ *Overbearing pressure of expedited clinical development pathways on the CMC teams*

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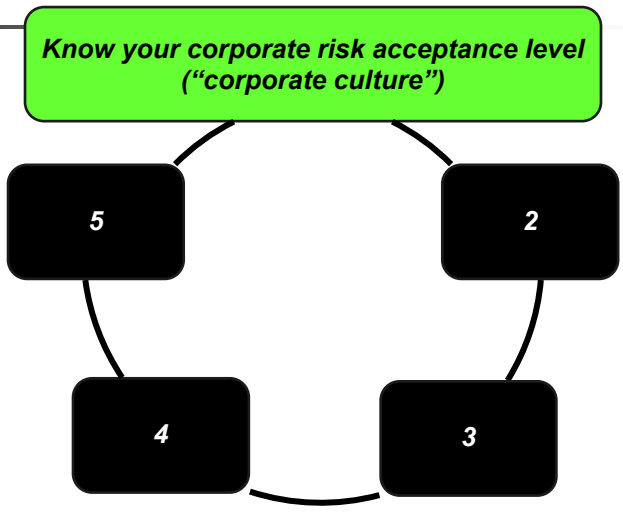
5 design elements of an effective risk-managed CMC regulatory compliance strategy



50

Know your corporate risk acceptance level

(levels in between)

risk adverse

'plodders'
slow and thorough
unexpected problems not tolerated

risk tolerant

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

While slow is good, the competition is not waiting around

Sometimes being too risk-accepting leads to under-estimating a risk!

Sometimes moving too fast leads to overlooking risk signs!

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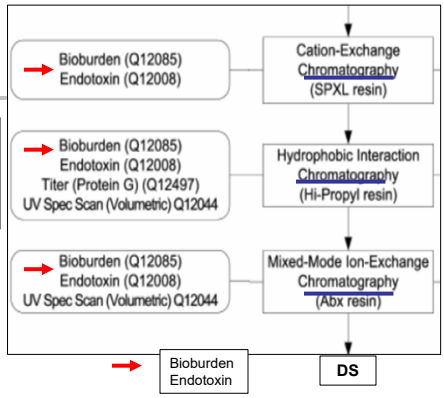
Illustration of Corporate CMC Risk Acceptance Level

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 if we only test at the DS?*
- *What is the statistical probability that a problem/ patient harm could occur?*
- *What is the perceived probability that a problem/ patient harm could occur?*
- *(Wonder why regulatory authorities are so insistent on this testing?)*

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What possibly could go wrong?

Might we miss excreted toxins in an in-process high bioburden load?
(patient safety)

***not* tested in DS** **tested in DS**

Might we miss peptidase excretion in an in-process high bioburden load?
(shelf life instability)

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

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Case Example: inappropriate risk acceptance level

'can't happen to us' – not responding to risk warning signs!

(Genzyme – Vesivirus 2117 bioreactor contamination)

- ***2003*: Vesivirus 2117 found to proliferate in CHO cells**
- ***2006*: Evidence of widespread Vesivirus 2117 infections in cattle across a large area of the United States – biologic manufacturers who source FBS put on notice; PCR test available to give rapid detection of Vesivirus (but it cost ~$2000 per sample)**
- ***2008*: Genzyme encountered loss of CHO cell productivity in a 4000L bioreactor at their Belgium site, and a 2000L bioreactor in the USA – *but manufacturing saw changes in cell growth profile and did not break bioreactor integrity* – instead killed the cells and decontaminated the suspected virus inside the bioreactor; no indication that Genzyme considered adding the prior-to-harvest Vesivirus 2117 PCR test**
- ***2009*: The nightmare hits! Genzyme confirms Vesivirus 2117 in a bioreactor, *but only after containment was broken!* Now, the virus was spread into the purification suite and throughout the entire facility!**

Rosenberg, A.S., Cherney, B., et.al., *Risk Mitigation Strategies For Viral Contamination of Biotechnology Products: Considerations of Best Practices* ; PDA J. Pharm. Sci. and Tech. 2011, 65: 563-567

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Genzyme Temporarily Interrupts Production at Allston Plant

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

Because pediatric orphan drug recombinant protein enzymes shortages might result, Genzyme has to go public with contamination – issues Press Releases

Terms:

Dateline City:
CAMBRIDGE, Mass.

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.

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.

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Genzyme Press Release Sept 2009

- 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***
- ***Estimated (Wall Street) impact on company: ~$500 million loss***
- ***Consent decree signed with FDA – May 2010*** ***Sanofi buys Genzyme – February 2011***

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)

56

5 design elements of an effective risk-managed CMC regulatory compliance strategy

Know your corporate risk acceptance level ("corporate culture")

Manage the CMC needs of your specific biopharmaceutical product

5

3

4

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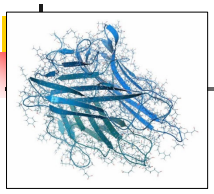
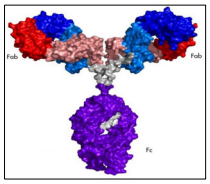
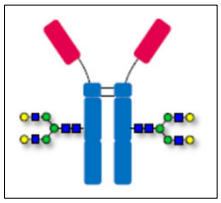
Biopharmaceuticals are …



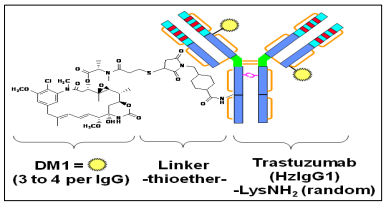
Recombinant Proteins



Monoclonal Antibodies



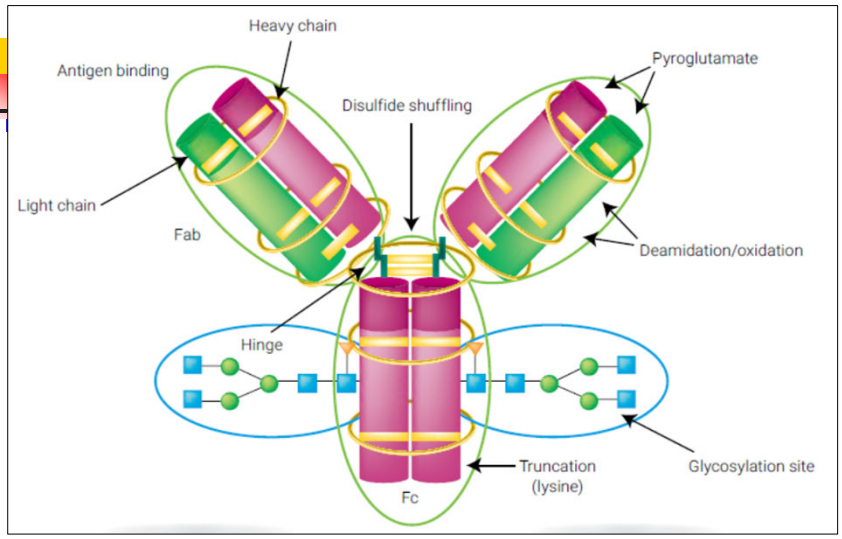
Fc-Fusion Proteins



Antibody Drug Conjugates (ADCs)

58

Recombinant proteins and monoclonal antibodies are complex due to an abundance of molecular variants!



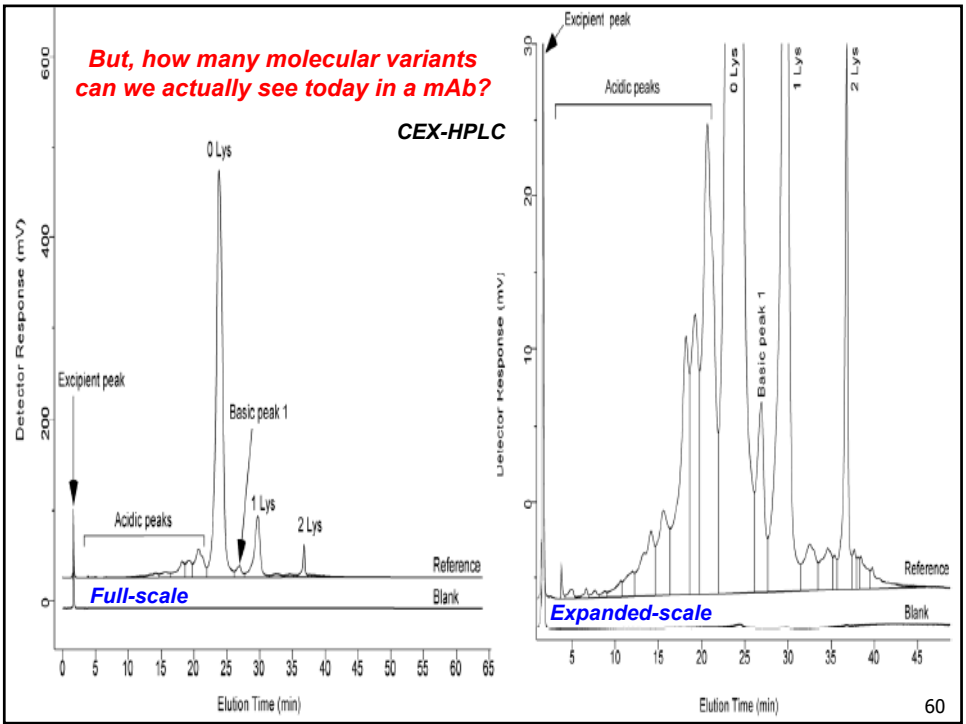
Kozlowski and Swann, Current and Future Issues in the Manufacturing and Development of Monoclonal Antibodies; Advanced Drug Delivery Reviews, 58 (5-6), 7 Aug 2006, pp 707-722

Total theoretical molecular variants = 100 million

59

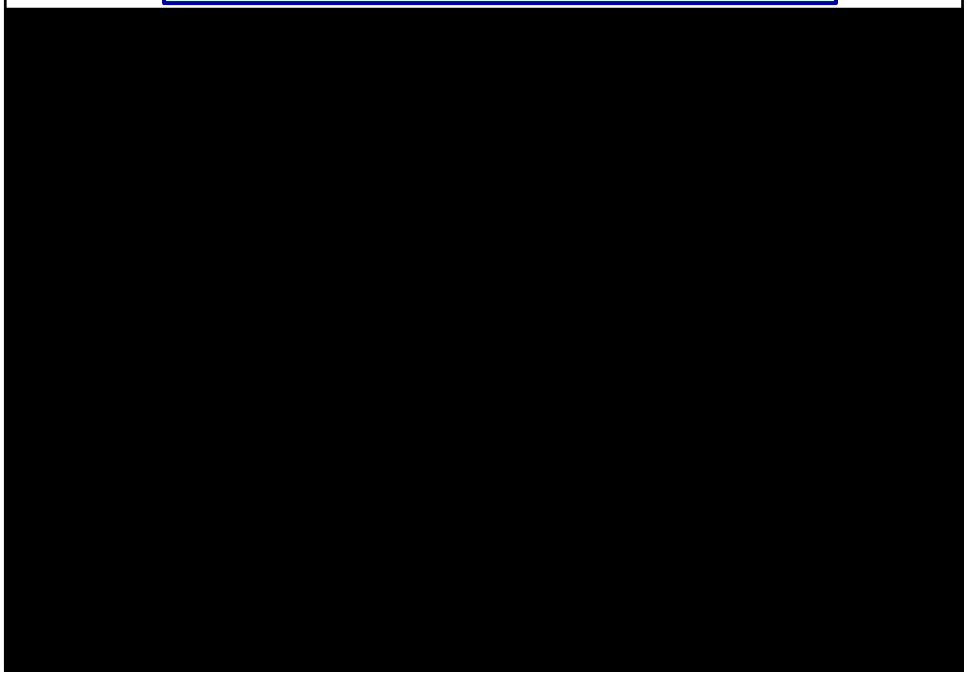
But, how many molecular variants can we actually see today in a mAb?

CEX-HPLC



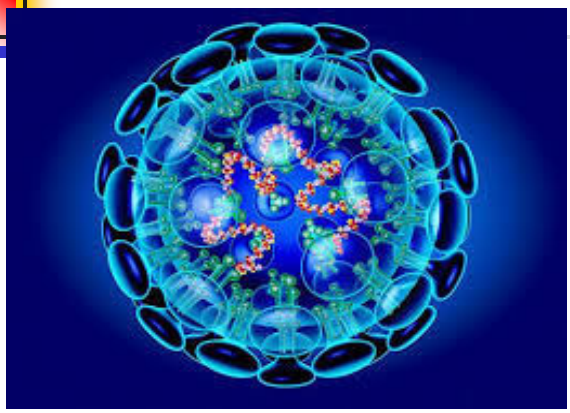
60

Gene Replacement with a Genetically Engineered Living Viruse



Increasing complexity of a genetically engineered living virus

mAb: ~10 nm → *virus: ~20-100 nm*



genome (DNA or RNA) incorporated inside a protein shell (capsid)

Capsids: *full, partial full, empty*
Capsid proteins: *amino acid sequence, glycosylation, molecular variants*
Genome: *gene sequence, host cell DNA contamination*

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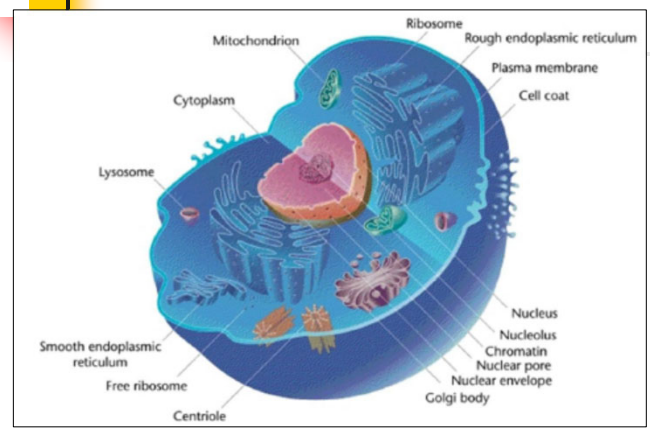
Enormous complexity of a genetically engineered living cell

mAb: ~10 nm ⟶ cell: ~10 µm



A cell has over 18,000 genes (proteins)

Cell Type: *selected cells, non-desired cell types*
Gene: *transduced cell : non-transduced cell*
Potency: *functionally active gene : non-functionally active gene*

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No one-size CMC regulatory strategy fits <u>all</u> biopharmaceutical products!

Many things in common, but no magic formula!

Each biopharmaceutical product has specific regulatory compliance concerns that need to be addressed

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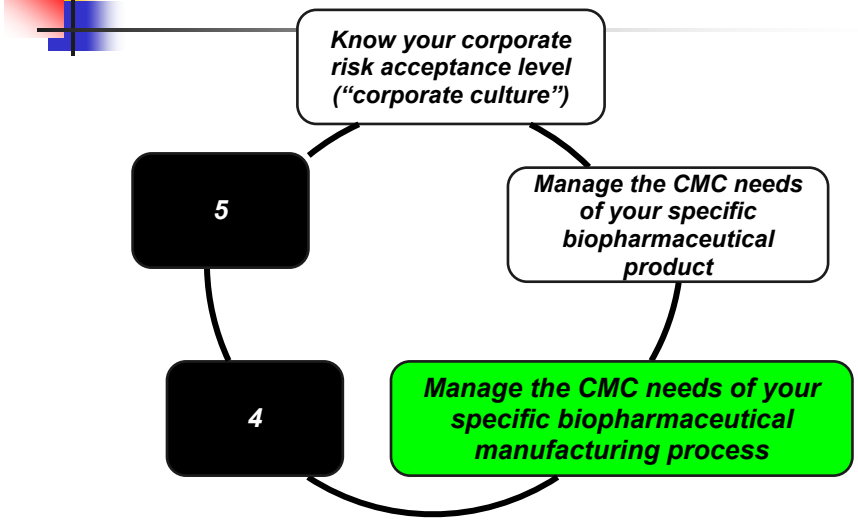
***5* design elements of an *effective* risk-managed CMC regulatory compliance strategy**



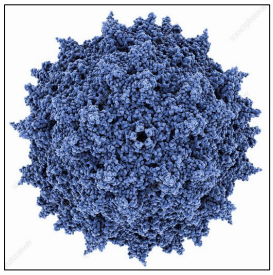
65

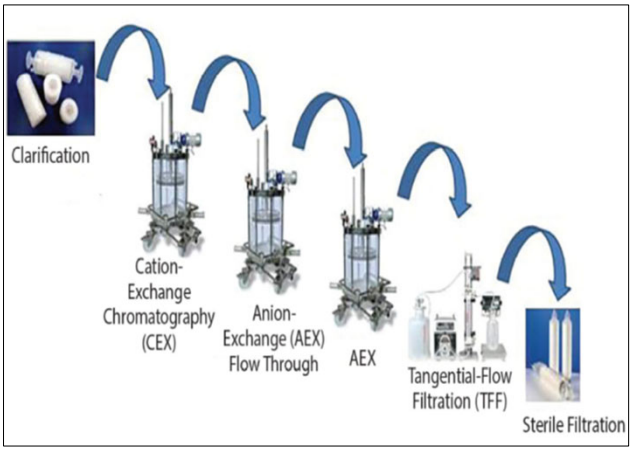
Manufacture of recombinant proteins and monoclonal antibodies

300,000L of biomanufacturing capacity (20 x 15,000 L)

Manufacture of genetically engineered viruses

(process looks similar to that of recombinant proteins)





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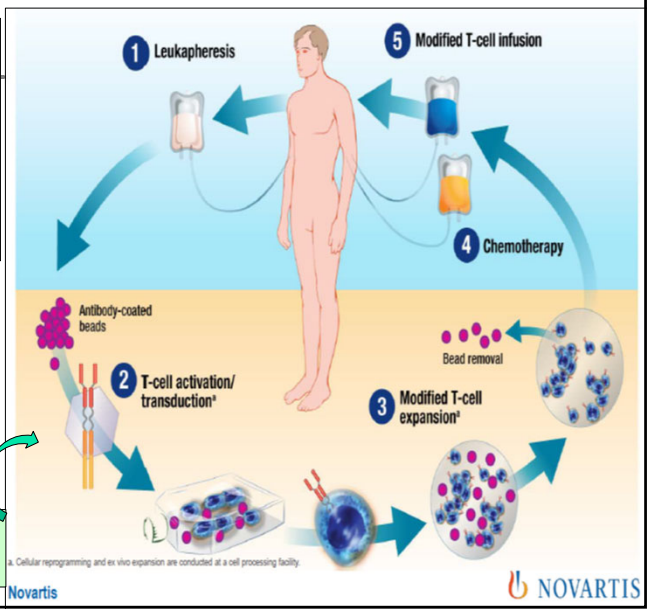
Manufacture of Genetically Engineered Living Cells (gene addition)

Novartis KYMRIAH
Kite YESCARTA

autologous genetically modified T-cells (CAR – chimeric antigen receptor) to bind/kill CD19-containing leukemia cells

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



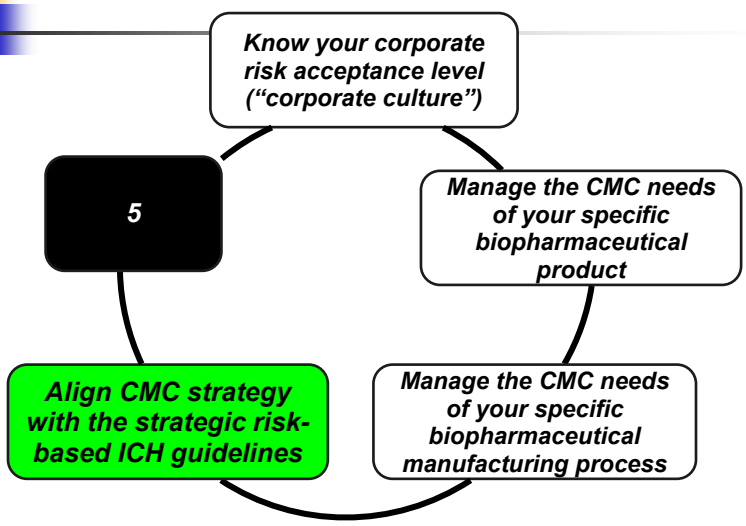
No one-size CMC regulatory strategy fits all manufacturing processes!

Many things in common, but no magic formula!

Each biopharmaceutical manufacturing process has specific regulatory compliance concerns that need to be addressed

69

5 design elements of an effective risk-managed CMC regulatory compliance strategy



70

International Council for Harmonisation

ICH harmonisation for better health

USA/EU/Japan + China/South Korea/Brazil

CMC content

consensus guidelines

(immensely helpful for decades)

"Q" CMC (specific focus on recombinant proteins & mAbs)

- **Q5A** *Viral Safety Evaluation* **[1997]**
- **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]**

(applicable to both chemical drugs and biologics)

- **Q2** *Validation of Analytical Procedures* **[1994]**
- **Q7** *GMP of Active Pharmaceutical Ingredients (APIs)* **[2000]**
- **M4Q** *Common Technical Document (CTD) Format* **[2000]**
- **Q12** *Pharmaceutical Product Lifestyle Management* **[2019]**
- **Q13** *Continuous Manufacturing*
- **Q14** *Analytical Procedure Development*

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ICH harmonisation for better health

CMC strategy ('systematic')

consensus guidelines

1) ICH Q8(R2) Pharmaceutical Development (2008)

- *Quality by Design (QbD)*

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.

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ICH Q8: QbD – Four Steps to Implementation

73

ICH harmonisation for better health

CMC strategy ('systematic')

consensus guidelines

1) ICH Q8(R2) Pharmaceutical Development (2008) Quality by Design (QbD)

2) ICH Q9 Quality Risk Management *(2005)*

- ***Quality Risk Management (QRM)***

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.

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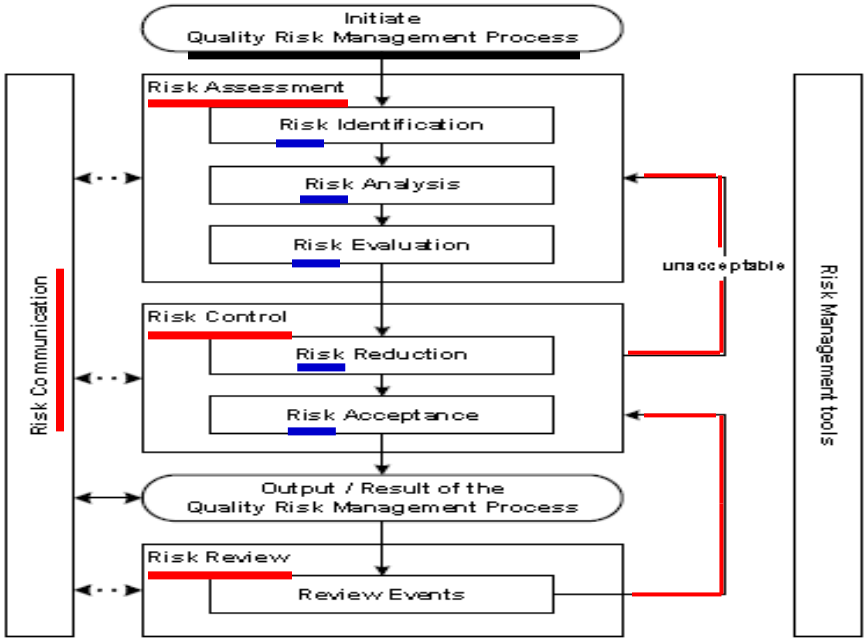
QRM – prioritization and management of risks!



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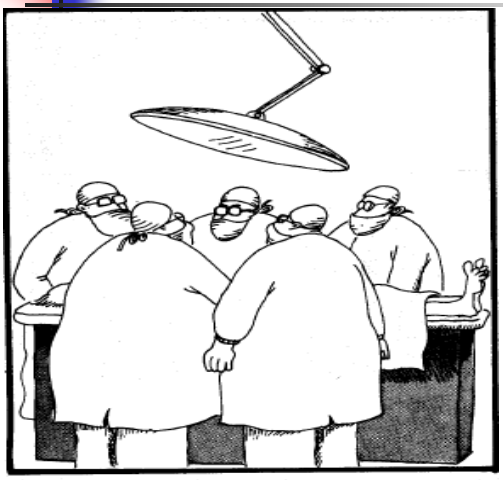
What is the weakest link in QRM prioritization and management of risks in a biologic manufacturing process?



"Okay, Williams, we'll vote . . . how many here say the heart has four chambers?"

Reaching corporate consensus of the risks

- ***wrong people involved***
  - *inexperienced*
  - *non-competent*
- ***wrong environment***
  - *fatigue*
  - *herd-mentality*
  - *3 pm on Fridays*

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A toolkit to select from for managing and prioritizing risk

QRM
project management tools

QRM
statistical analysis tools

Risk Ranking and Filtering* (RRF)

Failure Mode Effects Analysis (FMEA)

Preliminary Hazard Analysis (PHA)

Control Charts (Shewhart)

Process Capability Analysis (Cpk)

Design of Experiments (DOE)

* will be discussed shortly

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OFAT – 'one factor at a time'

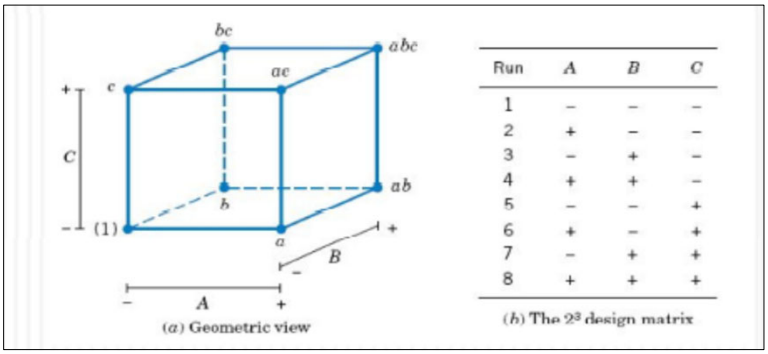
works for simple processes

Chemical Synthesis L^{PP}

2 Levels
low
high

3 Process Parameters
temperature
pressure
duration

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



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

(b) The 2^3 design matrix

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DOE – 'Design of Experiments'

critically needed for complex processes

2 Levels

low
high

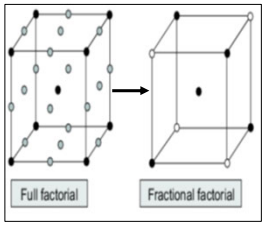
9 Process Parameters

starting cell viability
in vitro cell age
antifoam conc
dissolved oxygen
glucose feed level
glucose feed timing
temperature
elapsed time
pH

Biologic Bioreactor L^{PP}

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

No lack of DOE instructional videos on YouTube



But DOE costs $$$

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

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

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CMC strategy ('systematic')

consensus guidelines

1) ICH Q8(R2) Pharmaceutical Development (2008) — Quality by Design (QbD)
2) ICH Q9 Quality Risk Management (2005) — Quality Risk Management (QRM)

3) ICH Q10 **Pharmaceutical Quality System** (2008)
   - Knowledge Management (KM)

> **Knowledge Management:**
> Systematic approach to acquiring, analysing, storing, and disseminating information related to products, manufacturing processes and components. (ICH Q10)

Importance of 'passing forward' technical knowledge

80

CMC strategy ('systematic')

consensus guidelines

1) *ICH Q8(R2) Pharmaceutical Development (2008)* — *Quality by Design (QbD)*
2) *ICH Q9 Quality Risk Management (2005)* — *Quality Risk Management (QRM)*
3) *ICH Q10 Pharmaceutical Quality System (2008)* — *Knowledge Management (KM)*
4) *ICH Q11 Applied ICH Q8-10 to Chem/Biotech APIs (2012)*

Provides examples and further clarification on the principles and concepts described in ICH Q8, Q9 and Q10 applied to the development and manufacture of drug substances

- *Drug Substance Critical Quality Attributes (CQAs)*
- *Linking Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs) to CQAs*
- *Development of the Control Strategy*

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What is the overall impact of ICH Q8/Q9/Q10/Q11 on biopharmaceutical CMC regulatory compliance strategy?

- *Be prepared to know not only the 'WHAT' but also the 'WHY' – justify, justify, justify,...!*
- *Learning never ends – keep eyes open for early warning signs of potential CMC issues; work toward real corrections and effective preventative actions (CAPA)!*
- *Think 'big picture' risk analysis – not that a CMC step works but how can it continue to work time and time again*

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Consideration

catastrophic event plan for the biopharmaceutical source material

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

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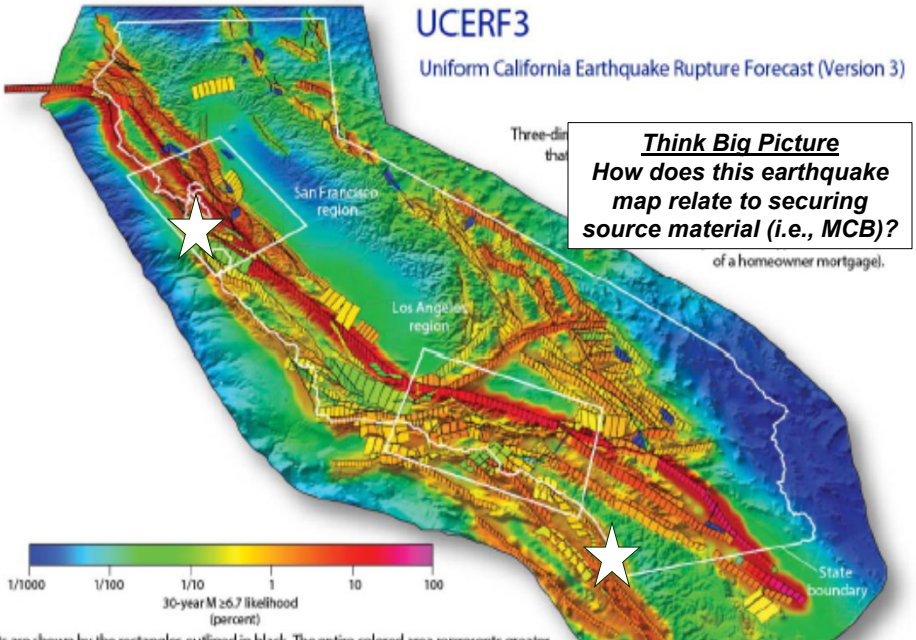


Think Big Picture
How does this earthquake map relate to securing source material (i.e., MCB)?

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.

84

Consideration

How many Process Performance Qualification (PPQ) batches?

Industry Standard (for decades)

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

Why 3 and not 5?

Statistical value of 3 runs?

Where did the '3 run' rule originate?

Monty Python 85

Monty Python – 'Quest for the Holy Grail'

ICH/EMA: '3 Run Rule' is Gone!

> 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

Manufacturing Process Understanding	Biologic Product Knowledge	Manufacturing Experience
Impact of unit operations on CQAs CPPs Control strategy robustness	CQAs Stability profile	Level of batch-to-batch variation Process capability knowledge

↓

Determine overall residual risk level

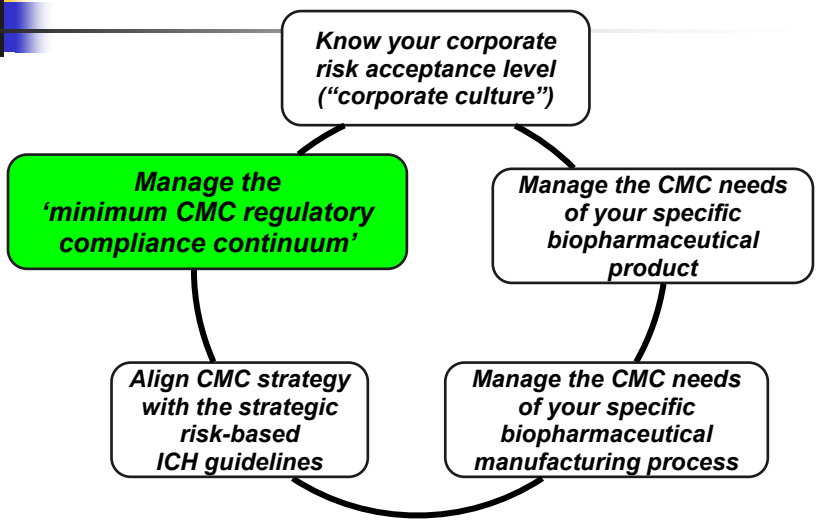
↓

Translate into number of PPQ batches to run

QUESTION: So how many PPQ batches will you run?

87

5 design elements of an effective risk-managed CMC regulatory compliance strategy



88

'minimum CMC regulatory compliance continuum'

definitions

- ***"minimum" – a recognition that there is a different level for CMC regulatory compliance at different clinical development stages***
- ***"continuum" – a recognition that the minimum CMC regulatory compliance level rises as clinical development advances***
  - ***Early clinical stage focus → product safety for patient***
  - ***Later clinical stage focus → product safety for patient + manufacturing process consistency of the biologic product batch-to-batch***

An immature quality development may compromise the use of the study in the context of a marketing authorisation application (e.g. if the product has not been adequately characterised). A weak quality system may also compromise the approval of the clinical trial if the safety of trial subjects is at risk.

Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials

31 January 2019
EMA/CAT/852602/2018

89

'minimum CMC regulatory compliance continuum'

risk-based approach provides necessary flexibility

U.S. FOOD & DRUG ADMINISTRATION

Present regulations allow a great deal of flexibility in the amount and depth of various data to be submitted in an IND depending in large part on the phase of investigation and the specific human testing being proposed. In some cases, the extent of that flexibility has not been appreciated.

Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products 1995

Manufacturers are responsible for the quality of the ATMPs they produce. The risk-based approach permits the manufacturer to design the organisational, technical and structural measures that are put in place to comply with GMP -and thus to ensure quality- according to the specific risks of the product and the manufacturing process. While the risk-based approach brings flexibility, it also implies that the manufacturer is responsible to put in place the control/mitigation measures that are necessary to address the specific risks of the product and of the manufacturing process.

EUROPEAN COMMISSION

Good Manufacturing Practice for Advanced Therapy Medicinal Products 22.11.2017

90

'minimum CMC regulatory compliance continuum'

risk-based approach is about protecting patients

- *A risk-based approach focuses Manufacturing and Quality on activities that may affect product quality, safety and/or efficacy (all of which, directly or indirectly, can impact patient safety)*
- *A risk-based approach attempts to avoid non-value-added activities, and focuses efforts, with the limited resources, on the value-added activities*
- *A risk-based CMC regulatory compliance approach does not mean doing less, but doing the right amount at the right time based upon the understanding of the potential risks to patient safety*
- *Thus, a risk-based approach actually enhances patient safety during clinical development phases, especially when product understanding and resources may be limited*

Risk-based management across the biologic development lifecycle
good regulatory sense and good business sense

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'minimum CMC regulatory compliance continuum'

embraced by EMA

recombinant proteins and monoclonal antibodies

IMPD CMC Area		*Risk-Based CMC Regulatory Compliance Strategy*
S.2.4	*Control of Critical Steps*	*It is acknowledged that due to limited data at an early stage of development (phase I/II) complete information may not be available.*
S.2.6	*Manufacturing Process Development*	*Manufacturing processes and their control strategies are continuously being improved and optimised, especially during the development phase and early phases of clinical trials.*
S.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.*
S.4.3	*Validation of Analytical Procedures*	*Validation of analytical procedures during clinical development is seen as an evolving process. For phase I and II clinical trials, the suitability of the analytical methods used should be confirmed. For phase III clinical trials: Validation of the analytical methods.*

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

September 2018
EMA/CHMP/BWP/534898/2008

92

'minimum CMC regulatory compliance continuum'

embraced by FDA

genetically engineered viruses and cells

CTD IND CMC Area		Recognized Risk-Based CMC Regulatory Compliance Strategy
3.2.S.2.5	Process Validation	Process validation studies are generally or typically not required for early stage manufacturing, and thus, most original IND submissions will not include process performance qualification.
3.2.S.2.6	Manufacturing Process Development	If you make significant manufacturing changes, then comparability studies may be necessary to determine the impact of these changes on the identity, purity, potency, and safety of the product. The extent of comparability testing will depend on the manufacturing change, the ability of analytical methods to detect changes in the product, and the stage of clinical development.
3.2.S.4.1	Specifications	For products in the early stages of clinical development, very few specifications are finalized, and some tests may still be under development.
3.2.S.4.3	Validation of Analytical Procedures	Validation of analytical procedures is usually not required for original IND submissions for Phase 1 studies; however, you should demonstrate that test methods are appropriately controlled.

U.S. FOOD & DRUG ADMINISTRATION

Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)

Food and Drug Administration
Center for Biologics Evaluation and Research
January 2020

93

'minimum CMC regulatory compliance continuum'

illustrated in 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.

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.

U.S. FOOD & DRUG ADMINISTRATION

Guidance for Industry
CGMP for Phase 1 Investigational Drugs
July 2008

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

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

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

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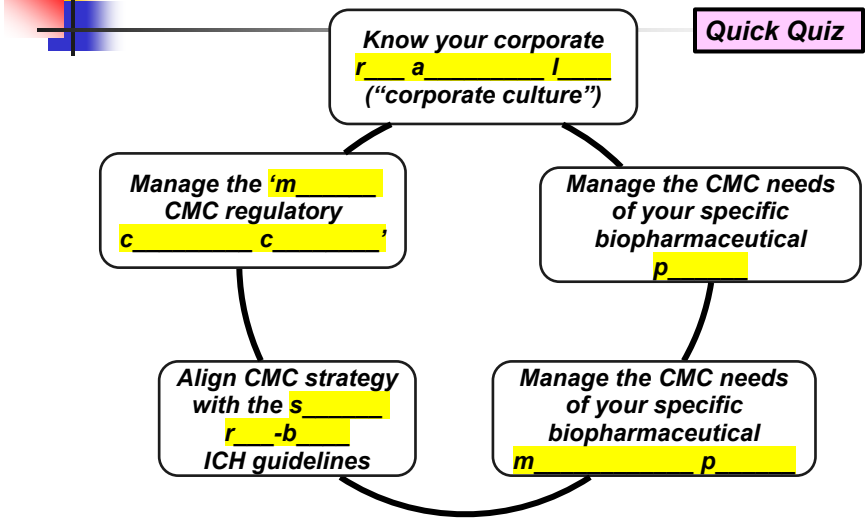
5 design elements of an effective risk-managed CMC regulatory compliance strategy



95

A major challenge is to develop, characterize, and validate the biopharmaceutical manufacturing process under compressed clinical development timelines, while ensuring product comparability of clinical data between process changes!

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)

FDA: Regenerative Medicine Advance Therapy (RMAT) designation

FDA Guidance for Industry: Expedited Programs for Regenerative Medicine Therapies for Serious Conditions (February 2019)

EMA: Primary Medicine (PRIME) designation

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

Exciting clinical speed opportunities to shorten the timelines …

… but stresses the CMC continuum timetable!

96

Recognized CMC pressure points applicable to biologics due to clinical expediting

EMA PRIME designation (especially challenging for advanced therapy biologics)

Perspective from EU-EMA (V. Jekerle (Quality Office, EMA))

The talk also illustrated the scientific challenges common to PRIME candidates including shortened timelines, which put constraints on the ability to complete commercial manufacturing sites set-up & description, compilation of validation and stability data and determination of the appropriate control strategy including specification setting. Product characterization, in particular, determination of biological activity and demonstration of comparability, is particularly challenging for many PRIME candidate products due to their highly innovative and complex features (i.e. genetically modified cells and viral vector–based products). Finally, global developments require applicants to put extra efforts into demonstrating comparability, where manufacturing processes are being changed or moved across geographic regions and suitable batch-release testing arrangements need to be identified in line with the applicable legal framework. An analysis examining scientific issues most commonly identified by PRIME applicants (as indicated by SA requests) revealed the following areas as the most critical: starting materials, comparability, process validation, analytical control strategy, specifications and stability.

In conclusion EU regulators view PRIME as a support scheme for development, whereby the product quality should not be compromised but considered in the context of the benefit/risk assessment.

Meeting Report:
Workshop with stakeholders on support to quality development in early access approaches (i.e. PRIME, Breakthrough Therapies)

25 July 2019
EMA/CHMP/BWP/812924/2018

97

FDA is VERY concerned about the CMC team if expedited clinical pathway is granted for gene therapy biopharmaceuticals!

In contrast to traditional drug review, where 80 percent of the review is focused on the clinical portion of that process, and maybe 20 percent is focused on the product issues, I'd say that this general principal is almost completely inverted when it comes to cell and gene therapy.

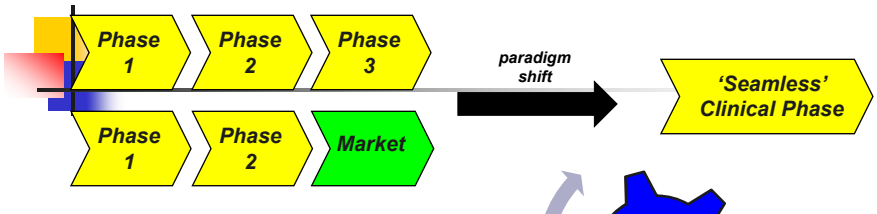
The initial clinical efficacy is often established early, and sometimes in small series of patients.

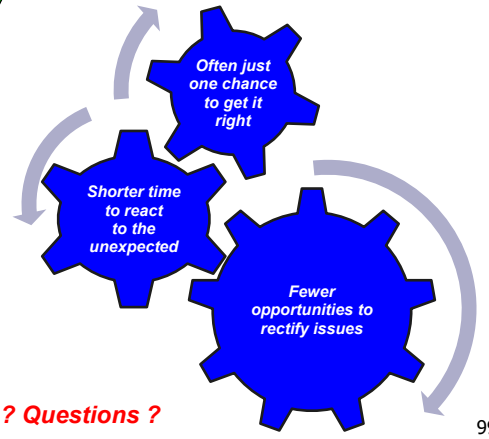
The more challenging questions relate to product manufacturing and quality, or questions like how much you can change, or enlarge, the gene cassette that you load into a vector before the gene insert will change the conformation of the vector in ways that also fundamentally alter the entire product's safety or performance.

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

98

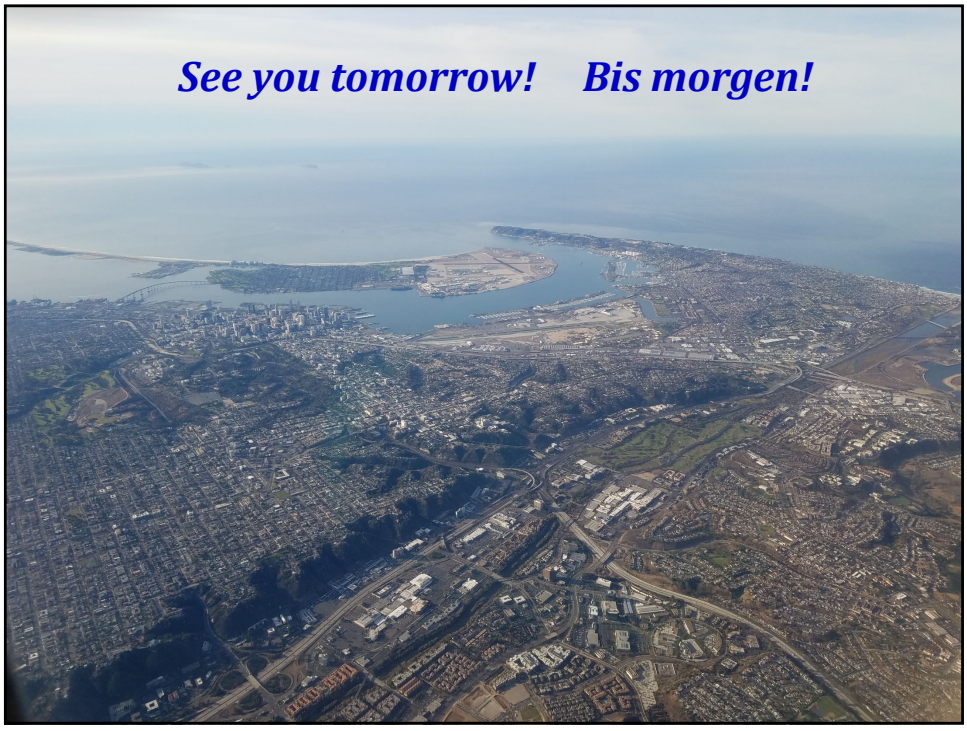
Always a danger in CMC's management of the continuum in keeping pace with clinical development, if going fast!





? Questions ?

99



CMC Regulatory Compliance Strategy For Biopharmaceuticals

Course Outline

3. *Applied* Risk-Managed CMC Regulatory Compliance Strategy

- ✓ *mAb: walk through entire manufacturing process from source material → drug substance → drug product*
- ✓ *Gene therapy virus: comparing/contrasting a protein-based manufacturing process (i.e., mAb) with a virus-based manufacturing process*

101

Manufacturing Process Flow Diagram

	Monoclonal Antibody	AAV Gene Therapy (Replacement Gene)
STARTING MATERIAL	Recombinant Master Cell Bank (rMCB)	
DRUG SUBSTANCE		
DRUG PRODUCT		

102

Starting Material *(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.

contains the genetic capability to make the product

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Assembling a Recombinant Master Cell Bank

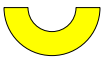
(Step 1 of 3) Development Genetics (stitching genetic components)

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

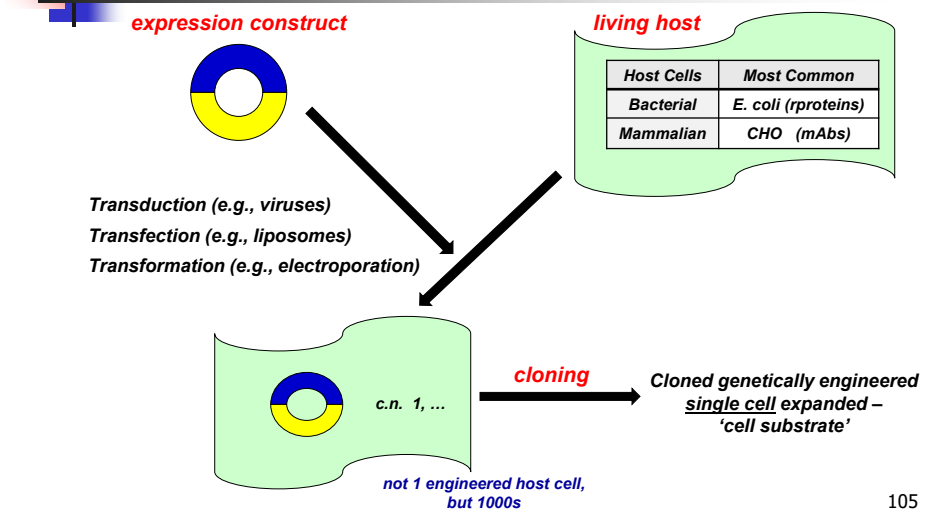


expression construct

104

Assembling a Recombinant Master Cell Bank

(Step 2 of 3) Preparing the Cloned Cell Substrate



105

Assembling a Recombinant Master Cell Bank

(Step 3 of 3) Laying Down the Cell Bank

Cloned Cell Substrate

↓

Master Cell Bank (MCB)

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

↓

If 1 aliquot is typically needed per production batch, MCB can provide up to 200 production batches

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

If 1 aliquot is typically needed per production batch, WCB can provide up to 40,000 production batches

106

Two myths about Recombinant MCBs!

"Myth" - a traditional or legendary story, with or without a determinable basis of fact, that explains some practice

Myth #1

Since a Master Cell Bank has been allowed by a regulatory authority to be used in clinical studies, the MCB must also be acceptable for commercial manufacturing!

107

Truth about MCBs during clinical development

1 of 2: minimum regulatory authority expectations

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.

EMA Guideline on the Requirements for Quality Documentation Concerning Biological Investigational Medicinal Products in Clinical Trials (September 2018)

108

Truth about MCBs during clinical development

2 of 2: regulatory authority reviewers do not catch everything

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)

109

'Primarily on Safety' Focus

(1) absence of adventitious agents of concern

- ***Prions – TSEs***
  - ***Prevented through risk minimization strategy in choices for raw materials used to prepare bank***
- ***Viruses* – insect/animal/human cell lines***
  - ***Extensive 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

****NGS – Next Generation Sequencing***

110

'Primarily on Safety' Focus

(2) absence of non-host cells

The purity of cell substrates can be compromised through contamination by cell lines of the same or different species of origin. The choice of tests to be performed depends upon whether opportunities have existed for cross-contamination by other cell lines. In some cases, it may be necessary to maintain growing cultures of different cell lines in the same laboratory. During procedures in cell banking where open manipulations are performed, care should be taken to ensure that simultaneous open manipulations of other cell lines are avoided to prevent cross-contamination. Whenever another cell

ICH Q5D

Absence confirmed by <u>documentation</u> of procedural controls

MCBs/WCBs are to be manufactured under cGMPs!

111

'Primarily on Safety' Focus

(3) 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*

ICH Q5B

ICH Q5D

Note, where was the genetic engineering done? In R&D?

112

Truth about MCBs for commercial manufacturing

- ***Patient safety continues to remain the primary regulatory evaluation of the MCB***
- ***But now, the MCB is also thoroughly reviewed to determine if it can meet the expectations for a stable, continuous, homogenous source for future ongoing commercial manufacturing***
- ***Emphasis shifts from "brief" to "detailed" descriptions in the BLA/MAA***

113

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.

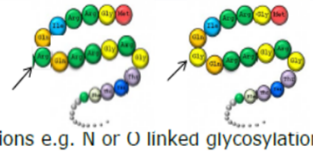
Final Gene Construct – A detailed description should be provided of the cloning process which resulted in the final recombinant gene construct. The information should include a step-by-step description of the assembly of the gene fragments and vector or other genetic elements to form the final gene construct.

FDA 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)

114

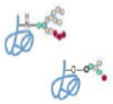
Monoclonality of Cell Banks

The DS could be a mixture e.g.



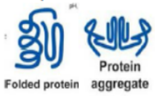
Different amino acid sequence

Different post translational modifications e.g. N or O linked glycosylation



Different impurity profile e.g. deamidation, oxidation, aggregation profile

Different functional activity



Consequences:

Complete physical, chemical and functional characterisation to confirm same DS

Investigations into the source of DS/DP (i.e. which clone) used in each CT

Possible repetition of CTs, rejection of MAH

Monoclonality should be confirmed before phase 1 CT

Preparing the CMC section of IMPD for biological/biotechnology derived substances

Dr. Una Moore
Health Products Regulatory Authority, Ireland

16th April 2014.

115

Clonal issues with monoclonal antibodies produced by CHO

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)

Ultragenyx Breakthrough Therapy

Testing for the identity, safety and genetic stability of the cell bank was performed. However, as the cell cloning procedure did not provide a high assurance of clonality of the master cell bank. The cell line genetic stability and product quality data submitted to the BLA provide assurance that the current manufacturing process is not impacted by the clonality of the cell bank; however it did not address the impact of different manufacturing conditions throughout the product life cycle.

To address this issue the Applicant agreed to perform additional testing of the master cell bank to support clonality as a postmarketing commitment.

FDA Drugs – Search Drugs@FDA: FDA Approved Drug Products: Zinplava (Bezlotoxumab) – Approval History, Letters, Reviews and Related Documents – Administrative and Correspondence Documents – Summary Review (October 21, 2016)

Merck Fast Track

116

Two myths about Recombinant MCBs!

"Myth" - a traditional or legendary story, with or without a determinable basis of fact, that explains some practice

Myth #2

Focus resources/attention on the Master Cell Bank, since a Working Cell Bank never causes any problems!

117

Regulatory authorities are aware of the risks associated with the introduction of new WCBs

Regulatory concern 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.

EMA Guideline on the Requirements for Quality Documentation Concerning Biological Investigational Medicinal Products in Clinical Trials (September 2018)

Caution only
(but no prior-approval required for introducing a new WCB into the manufacturing process during clinical development)

118

Heightened regulatory concern at the commercial stage

Case Example of what a regulatory authority can request before allowing the introduction of a new WCB into the manufacturing process

Qualification of the WCB will include

- ***safety testing,***
- ***an evaluation of the growth of WCB cultures relative to the growth of Master Cell Bank (MCB) cultures,***
- ***testing of end of production cells generated from the commercial scale process, and***
- ***a comparability assessment that includes the first three lots manufactured from the WCB using the commercial process.***

MCB was not confirmed to be clonal; typically only first lot

One lot manufactured using the commercial process will be placed on a stability protocol and the data will be submitted in the subsequent BLA annual reports.

The WCB qualification report will be submitted in a prior approval supplement.

No pre-approved contract in place for this protocol

FDA Drugs – Search Drugs@FDA: FDA Approved Drug Products: Unituxin (Dinutuximab) – Approval History, Letters, Reviews and Related Documents – Market Approval Letter (March 10, 2015)

United Therapeutics

119

FDA has discovered problems with WCBs during pre-approval inspections

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)

Genentech

more on this story when we get to process validation

120

FDA has discovered problems with WCBs during BLA Reviews

Identified in Complete Response Letter (CRL) at end of BLA review

PRODUCT QUALITY

1. Reference is made to the information and data provided to the Agency concerning the stability of the PF-05280014 Working Cell Bank (WCB) on January 22, 2018 and February 9, 2018. Although the likely root causes for the instability have been identified and corrective actions were implemented in late 2017, the information and data do not support the suitability of the current WCB for commercial production.

Pfizer

FDA Drugs – Search Drugs@FDA: FDA Approved Drug Products: Trazimera (Trastuzumab-qyyp) Biosimilar – Approval History, Letters, Reviews and Related Documents – Other Action Letters – Complete Response Letter (April 20, 2018)

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/761081Orig1s000OtherActionLtrs.pdf

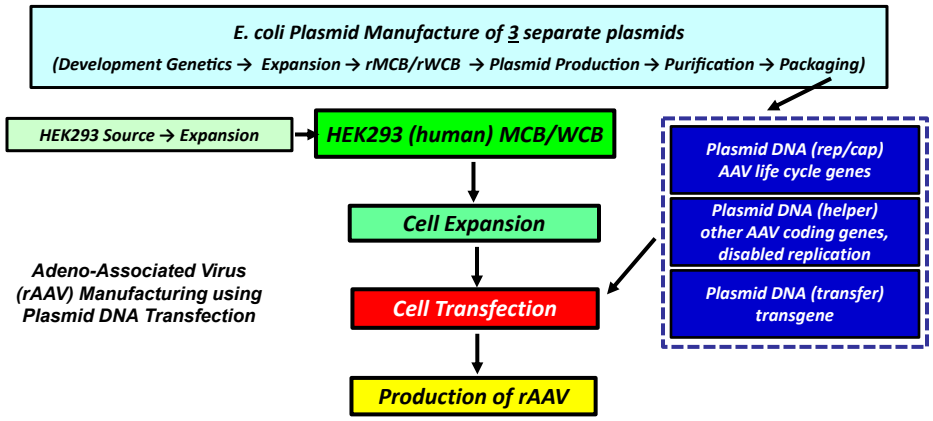
121

Manufacturing Process Flow Diagram

	Monoclonal Antibody	***AAV Gene Therapy (Replacement Gene)***
STARTING MATERIAL	***Recombinant Master Cell Bank (rMCB)***	***Variable – process and end use dependent***
DRUG SUBSTANCE		
DRUG PRODUCT		

122

Discussion: What are the source materials for this gene therapy manufacturing process?



123

Regulatory Concerns for Source Materials

Comparison of Regulatory Concerns for MCBs	
Monoclonal Antibodies	**AAV for Gene Therapy**
Absence of adventitious agents (prions, viruses, mycoplasma, bacteria/fungi)	Same, but … "In your IND, you should provide a description of the history and detailed derivation of the source material for the cell bank." Absence of replication competency
Absence of non-host cells	
Correct identity of genetic components (gene, vector, host)	

Note, for mAbs, the wording was ' brief description'

because gene therapy is frequently 'expedited', it is now 'detailed description'.

Regulatory Concerns for the Viral Vectors
You should also provide a complete description of all procedures used for gene modification (such as transfection, infection or electroporation of vectors, or genome editing components) and any additional culture, cell selection, or treatments after modification. The vector used should be described in detail as indicated above.

Challenge of 'Sole Source' source materials

***Case Example*: 12 month clinical start delay**

EDIT-101 – transient AAV manufacture, with CRISPR for in vivo gene editing

1 of 3 plasmid vectors did not meet incoming quality specs

May 15, 2017

> Editas Medicine on May 15 disclosed during a first quarter earnings presentation that its highly anticipated CRISPR gene-editing therapy would be delayed entering the clinic.

"The manufacturing delay related to production of input materials for AAV manufacturing"

November 30, 2018 — **Editas Medicine Announces FDA Acceptance of IND Application for EDIT-101**

***Case Example*: 3 month clincal hold + 12+ month partial clinical hold**

November 12, 2019

> Marker previously announced on November 12, 2019, that the FDA placed the trial on clinical hold. The FDA requested additional information and technical specifications for two legacy reagents supplied by third parties used in the MultiTAA-specific T cell manufacturing process. The technical specifications and data requested by the FDA could not be produced by the original suppliers. The Company identified alternative suppliers, satisfying the Agency's request.

August 10, 2020

"Marker currently estimates that the alternative supplier will deliver the final reagent, along with the final data and certificate of analysis required by the FDA, by the end of the Q3 2020."

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Manufacturing Process Flow Diagram

	Monoclonal Antibody	AAV Gene Therapy (Replacement Gene)
STARTING MATERIAL	Recombinant Master Cell Bank (rMCB)	Variable – process and end use dependent
DRUG SUBSTANCE	↓ Cell Culture Production of mAb ('upstream' USP) ↓ Purification of mAb ('downstream' DSP) ↓ DS (API)	
DRUG PRODUCT		

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***3 major* CMC regulatory compliance issues for a monoclonal antibody manufacturing process**

MCB/WCB → Upstream Process → Downstream Process

----------genetic instability---------

---------- limitations of scaled-down modeling----------

-- risk-based control of the manufacturing process – during clinical development

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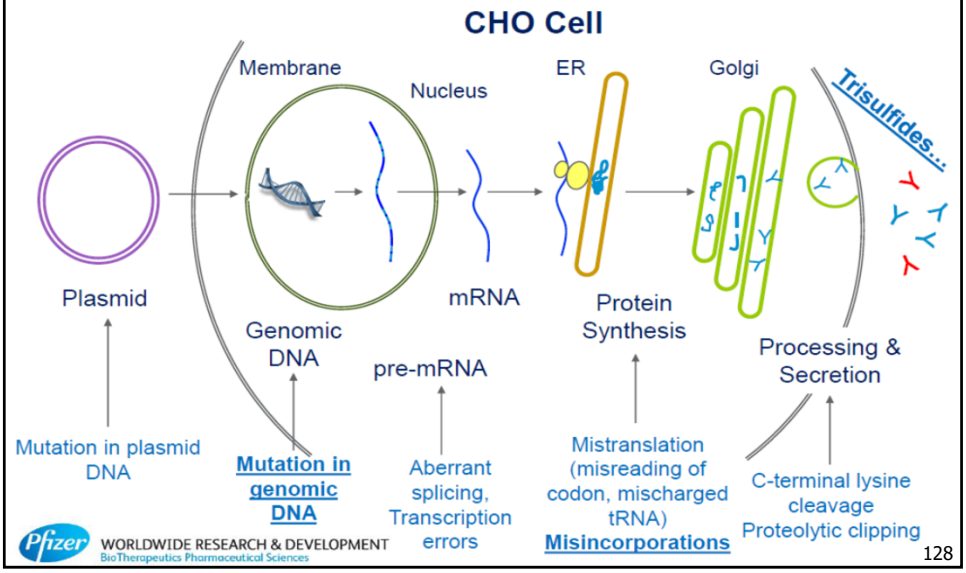
1st major CMC issue: Genetic Instability

A reality that occurs with all living systems – across the entire dogma of molecular biology – DNA → RNA → Protein!



Pfizer WORLDWIDE RESEARCH & DEVELOPMENT
BioTherapeutics Pharmaceutical Sciences

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***Protein Sequence Variants* – a reality with mAbs (and recombinant proteins)!**

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 this industry survey –

Next Generation Sequencing (NGS) of nucleotides + LC-MS/MS of amino acids

Frequency of genetic mutations detected in recombinant transgene: 5-20%

What if protein sequence variants are detected?

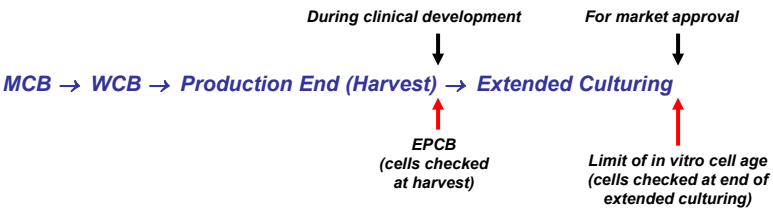
If in new cell line at > 1% protein sequence variants – discard

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

Evaluation of genetic stability a requirement

For clinical development: from MCB → EPCB
For market approval: from MCB → Extended culturing

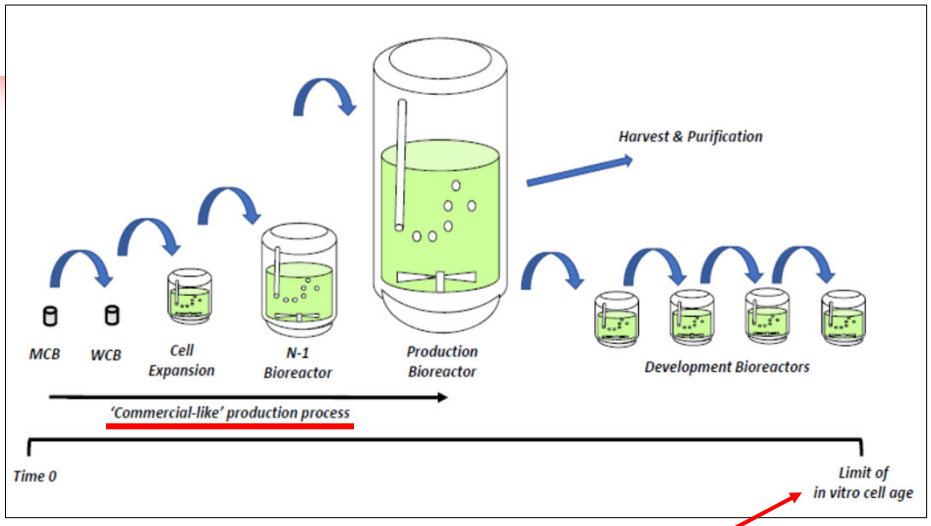
ICH Q5D provides recommendations on genetic stability evaluation



- ***Confirmation of no change of expressed protein amino acid sequence***
- ***Confirmation of no change on genetic DNA nucleic acid sequence***
- ***Confirmation of absence of latent virus induction (insect/mammalian cells)***

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

Traditional & *Expected* approach to genetic stability determination



No regulatory guidance on how long to passage in development

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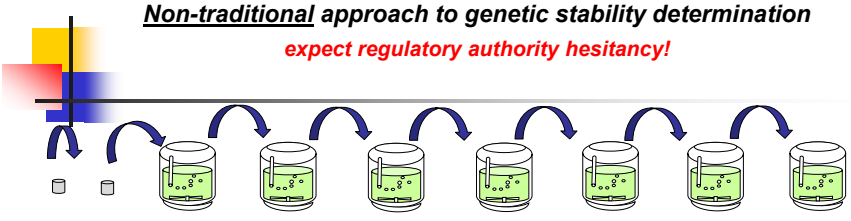
Non-traditional approach to genetic stability determination

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

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Genetic instability is occasionally observed!

Case Example

Copy number loss – productivity impacted, but not product quality!

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

Quality → CQA
Yield → KPP

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Genetic instability is occasionally observed!

Case Example

Chromosomal gene translocation ('jumping genes') – No impact on productivity nor on product quality!

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

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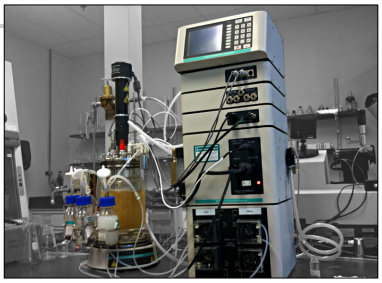
2nd major CMC issue: Limitations of Scaled-Down Modeling

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



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Scaled-down models are absolutely necessary for biologics!

Problems with using some large scale studies

- ***GMP Unacceptable***
  - *ill advised to contaminate a GMP process step in the manufacturing facility (e.g., spiking excess HCPs onto a GMP chromatography column)*
- ***Worker Safety***
  - *large quantities of live viruses would be needed for virus clearance spiking studies onto manufacturing scale columns*
- ***Costly***
  - *expensive at full-scale to run the studies, especially tying up a commercial manufacturing facility*

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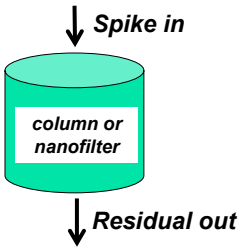
Biologic manufacturing is dependent upon scaled-down models!

UPSTREAM PROCESS

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

DOWNSTREAM PROCESS

- *Purification CPPs (DOE)*
- *Virus clearance evaluation (low pH, chromatography, nanofiltration)*
- *Process-related impurity clearance (host cell DNA and proteins, Protein A leachables)*
- *Molecular variant clearance (oxidation, deamidation, aggregates)*
- *Process hold times*
- *Chromatographic column resin use life*



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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

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Regulatory authorities expect justification of scaled-down studies with regard to the commercial scale manufacturing process!

(to be confirmed from commercial scale data, if possible)

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

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3rd major CMC issue: Risk-Based Control of the Manufacturing Process During Clinical Development

	FDA	***EMA***
Stage 1	***Process Design***	***Process Characterization***
	The goal of this stage is to develop a manufacturing process suitable for routine commercial manufacturing that can consistently deliver a product that meets its quality attributes (clinical development and scale-up activities)	
Stage 2	***Process Qualification***	***Process Verification***
	The goal of this stage is to confirm that the final manufacturing process performs effectively in routine manufacture and is able to produce a product of the desired quality on an appropriate number of consecutive batches produced with the commercial process and scale	
Stage 3	***Continued Process Verification***	***Ongoing Process Verification***
	The goal of this stage is to provide ongoing assurance of the manufacturing process	

Process Validation: General Principles and Practices

January 2011

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

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

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Stage	Manufacturing Process Understanding	Biologic Product Knowledge	Manufacturing Experience
1	**Process Design/ Process Characterization**		
	(a) Process Development Identification of pCMAs, pCPPs (b) Process Evaluation DOE, RRF and small scaled process validation studies pCPPs → CPPs Control Strategy finalized Scale-up/transfer as needed	Identification of pCQAs Preliminary specs Short-term and stressed product stability Thorough product characterization	Initially 1 or 2 manufactured batches Additional manufactured batches to supply ongoing clinical trials, as needed
2	**Process Qualification/ Process Verification**		
	Commercial-like process lock-down PPQ batches	Test methods validated CQAs identified Regulatory specs defined (or interim specs) Long-term product stability establishes shelf life specifications	Numerous (hopefully) manufactured batches to establish statistical-based controls

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Cautionary note about small-scale studies in Stage 1

Level of Quality Unit 'oversight'

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)

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Regulatory authority Stage 2 expectations of biologic process validation to be included in BLA/MAA

CTD Module 3.2.S: Drug Substance

3.2.S.2.4 Controls of Critical Steps
3.2.S.2.5 Process Validation/Evaluation
3.2.S.4 Control of Drug Substance

CTD Module 3.2.P: Drug Product

3.2.P.3.5 Process Validation/Evaluation

FDA sometimes attaches to a pre-BLA submission meeting minutes, a "hot topic" list of frequently encountered deficiencies in biologic process validation

Case Example

Pre-BLA Meeting Minutes Dompe Oxervate (recombinant nerve growth factor) January 2017

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Drug Substance (3.2.S.2.5)

- *Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).*
- *Three successful consecutive product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5). Hold time studies may not be required if closed single-use gamma-irradiated systems with in-line filter are used.*
- *Provide chromatography resin and UF/DF membrane lifetime study protocols and acceptance criteria for bioburden and endotoxin samples to demonstrate adequate microbial control at scale. In addition, provide the bioburden and endotoxin acceptance criteria for resin and membrane storage. Bioburden and endotoxin samples for the storage validation study should be taken at the end of storage prior to sanitization (3.2.S.2.5).*
- *Bioburden and endotoxin data obtained during manufacture of at least three PPQ lots (3.2.S.2.5).*
- *Information and summary results from the shipping validation studies (3.2.S.2.5).*
- *Drug substance bioburden release specifications (3.2.S.4).*
- *Summary report and results from bioburden and endotoxin test method qualification performed for in-process intermediates and the drug substance. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers (3.2.S.4).*

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Drug Product (3.2.P.3.5)

The following study protocols and validation data summaries should be included in Section 3.2.P.3.5:

- *Bacterial filter retention study for the sterilizing filter.*
- *Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three most recent requalification studies and describe the equipment requalification program. For information located in Drug Master Files (DMFs), provide Letters of Authorization which list the relevant depyrogenation and sterilization sites and which clearly identify the location of the relevant information within the DMF.*
- *In-process microbial controls and hold times. Three successful product intermediate hold time validation runs should be performed at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.*
- *Isolator decontamination, if applicable.*
- *Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Describe the environmental and personnel monitoring procedures followed during media fills and compare them to the procedures followed during routine production.*
- *Capping validation demonstrating maintenance of container closure integrity.*
- *Information and summary results from shipping validation studies.*

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Biologic process validation missteps unfortunately occur!

Case Example 1: withdrawal of filed BLA!

BLA submitted Dec 2019 BLA withdrawn Feb 2020 (right before RTF)
Refiled (by end of 2020?)

As previously disclosed, Coherus BioSciences, Inc. (the "Company") licensed U.S. rights from Biocq AG ("Biocq") to Biocq's Lucentis® (ranibizumab) biosimilar candidate. Biocq filed a Biologic Licensing Application ("BLA") with the U.S. Food and Drug Administration ("FDA") in December 2019.

At the request of a national European health authority addressed to Biocq's drug substance contract manufacturer, the manufacturer moved a piece of processing equipment to a different location within the same site after the production of Biocq's Lucentis® (ranibizumab) biosimilar candidate qualification batches was completed.

The FDA has requested additional manufacturing data for the equipment in its new location in the context of its review of the BLA application. The Company believes that it will take approximately four months to generate this additional data to comply with the FDA's request. As a result, Biocq has decided to withdraw its BLA application for its Lucentis® (ranibizumab) biosimilar candidate, provide the requested data and resubmit the application thereafter. The Company anticipates that such withdrawal and resubmission may delay the approval of a BLA for Biocq's Lucentis® (ranibizumab) biosimilar candidate.

COHERUS BIOSCIENCES, INC. FORM 8-K February 3, 2020

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Biologic process validation missteps unfortunately occur!

Case example 2: close call delay in obtaining market approval!

BLA submitted Dec 2011 FDA PAI March 2012

FDA CMC team internal discussion about the Genentech mfg facility for Perjeta

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

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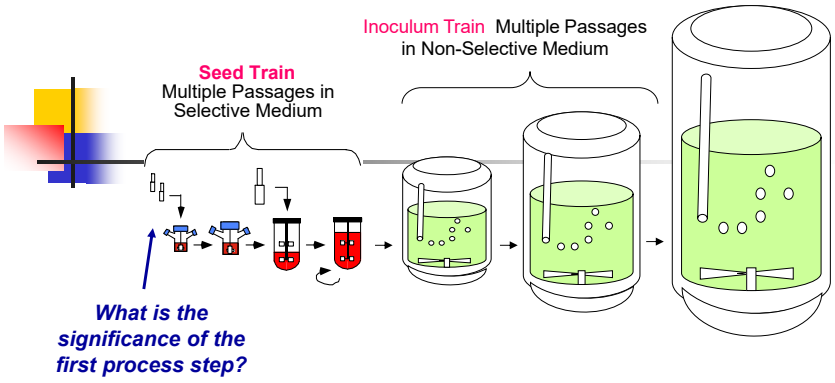

Summary Review for Regulatory Action

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.

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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.

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Biologic process validation missteps unfortunately occur!

Case example 3: 22 month delay in market approval!

BLA submitted Dec 2015 CRL received Aug 2016 (12 of 18 issues were CMC)

FDA meeting minutes with Portola Pharma on CMC issues in Complete Response Letter

We acknowledge that ANDEXXA 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.

BLA approved May 2018

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Manufacturing Process Flow Diagram

	Monoclonal Antibody	AAV Gene Therapy (Replacement Gene)
STARTING MATERIAL	Recombinant Master Cell Bank (rMCB)	Variable – process and end use dependent
DRUG SUBSTANCE	↓ Cell Culture Production of mAb ('upstream' USP) ↓ Purification of mAb ('downstream' DSP) ↓ DS (API)	↓ Cell Culture Production of g.e. virus ('upstream' USP) ↓ Purification of g.e. virus ('downstream' DSP) ↓ DS (API)
DRUG PRODUCT		

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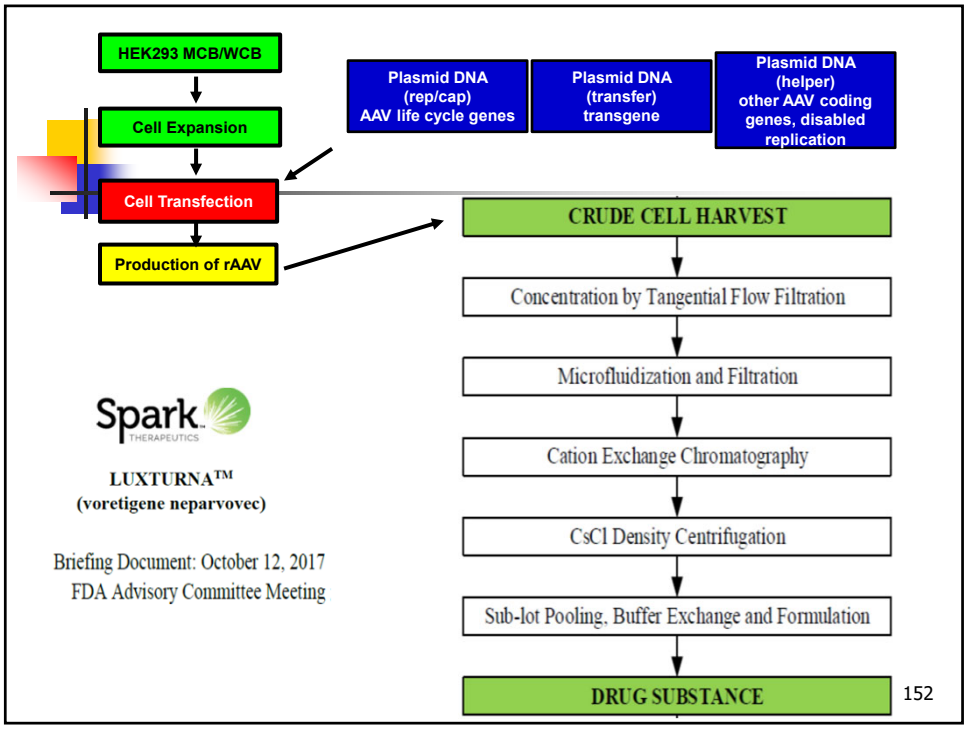

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***Major differences* for virus manufacturing**

extra safety precautions to protect staff from infectious virus

3.17. In addition, there should be appropriate training to prevent the transfer of communicable diseases from biological raw and starting materials to the operators and vice versa. Personnel handling genetically modified organisms ("GMOs") require additional training to prevent cross-contamination risks and potential environmental impacts.

EUROPEAN COMMISSION

Good Manufacturing Practice for Advanced Therapy Medicinal Products

critical importance of emergency plan for accidental spillages

An emergency plan for dealing with accidental release of viable organisms should be in place. This should address methods and procedures for containment, protection of operators, cleaning, decontamination and safe return to use. An assessment of impact on the immediate products and any others in the affected area should also be made.

PIC/S

MANUFACTURE OF ADVANCED THERAPY MEDICINAL PRODUCTS FOR HUMAN USE ANNEX 2A

Lessons learned the hard way (from biopharmaceutical protein processes contaminated with viruses and/or mycoplasma): Accidental release is not the time to call a committee meeting, but needs timely, prospective, well-thought-out action!

PDA TECHNICAL REPORT 83 (2019)

Virus Contamination in Biomanufacturing: Risk Mitigation, Preparedness, and Response

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***Same* 3 major CMC regulatory compliance issues for a g. e. virus manufacturing process**

MCB/WCB + 3 plasmids → ***Upstream Process*** → ***Downstream Process***

----------genetic instability---------

---------- limitations of scaled-down modeling----------

-- risk-based control of the manufacturing process – during clinical development

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***Same* risk-based control of the manufacturing process during clinical development of a g. e. virus**

	FDA	EMA
Stage 1	Process Design	Process Characterization
	The goal of this stage is to design a process suitable for routine commercial manufacturing that can consistently deliver a product that meets its quality attributes	
Stage 2	Process Qualification	Process Verification
	The goal of this stage is to confirm that the final manufacturing process performs effectively in routine manufacture and is able to produce a product of the desired quality on an appropriate number of consecutive batches produced with the commercial process and scale	
Stage 3	Continued Process Verification	Ongoing Process Verification

including process validation deficiencies in submitted BLA/MAA →

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Biologic process validation missteps unfortunately occur!

Case example: close call delay in obtaining market approval of CAR T-cells!

BLA submitted Feb 2017 FDA Mid-Cycle Communication meeting May 2017

FDA meeting minutes with Novartis on Kymriah significant unresolved CMC issues

During the pre-license inspection (PLI) at the Novartis Morris Plains Manufacturing Facility for CTL019, the FDA identified deficiencies in the process validation studies. Specifically, the process performance qualification (PPQ) study was conducted according to the clinical manufacturing process rather than the intended commercial process, and, clinical batch production records were used rather than commercial batch production records. In addition, some methods used in the PPQ study were not the same as those specified in the commercial batch record. Some critical process parameters (CPP) and key process parameters (KPP) were too broad to ensure meaningful process controls. The PPQ study also did not include leukapheresis materials that contain high levels of monocytes, which is one of the intended starting materials. Finally, some hold steps were not defined in the Master Batch Production Record.

Novartis has responded to the 483 letter and proposed to submit additional validation data and revised commercial batch records by June 7, 2017 to address the 483 issues.

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Manufacturing Process Flow Diagram

	Monoclonal Antibody	AAV Gene Therapy (Replacement Gene)
STARTING MATERIAL	Recombinant Master Cell Bank (rMCB)	Variable – process and end use dependent
DRUG SUBSTANCE	↓ Cell Culture Production of mAb ('upstream' USP) ↓ Purification of mAb ('downstream' DSP) ↓ DS (API)	↓ Cell Culture Production of g.e. virus ('upstream' USP) ↓ Purification of g.e. virus ('downstream' DSP) ↓ DS (API)
DRUG PRODUCT	↓ Formulation (excipients added) ↓ Filter Sterilization (0.2 µ x 2 in series) ↓ Aseptic Filling (into container closure) ↓ DP	

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Biologics are formulated with excipients

but needs a justifiable reason for its presence

Function of Excipients

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

For market approval, the excipients present and their assigned level will need to be justified: 3.2.P.2.1.2 and 3.2.P.2.2.1

Common excipients used with mAbs

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

Excipients used with g.e. viruses

- Poloxamer 188
- Sodium chloride
- Sodium phosphate

Excipients used with g.e. cells

- Human serum albumin
- Sodium chloride
- DMSO

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

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Avoid 'novel' excipients unless absolutely required!

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

Afrezza, Inhaled Human Insulin

FDA 2014

Novel Excipient: FDKP

(fumaryl diketopiperazine) – critical to impart correct micron size particles for inhalation

Anything bigger – sticks to back of throat
Anything smaller – exhaled

FDKP – required a 2 year tox study!

Ervebo, Ebole Zaire Vaccine, recombinant, live

EPAR 17 October 2019 EMA/606159/2019

Novel Excipient: recombinant human serum albumin

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

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Formulation changes do occur with biologics (even commercial ones)

but, should be a high value benefit to offset risk of change!

Change due to increased mAb concentration

Roche Rituxan commercial mAb

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

Change from innovator to biosimilar

Enbrel commercial recombinant fusion protein

Amgen (innovator)	***Sandoz*** (biosimilar)	***Samsung*** (biosimilar)
Etanercept	***Etanercept***	***Etanercept***
Sucrose	***Sucrose***	***Sucrose***
Sodium phosphate	***Sodium citrate***	***Sodium phosphate***
Sodium chloride	***Sodium chloride***	***Sodium chloride***
L-arginine	***L-lysine***	~~***L-arginine***~~

But not all biologic formulation changes are successful!

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

Dash of EDTA!

- ***Immunex Leukine (rh GM-CSF) lyophilized originally approved by the FDA in 1991;***
- ***Immunex Leukine liquid – choice between 2 liquid formulations (one with EDTA, dropped) (one without EDTA, which the FDA approved in 1996) [I was VP Q at the time]***
- ***Amgen acquired Immunex (and Leukine) in 2002, then sold off Leukine to company A, which sold it off to company B, which finally sold it off to Bayer***
  - ***How effective is Knowledge Management?***
- ***In 2006, Bayer received FDA approval to add a 'touch' of EDTA to the liquid formulation***
  - ***EDTA, a chelating agent, traps metal impurities and thereby extends the shelf life of protein products such as Leukine***
  - ***Studies showed that Leukine with and without EDTA was comparable***
- ***After 2 years in the marketplace, enough pharmacovigilance data confirmed that the liquid Leukine with added EDTA had a new patient adverse event → January 2008 RECALL***

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- ***Investigation revealed why 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"***
  - ***Fainting due to lack of oxygen to the brain – body's defense system***
- ***Pharmacovigilance, sometimes takes years, to pick up low-frequency adverse events (such as syncope) – not product comparability studies!***
  - ***Explains why formulation changes are considered 'high risk' for biologics***

May 2008, 5 months later, Bayer reintroduces the original liquid Leukine formulation (without EDTA) ***(A+ to Marketing)***

Bayer HealthCare Pharmaceuticals

Back to the Future:
Original Liquid Leukine® Coming Soon

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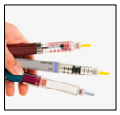
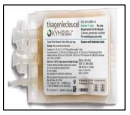
Container Closures for Biologics

heightened concern for interaction at product-contact surfaces

Injection ('Parenteral') – IV, IM, SC

- *Glass vial with rubber stopper (rproteins/mAbs and G. E. viruses)*
- *Pre-filled syringe*
- *Pre-filled plastic patient administration bag (G. E. cells)*

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, chemically synthesized)*

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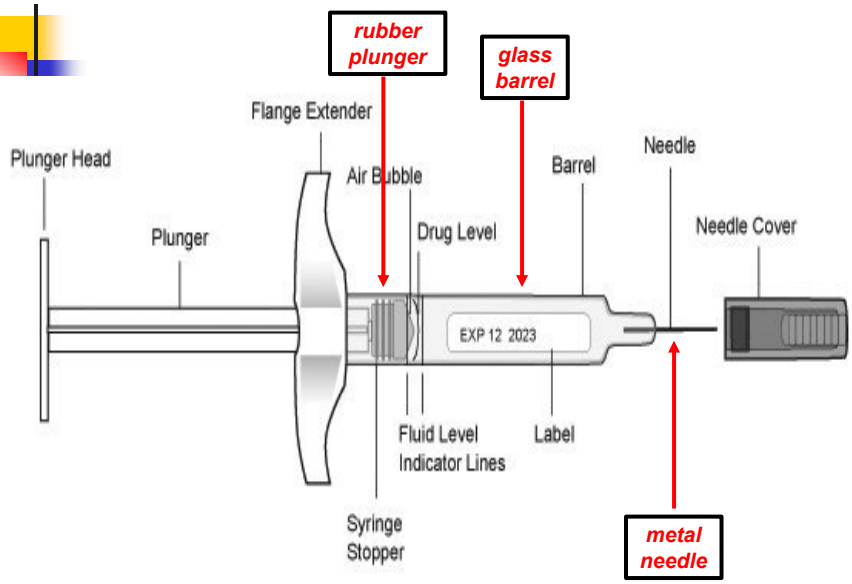
Biologics are not inert to product-contact surfaces of the container closures

(extractables, delamination, particles, silicon oil)



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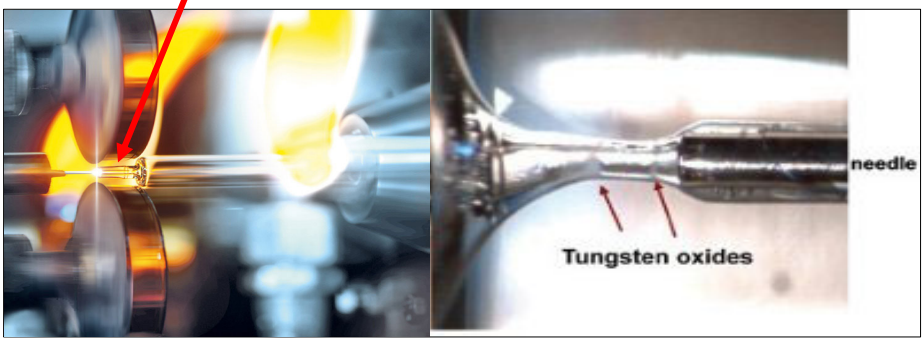
Pre-filled Syringes – discovery of tungsten oxide residuals

Impact of container closure on biologic

During glass syringe manufacture, while the glass barrel is being formed at high temperature (~1200ºC), 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***

165

Glass vials - discovery of glass delamination

Impact of biologic on container closure

Micro-Flow Imaging (MFI)
(counting and photographing each type of particle present)

Discovered glass shards in solution in 2010

Glass lamellae

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

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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*
- *Drug solutions formulated at high pH (alkaline) and with certain buffers (e.g., citrate) are more susceptible*
- *Drugs stored at room temperature have a greater chance of glass lamellae formation than do products stored at colder temperatures*

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Container Closures (other than glass vial-stopper) are DEVICES

device regulations (in addition to biologic regulations) must be met

- *Glass vial/rubber stopper*
- *Pre-filled syringe*
- *Autoinjector*
- *Inhalers*

} *medical devices 'combination products'*

- *FDA – 21 CFR 820 (Quality System Management) - CDRH*
- *EU Regulation – Medical Device Regulations (2017/745)*
- *ISO 10993 Biological evaluation of medical devices*
- *ISO 11608-1 Needle-based injection systems for medical use: Requirements and test methods*
- *ISO 11608-4 Requirements and test methods for electronic and electromechanical pen injectors*
- *ISO 11608-6 Needle-based injection systems for medical use: Requirements and test methods – bolus injectors*

Device functionality: both at time of release and throughout the entire shelf life

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Human engineering studies are most important!

If someone can do something dumb with your device, it will happen!

In an emergency, do you know which end to push into the skin?

Life saving for diabetic hyperglycemia coma

Life saving for anaphylactic shock

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Manufacturing Process Flow Diagram

	Monoclonal Antibody	***AAV Gene Therapy (Replacement Gene)***
STARTING MATERIAL	*Recombinant Master Cell Bank (rMCB)*	*Variable – process and end use dependent*
DRUG SUBSTANCE	*↓ Cell Culture Production of mAb ('upstream' USP) ↓ Purification of mAb ('downstream' DSP) ↓ DS (API)*	*↓ Cell Culture Production of g.e. virus ('upstream' USP) ↓ Purification of g.e. virus ('downstream' DSP) ↓ DS (API)*
DRUG PRODUCT	*↓ Formulation (excipients added) ↓ Filter Sterilization (0.2 µ x 2 in series) ↓ Aseptic Filling (into container closure) ↓ DP*	

? Questions?

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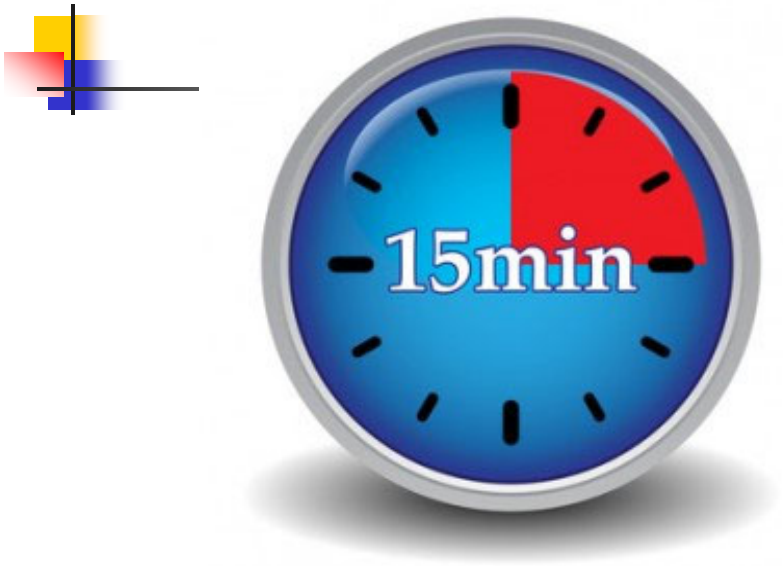

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CMC Regulatory Compliance Strategy For Biopharmaceuticals

Course Outline

4. Demonstrating Comparability After Manufacturing Process Changes

- ✓ ***Three (3) key design elements of an <u>effective</u> risk-managed comparability study***

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Change is inevitable!

There is always something about the biologic manufacturing process that can (or needs to) be changed!

- ***Improvements in the biologic manufacturing process***
  - *Cell line change (e.g., switch to a higher productivity cell line)*
  - *Switch to continuous manufacturing (e.g., perfusion cell culture, chromatographic columns in parallel)*
  - *Manufacturing site change (e.g., scale-up, switch from clinical GMP to commercial cGMP facility)*
- ***Improvements in the biologic product quality***
  - *Improved chromatography to reduce residual impurities*
  - *Exchange to more sensitive QC analytical techniques (e.g., SDS-PAGE → CE-SDS; IEF → cIEF)*

But every change carries a risk!

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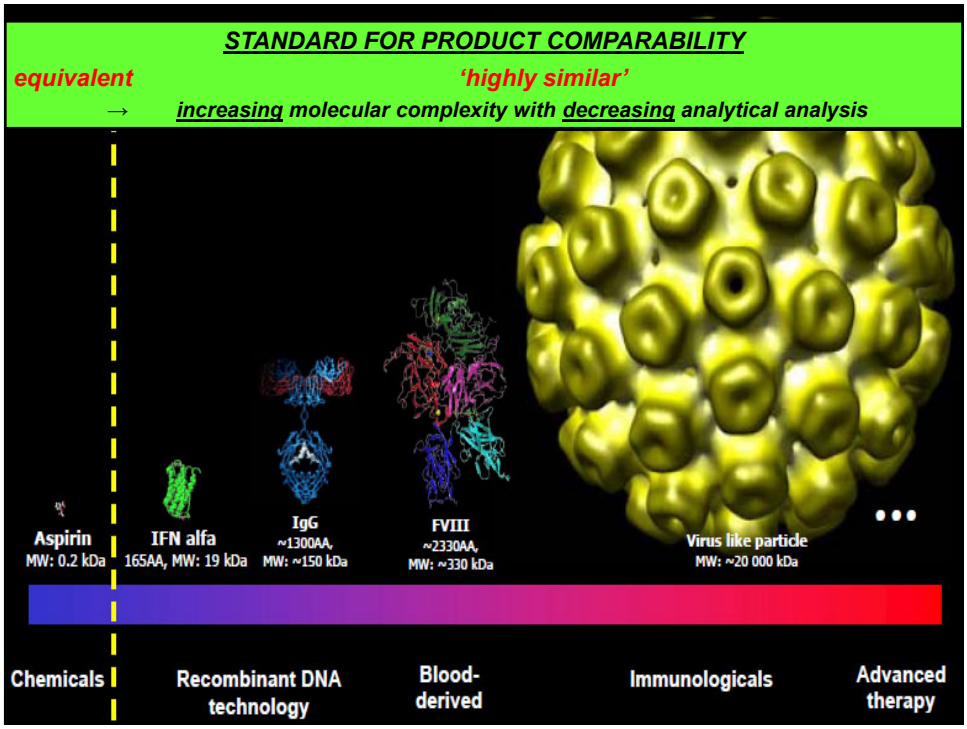
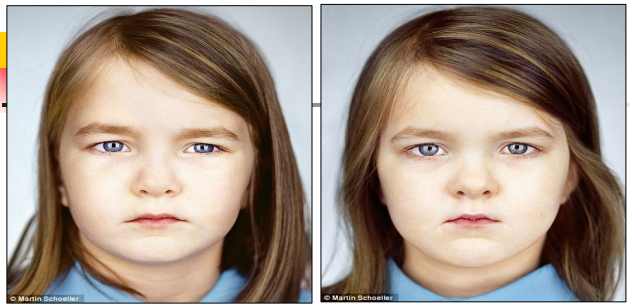


Same standard for all biologics: "highly similar" (ICH Q5E)



'not identical'

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

Note: is subjective

- ***Applies to innovator recombinant protein and mAb manufacturing***
- ***Applies to biosimilar recombinant protein and mAb manufacturing***

- ***Applies to recombinant virus manufacturing***
- ***Particularly challenging for cell-based manufacturing***

Questions and answers
Comparability considerations for Advanced Therapy Medicinal Products

6 December 2019
EMA/CAT/499821/2019

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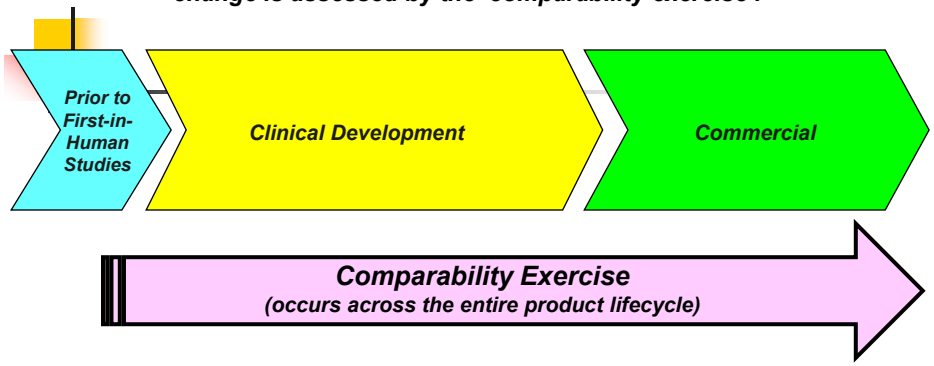
Risk involved to a biologic due to a manufacturing process change is assessed by the 'comparability exercise'!



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

ICH Q5E

Bottom-Line: Is the benefit of the change worth the risk?

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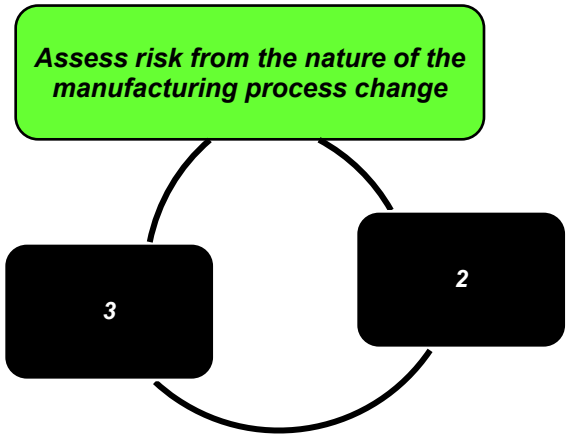
3 key design elements of an effective risk-managed comparability exercise



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Each manufacturing process change carries a different risk to the product!

- *The nature of each manufacturing process change carries its own level of potential risk for the biologic*
- *Increasing levels of potential risk require increasing amounts and types of test data to support biologic comparability after the change*
- *Increasing levels of potential risk also require increasing oversight and/or pre-approval by the regulatory authorities*

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The higher the potential risk level to the biologic, the greater the amount/types of data required to confirm comparability after the process change!

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Regulatory authority 'help' in evaluating potential risk of manufacturing process change <u>during clinical development</u>

Risk Level	*Examples of Biologic Process Changes*
Significant ***(FDA CMC Amendment)***	– ***Any process change that impacts the impurity profile, microbial contamination, viral safety, or TSE***
	– ***Change in source material (e.g., new MCB)***
	– ***Addition or removal of a purification step***
Substantial ***(EU NCA prior-approval)***	– ***Change in formulation and/or container closure system***
	– ***Changes that require changes to product specifications (e.g., widening of an acceptance criteria, changing of test method for analysis)***
Not Significant ***(FDA AR)*** ***Non-substantial*** ***(EU NCA not reported)***	– ***Anything that is not significant or non-substantial***

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

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

September 2018
EMA/CHMP/BWP/534898/2008

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*Regulatory authority 'help' in evaluating potential risk of manufacturing process change **after 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

Lots of published guidance for chemical drugs – limited guidance for biologics
(need to read the scope)

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EMA Recommendations – after market approval

APPLICATION FOR VARIATION TO A MARKETING AUTHORISATION

B.I.a.3 Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance		Procedure type	
☐ a)	Up to 10-fold increase compared to the originally approved batch size	☐IA	☐IB*
☐ b)	Downscaling down to 10-fold	☐IA	☐IB*
☐ c)	The change requires assessment of the comparability of a biological/immunological active substance		II

Consistent with FDA PAS for biologics

Scale-up requiring a larger fermentor, bioreactor, and/or purification equipment (applies to production up to the final purified bulk). ***no '10X' allowance***

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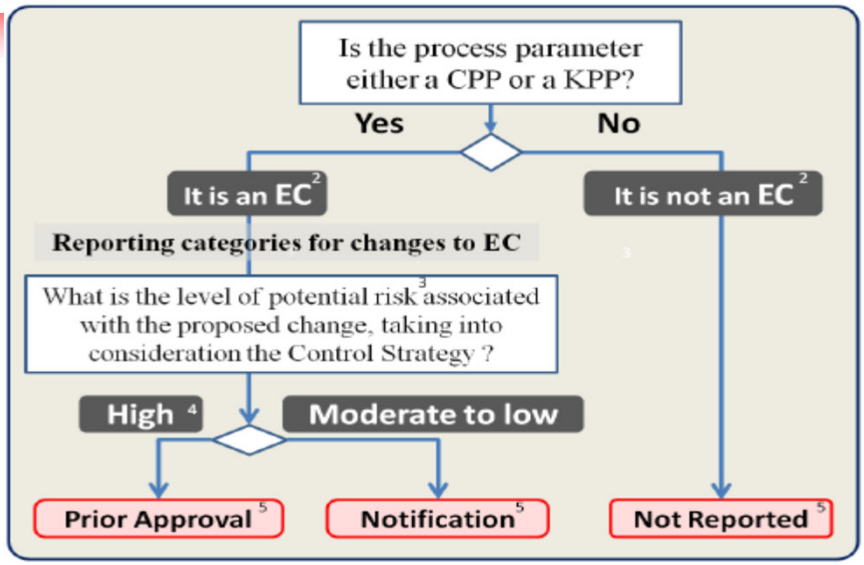
ICH harmonisation for better health

TECHNICAL AND REGULATORY CONSIDERATIONS FOR PHARMACEUTICAL PRODUCT LIFECYCLE MANAGEMENT **Q12**

20 November 2019

EC – Established Condition



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ICH guideline Q12 Annexes

Unit operation	Input/Output		Acceptable ranges and reporting categories (White boxes are ECs and grey ones are not-ECs.) Parameter Based Approach	Enhanced Approach	Performance Based Approach	Comments
Low pH	Input	Operating temperature	18°C – 23°C CPP **(PA)**	15°C – 25°C CPP **(PA)**	15°C – 25°C CPP **(PA)**	Performance based approach is not applicable due to intrinsic viral safety risk (i.e., meaningful output cannot be tested); Such situation should follow parameter based or enhanced approach.
		pH	2.0 – 4.0 CPP **(PA)**	2.0 – 4.0 CPP **(PA)**	2.0 – 4.0 CPP **(PA)**	
		Incubation time	120 -240 min CPP **(PA)**	120 -360 min CPP **(PA)**	120 -360 min CPP **(PA)**	
Anion-Exchange Chromatography	Input	Feedstock Conductivity	6.0 – 8.0 mS/cm CPP **(PA)**	6.0 – 8.0 mS/cm CPP **(PA)**	6.0 – 8.0 mS/cm PP	**Enhanced Approach:** - Scale down studies demonstrate that feedstocks conductivity, pH, resin age and input XX can impact CQA and are considered CPP. - Ongoing validation protocol includes time points beyond the claim of 100 cycles up to 3 years for the resin age. A downgraded reporting (NL) is proposed to extend the maximum number of cycle / lifetime in accordance to validation protocol.
		Feedstock pH	4.8 – 5.2 CPP **(PA)**	4.5-5.5 CPP **(PA)**	4.0-6.0 PP	
		Resin age	≤ 20 cycles, ≤ 3 yrs CPP **(PA)**	≤ 100 cycles, ≤ 3 yrs CPP **(NL)**	≤ 100 cycles, ≤ 3 yrs PP	
		Input XX	### CPP **(PA)**	### CPP **(PA)**	XX PP	
	output	Bioburden	≤ 10 CFU/10 mL IPC **(PA)**	≤ 10 CFU/10 mL IPC **(PA)**	≤ 10 CFU/10 mL IPC **(PA)**	**Performance Based Approach:** In addition to parameter based: - Outputs of this step were linked to subsequent steps - Inline tests are used to control outputs in a real time manner - Inputs are adjusted realtime based on a model accounting for the inline measurements of outputs.
		Endotoxin	≤ 5 EU/mL IPC **(NM)**	≤ 5 EU/mL Monitored	≤ 5 EU/mL Monitored	
		HCP (CQA)	*Tested in DS specification*	*Predicted through process model*	≤ 100 ppm IPC inline UPLC UV/MS **(PA)**	
		CQA XXX	*Tested in DS specification*	*Predicted through process model*	Inline IPC **(PA)**	

Biologic companies aggressively make changes during the early clinical stages

Case example

Vimizim elosulfase alfa BioMarin

20 February 2014
EMA/357933/2014

Manufacturing process development

The active substance is manufactured using a standard fermentation and purification process. A number of changes were made during product development, which can be grouped in four categories:

- Cell culture: the cell culture process was scaled up prior to Phase 3, and adapted to the planned commercial process. A WCB was introduced.

- Purification: modifications were made to the purification process, including optimisation of chromatography steps, increasing the diameters of the chromatography columns, and optimisation of storage conditions for 3 mg/mL BDS.

Formulation: the formulation was optimised after Phase 1/2 to enhance product stability.

Facility: the process was moved to the commercial facility during Phase 3 manufacture.

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Get the assigned risk level wrong after commercial market approval – incur the wrath of the FDA!

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

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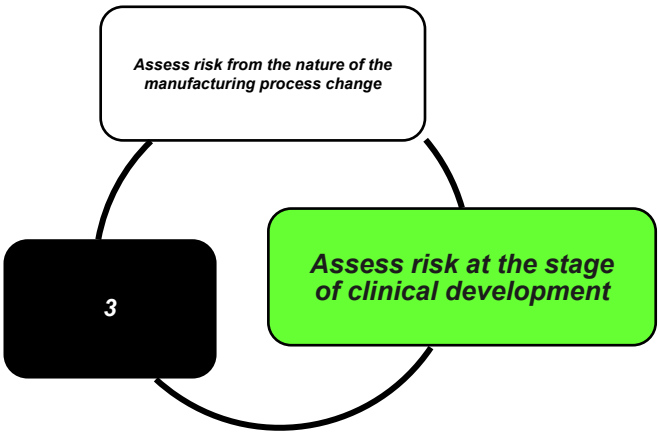
3 key design elements of an effective risk-managed comparability exercise



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Each clinical development stage carries a different level of risk for a manufacturing process change

- *The greater the potential impact of a manufacturing process change on the biologic's efficacy or safety, the higher the level of risk to the patient*
- *Early stage clinical studies – lower risk level – studies primarily for patient safety assessment and trying to assess which target might have the best medical benefit for the product*
- *Late stage clinical studies – higher risk level – studies to gather pivotal efficacy data which must meet predefined statistical thresholds; the threshold must not be impacted by a manufacturing process change*

ICH Q5E

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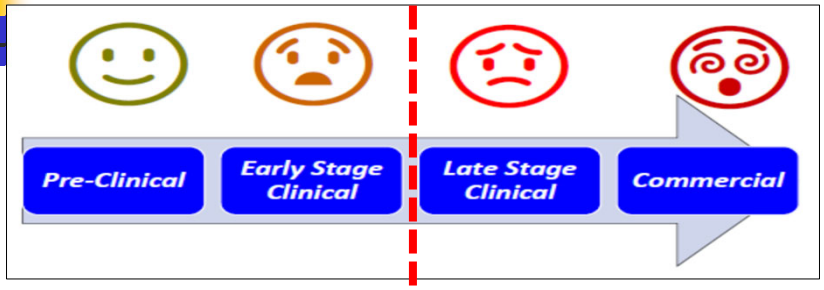
As the risk increases on potentially impacting efficacy, so does the concern of the regulatory authority!



gathering efficacy data to meet pre-defined criteria

established efficacy and adverse event product profile

Comparability Exercise Standard

'not as extensive' 'adequate' → ***'comprehensive and thorough'***

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Case Example: FDA's concern for manufacturing process changes immediately before the pivotal clinical study

Novartis at an EOP2 meeting sought FDA advice on changing the MCB and manufacturing sites for one of their mAbs

Suitability of bridging data package between Selexys and Novartis materials

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

Does the Agency agree with this approach?

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FDA Response to Question 7:

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

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

MEMORANDUM OF MEETING MINUTES

ADAKVEO® (crizanlizumab-tmca)

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

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

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For advanced therapies, manufacturing process changes earlier than later in clinical development

Due to speed of clinical development and due to the limited analytical and functional characterization tools currently available for advanced therapy products today

At early stages of development, characterisation and analytical tools to support future needs for comparability demonstration should be explored and gathered as early as possible. At this stage, batches are manufactured often at laboratory scale. In this scenario, changes are frequent and can be quite extensive and, as such, comparability is not expected. What is required is to present relevant analytical data that can support data filiation, i.e. to demonstrate representativeness of the non-clinical safety profile of the batches studied to those to be used in the exploratory clinical trials.

In later stages of development, when more product knowledge is gained, the manufacturing process evolves and pivotal clinical studies take place, a full comparability exercise is required, encompassing a series of in-process tests and parameters, release tests as well as extended characterisation assays.

The introduction of substantial changes to the manufacturing process and the final product during pivotal clinical studies are not recommended due the complexity of the comparability exercise and the possible impact of its results on the acceptability of the clinical data. In cases where late stage changes in the manufacturing process are unavoidable, it is recommended to seek for EMA scientific advice.

Questions and answers
Comparability considerations for Advanced Therapy Medicinal Products (ATMP)

6 December 2019
EMA/CAT/499821/2019

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CASE EXAMPLE for CAR T-cells on how much manufacturing process change may be necessary to move from academic to industry manufacturing process!

The NCI's Legacy Process vs. Kite's Commercial Process

Old NCI Process		Serum Free Process
	Apheresis product	
	Enrich for lymphocytes	
• Manual Ficoll Separation of PMBC		• Ficoll Separation of PBMC by Sepax 2 (closed process)
• Stim in T175 Flask (open) • AIM V+ 5% Hu serum supplemented with anti-CD3 Ab and rIL2 • Wash cells after Stim (open)	**Days 0-2** **T Cell Activation** **Days 0-2**	• Stim in Culture bags (closed) • Serum-free medium with anti-CD3 Ab and rIL-2 • Wash cells after Stim (Sepax 2, closed process)
• Transduction in 6-well plates by Spinoculation (open process)	**Days 2-3** **Retroviral Transduction** **Days 2-3**	• Transduction in Culture bags (closed process)
• Expansion in T-175 flasks (open process) • **7 day** expansion	**Days 3-10** **T Cell Expansion** **Days 3-6**	• Expansion in bags (closed process) without antibiotics • **3 day** expansion
• Cell concentration and wash (open process)	**Harvest**	• Cell concentration and wash (closed process)
Administer fresh cells		**Cryopreserve product**

Sadik H. Kassim, Ph.D.

From Academia to Industry: Lessons Learned in the Development of CAR-T Therapies

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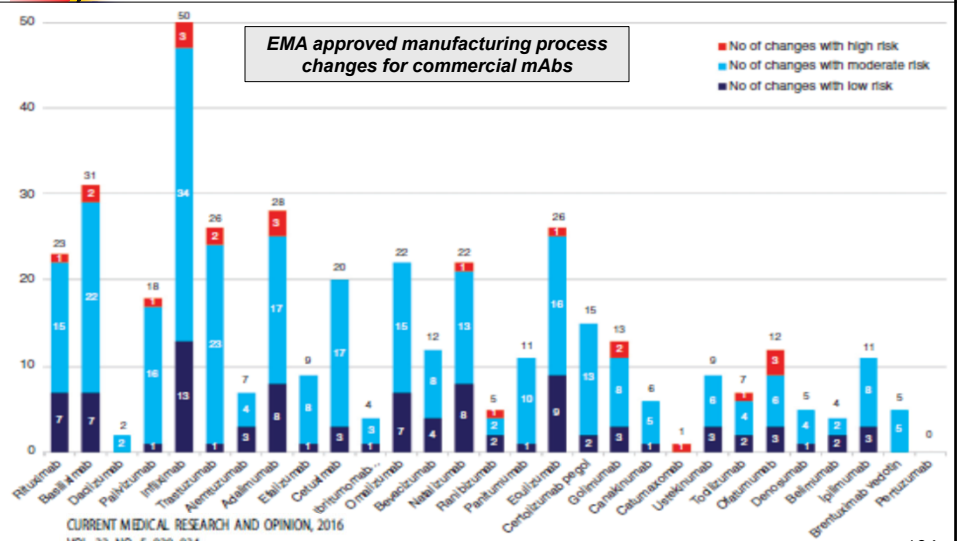
The regulatory encouragement is to introduce manufacturing process changes earlier into the clinical development process

But that doesn't mean that one cannot successfully manage changes even after commercial approval! It's just a higher potential risk!



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

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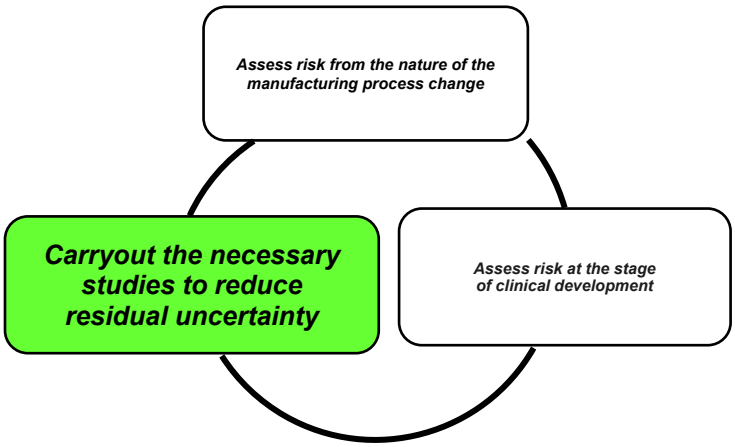
3 key design elements of an effective risk-managed comparability exercise



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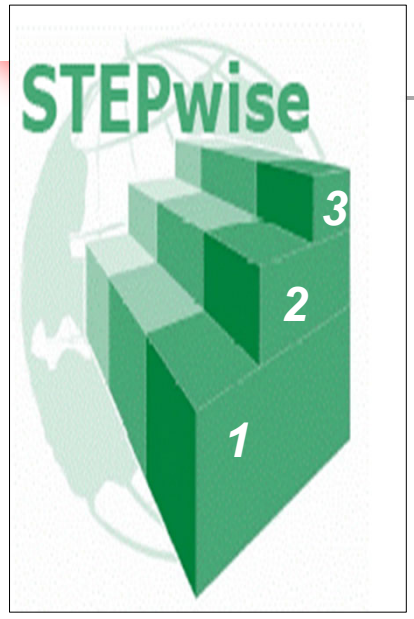
Approach the comparability study exercise in a series of distinct steps



Step 3 (If residual uncertainty still remains)
human clinical studies

Step 2 (if residual uncertainty remains)
animal nonclinical studies

Step 1 – analytical/functional studies

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Step 1 — Analytical/Functional Studies

ICH Q5E

Composed of 4 studies

1) ***Consistency batches (spec comparison before and after change)***
2) ***Relevant, comprehensive physicochemical, biological and functional assay characterization (head-to-head testing preferred)****
3) ***Accelerated and Stress stability slope comparison (differences in rate of molecular variant formation)****
4) ***Historical data analysis ("drift" in CQAs)***

*** Predefined acceptance criteria for defining 'highly similar'***

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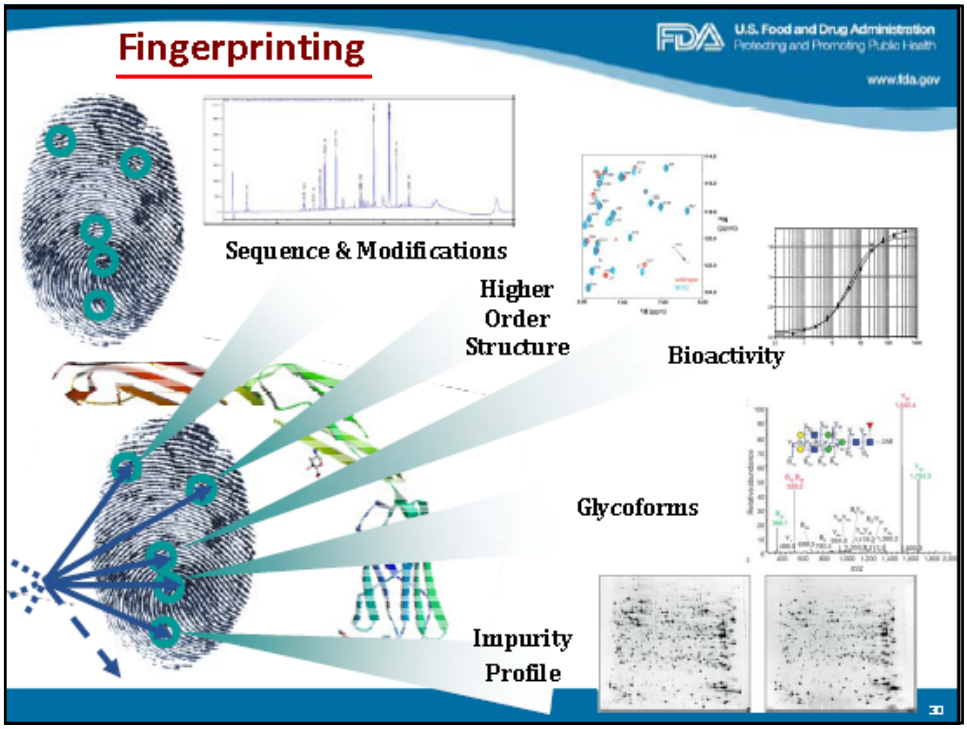


Recognize the limitations of '<u>characterization</u>' in the comparability studies during clinical development

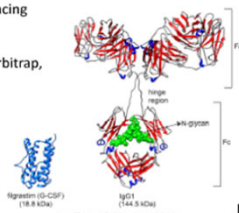
availability of test methods (suitable not required to be validated), meaningfulness of test results (preliminary wide specs)

<u>Mature</u> testing tool box for recombinant protein & mAb products

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

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

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



Japelj et al Sci Reports 2016

Charge
cIEF
icIEF
ICE
IEX- HPLC
CZE

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

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

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

Safety
Bioburden
Sterility
Endotoxin
LAL
KT

<u>Under development</u> testing tool box for advanced therapies

Sequencing of nucleic acid
Analytical ultracentrifugation (AUC)
Fluorescent Microscopy
qPCR (DNA residuals)
Flow cytometry
Bioassay
ELISA

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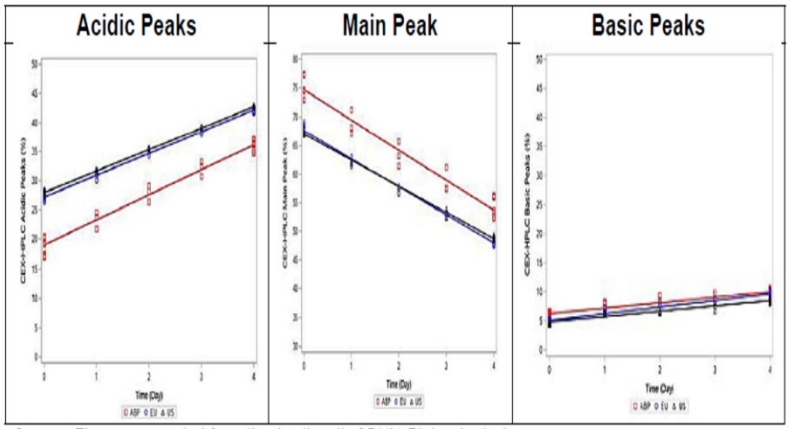
Stress stability slope comparison (<u>differences in rate</u> of molecular variant formation)

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

13 July 2017 Oncologic Drugs Advisory Committee Meeting Briefing Document
ABP 215, a proposed biosimilar to Avastin® **Amgen Inc**

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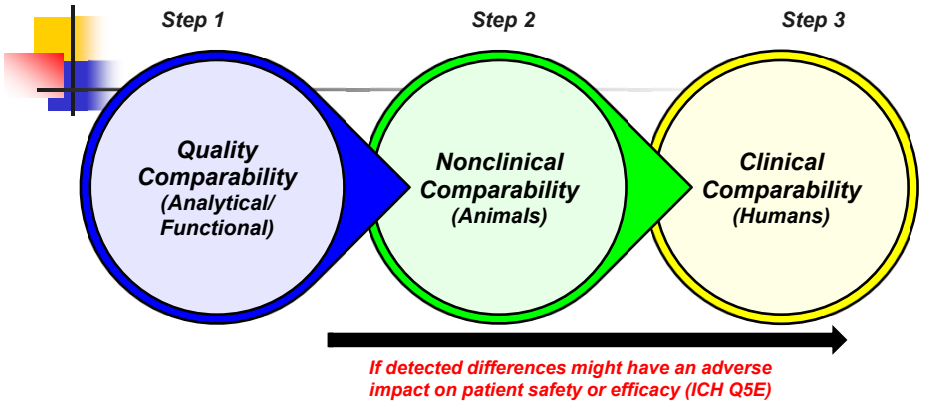
Stepwise Reduction of Residual Uncertainty



Innovator Biologic Advanced Therapy	***Optional**, only if necessary to reduce residual uncertainty*
Biosimilar	***Mandatory** (does not have in-depth CMC knowledge of innovator's manufacturing process)*

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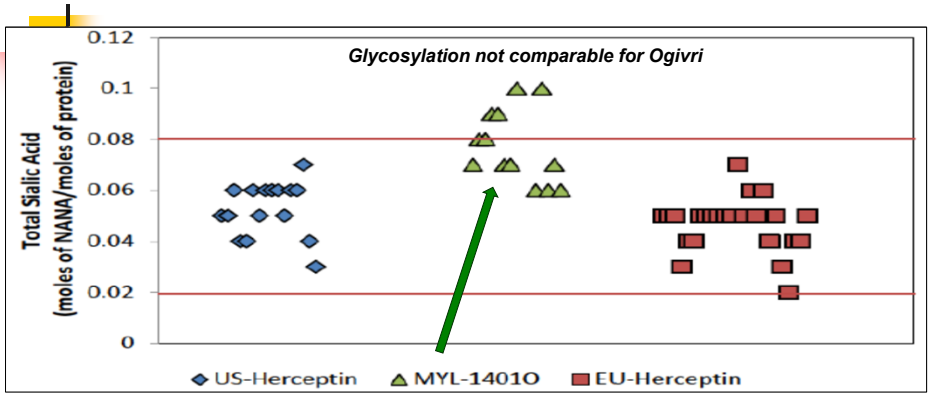
Biosimilar mAb Case Example: Step 1 → Step 3

residual uncertainly about glycosylation differences addressed by 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

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Case Example: EMA major concern over limited Step 1 comparability

Initial: "mAb used for clinical trials not comparabie to commercial mAb"

Final: comparable after comprehensive Step 1 study provided

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.

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.

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

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Case Example: EMA major concern over limited Step 1 comparability

Initial: "G.E. cells used for clinical trials not comparabie to commercial G.E. cells"

Final: Because this was PRIME, comparable after tightening potency spec

Changes made to the manufacturing process at the commercial manufacturing site were supported by data that demonstrate that consistent potency can be obtained. Comparability between the refined manufacturing process and the commercial manufacturing process was not sufficiently addressed. In response to questions, the Applicant indicates that the change was aimed to target VCNs to retain product efficacy while reducing theoretical risk of oncogenesis. The available data were, however, initially too limited to conclude on comparable product efficacy as it was insufficiently demonstrated that clinical data from base manufacturing process batches, can be considered representative of the commercial process. Tight control of potency attributes (i.e. within the range of refined process batches) was therefore considered necessary but was not provided by the proposed specifications. This issue was raised as a Major Objection because sub-potent batches are a considerable risk to the patient in case of sub-optimal efficacy because, based on the SmPC, the treatment cannot be repeated. In response, the Applicant agreed to revise the acceptance limits or provided further justification to maintain the proposed criteria for potency attributes. The Applicant provided a commitment to re-evaluate the acceptance criteria for potency attributes when batch release data from an additional 20 commercial FP batches are available.

Zynteglo (autologous CD34+ cells encoding $\beta^{A\text{-}T87Q}$-globin gene)

26 April 2019
EMA/CHMP/226273/2019

Bluebird Bio

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Case Example: FDA major concern over comparability

"G.E. cells used for clinical trials not comparabie to commercial G.E. cells"

G.E. cells commercial actually better than clinical!

Novartis significantly modified the manufacturing process for CD19 CAR-positive T cells developed by the University of Pennsylvania. The most significant changes were designed to improve the manufacturing process controls for product consistency and yield. These changes have been designed to reduce non-T cells that negatively affect manufacturing ability, maximize the yield, and improve the quality of the final cell product.

A site-to-site comparability study was conducted at the Novartis and University of Pennsylvania facilities, and demonstrated that CD19 CAR-positive T cells manufactured by both facilities met all lot release specifications. However, the characterization of cell growth and transduction efficiency showed statistically significant differences. Thus, the products produced by the University of Pennsylvania and Novartis are not considered to be comparable.

Significantly, the modified manufacturing process at the Novartis Manufacturing Facility at Morris Plains is able to produce a more pure intermediate T cell population before the transduction steps. This important change is expected to improve the vector transduction efficiency and cell growth. Furthermore, from safety standpoint, this change is expected to reduce the chance of transduction of non-T cells (e.g., B cell blast, residual levels of stem cells) that would pose a potential risk for the patients.

FDA **Summary Basis for Regulatory Action** August 30, 2017 **Kymriah**

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Summary of 3 Key Design Elements

of an effective risk-managed comparability exercise'

Quick Quiz

Assess risk from the n_____ of the manufacturing process change

Carryout the necessary studies to reduce r_____ u_____

Assess risk at the s_____ of clinical development

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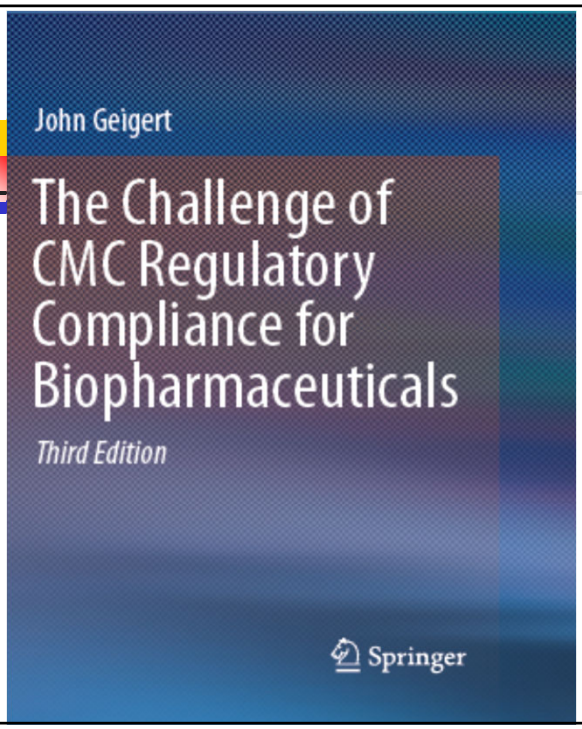
Demonstrating biologic 'highly similar' after a manufacturing process change

Exercise caution, be conservative and objective in your conclusions

Helps to get a honest second unbiased opinion (e.g., independent, experienced consultant)

? Questions?



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