CMC Regulatory Compliance Strategy For Biopharmaceuticals

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

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

- *40+ years experience in Chemistry, Manufacturing & Control (CMC) strategies for the clinical development and commercialization of biopharmaceuticals (recombinant proteins, monoclonal antibodies, and now gene therapies)*
  (Betaseron, Proleukin, Leukine, Enbrel, Rituxan, Zevalin)
- *Senior CMC Expert and Vice President Quality in the industry*
  (Cetus, Immunex, IDEC Pharmaceuticals)
- *Past Chair PDA Biopharmaceutical Advisory Board*
- *15+ years as an independent CMC regulatory compliance consultant to the biopharmaceutical industry*

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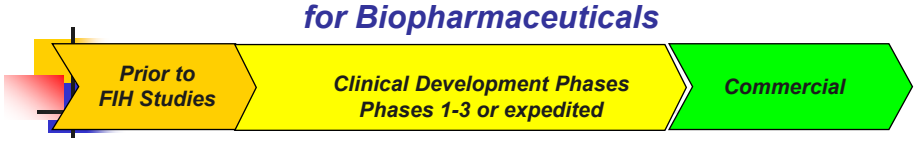
CMC Regulatory Compliance Strategy for Biopharmaceuticals



Course Overall Outline

1. **CMC Regulatory Compliance is Challenging for Biopharmaceuticals**
   Discussion of the increasing diversity of biologics, and the regulatory authority systems (FDA/EMA) in place to control these evolving manufacturing processes and products
2. **Risk-Managed CMC Regulatory Compliance Strategy**
   3 interactive components to protect patients; what the 'minimum CMC regulatory compliance continuum' means for biopharmaceuticals
3. **Applied Risk-Managed CMC Regulatory Compliance Strategy**
   CMC strategy applied across the manufacturing process from starting materials → production → purification → formulation → drug product → administered drug product
4. **Demonstrating Comparability After Manufacturing Process Changes**
   3 key design elements of an effective risk-managed comparability exercise

(Continuous presentation over the 6 hours of instruction) *(Please ask your questions)* 3

CMC Regulatory Compliance Strategy for Biopharmaceuticals

Course Outline

1. **CMC Regulatory Compliance is Challenging for Biopharmaceuticals**
   - *Discussion of the increasing diversity of biopharmaceuticals*
   - *Introduction to the regulatory authority systems in place (FDA/EMA) to regulate these evolving manufacturing processes and products*

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EMA's definition of a 'biological' is straightforward

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Definition of biological medicinal product

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

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

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

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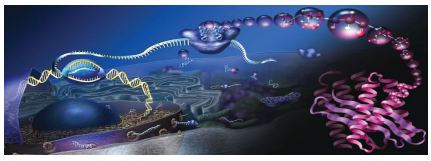
Biological Medicines

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

Before mid-1980's
- *Immune serums (antitoxins)*
- *Vaccines*
- *Human plasma-derived proteins*
- *Natural protein hormones*

+

After mid-1980's



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

'biopharmaceuticals'

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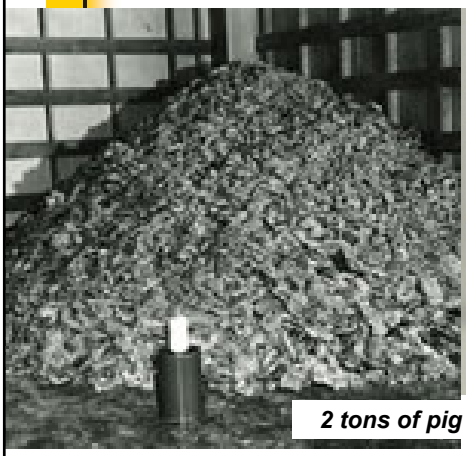
Impact of the new genetic engineering approach

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



2 tons of pig pancreases → ~200 g pig insulin

Since 1982, replaced by recombinant human insulin

50L bioreactor → > 200 g human insulin!
bacteria/yeast

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'Biopharmaceutical' (initial definition)

but … caution …

Company Websites/Press

(unfortunately, no consensus definition today)

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

FDA/EMA Guidances

(do not use the term 'biopharmaceutical')

biotechnology-derived, recombinant DNA-derived

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

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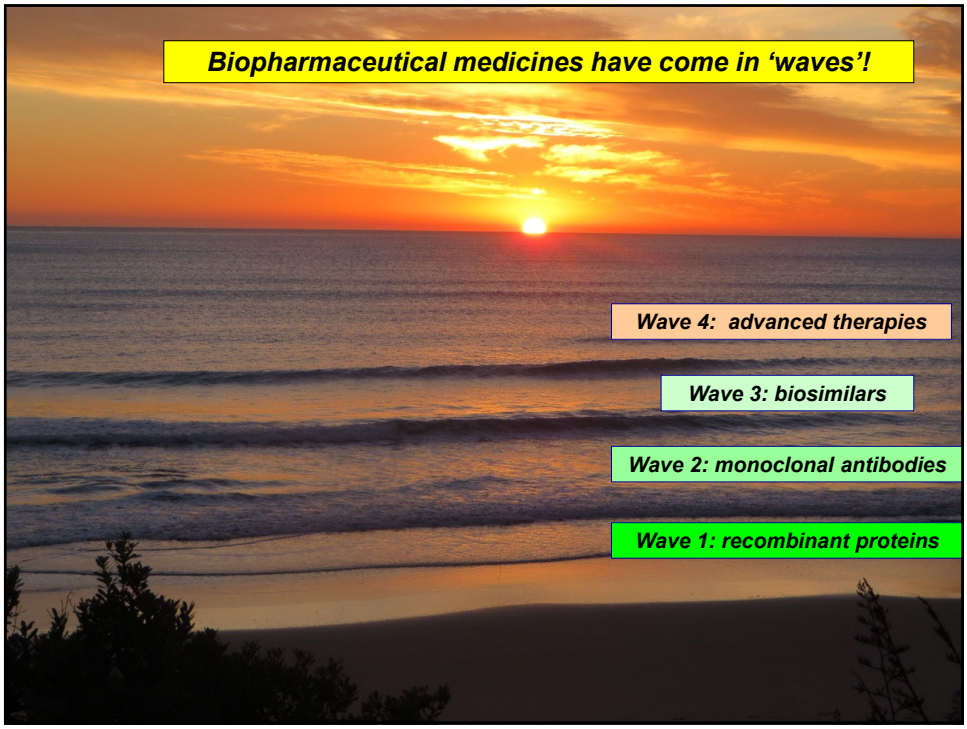
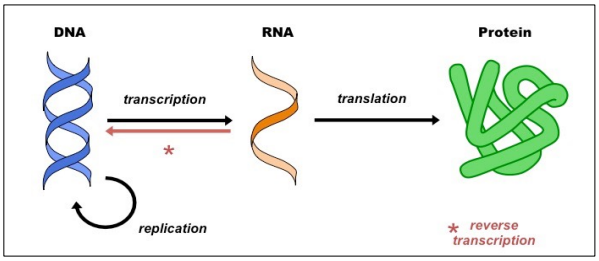


Biopharmaceutical waves 1, 2, 3

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

Production in a Bioreactor – recombinant protein/mAb

Central Dogma of Molecular Biology



Harvest, purify, formulate, fill

Administration of recombinant protein/mAb to patients to treat the medical problem/disease

(e.g., human insulin, Factor VIII, mAbs for cancer therapy)

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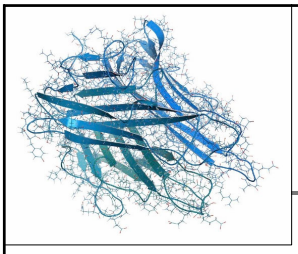

WAVE 1
Recombinant Proteins

1982 1st recombinant protein

Global human insulin market: > $30 billion annually

TODAY

100+ recombinant protein medicines market approved by FDA/EMA

Recombinant proteins have made major inroads into vaccine antigens and human plasma-derived proteins

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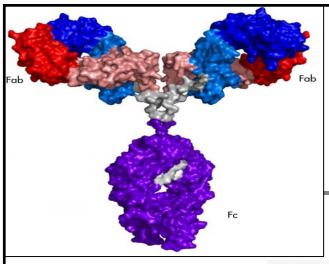

WAVE 2
Monoclonal Antibodies

recombinant immunoglobulin protein – specific single binding site

1986 1st mAb (murine)

1997 1st commercially successful monoclonal antibody (chimeric)

TODAY

100+ monoclonal antibody medicines market approved by FDA/EMA

Humira (adalimumab) best selling medicine in the world: > $20 billion annually

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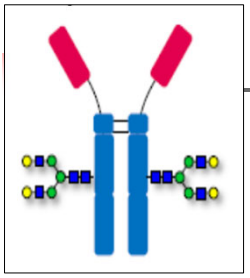
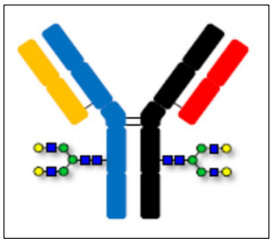
WAVE 2 ripples

Re-engineered Antibodies



Bispecific Antibody

Blincyto	CD19	CD3
Hemlibra	Factor IX	Factor Xa

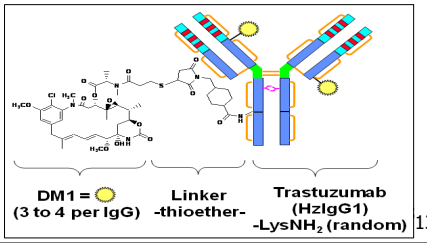


Fc-Fusion Protein

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

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

approved in Europe since 2006; approved in USA since 2015

INNOVATOR Manufacturer → **commercial biopharmaceutical** (rprotein or mAb)

Must prove STATISTICAL safety & efficacy

'medical benefit'

blocked until innovator's marketing exclusivity and patent coverage ends

BIOSIMILAR Manufacturer → **commercial biosimilar** (rprotein or mAb)

Must prove COMPARATIVE safety & efficacy

'no clinically meaningful differences'

55+ biosimilars market approved by FDA/EMA

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Biosimilars are NOT Bio-Generics

Chemical Drug	Biopharmaceutical
Generic Chemical Drug	**Biosimilar**
CMC standard is EQUIVALENT	CMC standard is HIGHLY SIMILAR
Exact structure between 3 batch generic and innovator chemical drug + ~~Non-Clinical~~ + Clincial bioequivalence (~30 volunteers, AUC)	Extensive CMC comparability between biosimilar and innovator biopharmaceutical + Non-Clinical comparability + Clincial comparability (multiyear clinical study)
automatically interchangeable (at pharmacy, by insurance)	must be FDA approved as interchangeable

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WAVE 4 Advanced Therapy

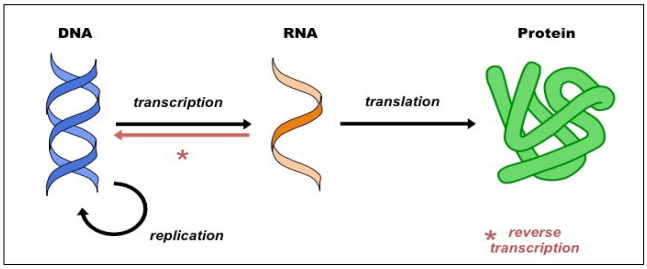
Living, Genetically Modified Viruses/Cells

Gene inserted into a living human to fix a defective genetic capability or add a new genetic capability

In vivo – gene transfer directly into human patient
Ex vivo – gene transfer into human cells, then into patient

The patient produces the desired gene product (protein), in situ to fix a faulty human gene(s) or add a new gene(s)

Central Dogma of Molecular Biology



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Genetically Engineered Living Viruses (in vivo gene replacement)

Spinal Muscular Atrophy (SMA)

SMA is an autosomal recessive, early childhood neuromuscular disease with an incidence of approximately 1: 10,000 live births, of which approximately 45-60% of cases are SMA Type 1. SMA patients lack the *SMN1* gene which leads to progressive loss of motor neurons and causes muscle weakness and death due to respiratory failure. Disease severity is negatively correlated with the amount of *SMN2* copies, with the majority of patients with type 1 having 2 copies. Of the patients with 3 copies of *SMN2*, based on natural history approximately 15% is expected to develop type 1 (will never be able to sit independently), 55% is expected to develop type 2 (will never be able to walk) and approximately 30% is expected to develop type 3a.

Genetically engineered AAV IV injection

NOVARTIS ZOLGENSMA **March 15, 2021** *SMN1 protein expression in situ*

Long-term follow-up data from two studies continued to demonstrate that children treated with Zolgensma experienced a sustained benefit from gene therapy in the years following dosing, with no evidence of new or delayed safety signals. Zolgensma led to achievement of new milestones years after treatment – including sitting – with sustained durability in children now up to six years old and more than five years post-treatment.

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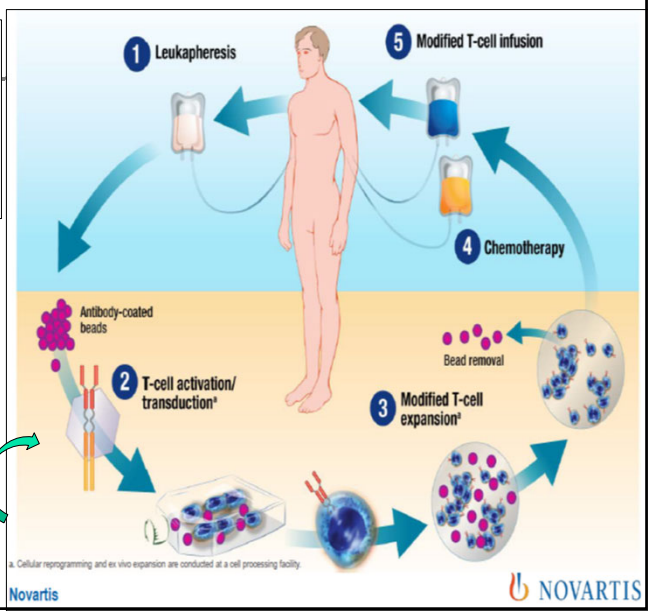
Genetically Modified Living Cells (ex vivo new gene insertion)

Novartis KYMRIAH
Kite YESCARTA

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

(CAR – chimeric antigen receptor)

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



Regulatory authorities predict CGTPs 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

Note: this is the same annual market approval rate for new mAbs today!

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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Most large biologic companies and CMOs have quickly jumped in!

GILEAD		Yescarta Tecartus	Kite (A GILEAD Company)	~$12 billion
NOVARTIS	Kymriah	Zolgensma	avexis	~$9 billion
Roche		Luxturna	Spark Therapeutics	~$5 billion
Bristol-Myers Squibb	Celgene	Zynteglo Skysona Abecma Breyanzi	bluebirdbio Juno Therapeutics	~$74 billion

Janssen · Bayer · astellas · AMGEN · Biogen · Takeda

Lonza · FUJIFILM Diosynth biotechnologies · ThermoFisher Scientific · Catalent Biologics

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Regulatory Authority Landscape for Biopharmaceuticals,
(EU and USA to be discussed)

How do they handle this ever evolving manufacturing process and diverse product types?

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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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1940's – awakening in USA for evidence-based medicine authorization

Elixir of Sulfanilamide (1937)

Children have a hard time taking medicine; therefore, oral formulations

Antibacterial syrup for children was formulated with diethylene glycol

Diethylene glycol is sweeter and cheaper than propylene glycol (used in many children's oral drugs)

BUT, diethylene glycol is 'antifreeze'; highly poisonous!

107 CHILDREN DIE

No drug safety testing was required!

Medicine was perfectly legal to sell!

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

Public outcry
U.S. Congress reacts →

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U.S. Congress

1938 Food Drug & Cosmetics (FD&C) Act

'new drugs must show safety testing before selling'

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

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

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

→

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

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Between 1938 and 1944

- ***Increased awareness of disconnected and disjointed federal public health services***
- ***Federal lead for all public health emergencies not legally established (especially for dealing with infectious diseases) … (COVID-19)***
- ***Awareness that certain drug types (referred to as 'biologicals') under the FD&C Act needed a separate pathway of market approval***
  - ***More testing required than for chemical drugs (many biologicals were undefined mixtures in 1944)***
  - ***Tighter control over the manufacturing process than for chemical drugs***

U.S. Congress Reacts →

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U.S. Congress

1944 Public Health Services (PHS) Act

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

PHS Act: Biologic License Application (BLA) Pathway

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

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Identified Biological Product Classes

CFR changes over time

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

Note: FDA legal definition of 'biological product' different from the 3-fold components of defining a biological

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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 biologic, which FDA Center would I work with?

has changed over time … →

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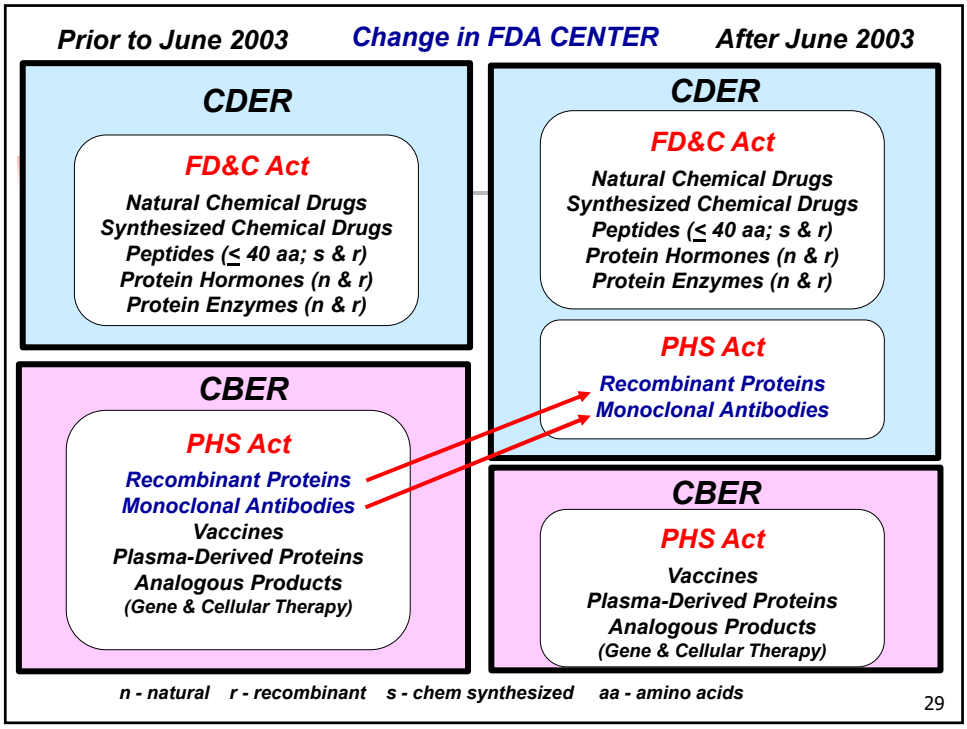
Prior to June 2003
Change in FDA CENTER
After June 2003
CDER
FD&C Act
Natural Chemical Drugs
Synthesized Chemical Drugs
Peptides (≤ 40 aa; s & r)
Protein Hormones (n & r)
Protein Enzymes (n & r)
CBER
PHS Act
Recombinant Proteins
Monoclonal Antibodies
Vaccines
Plasma-Derived Proteins
Analogous Products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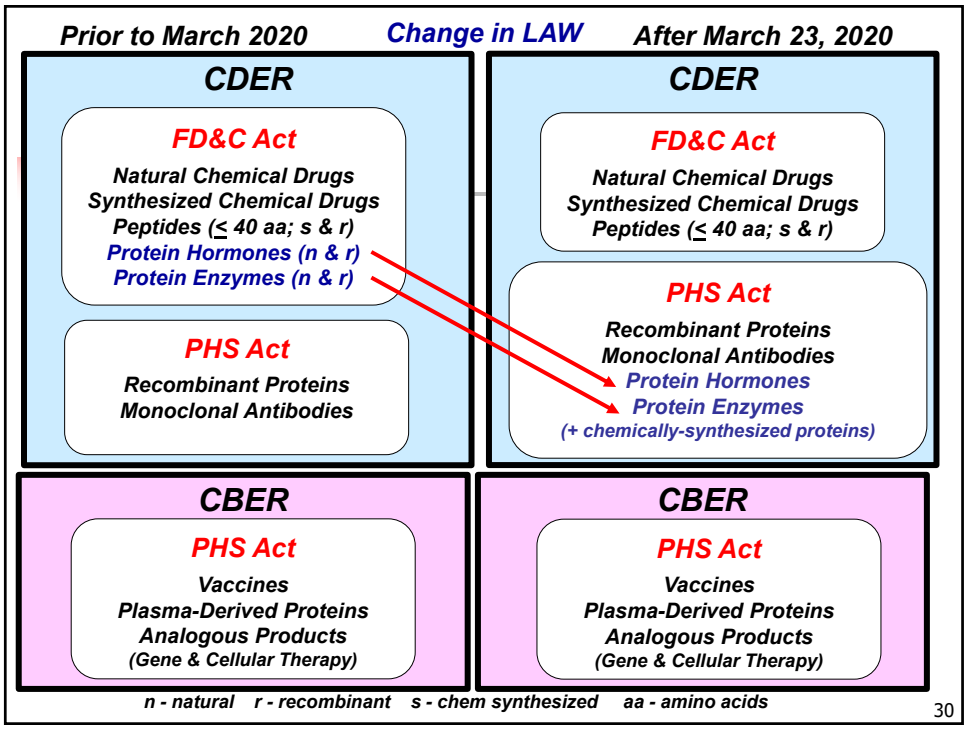
Prior to March 2020
Change in LAW
After March 23, 2020
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(+ chemically-synthesized proteins)
CBER
PHS Act
Vaccines
Plasma-Derived Proteins
Analogous Products
(Gene & Cellular Therapy)
n - natural r - recombinant s - chem synthesized aa - amino acids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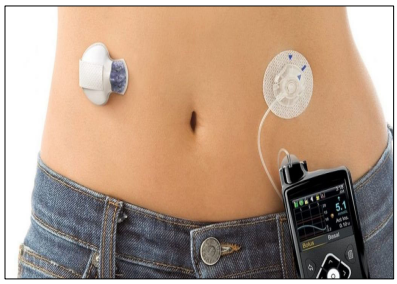
U.S. Food and Drug Administration

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 Affairs***

- ***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 Compliance – during clinical development***

Yes! ***CMC Regulatory Compliance – after market approval***

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 (content ID test after labeling)	STILL IN EFFECT

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Case Example

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! (QA solely determines release to commercial inventory)

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FDA pre-release of Vaccines required for all!

Ervebo – Ebola Zaire Vaccine, Live (Recombinant) (December 19, 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!

Zembifi – Immune Globulin Subcutaneous (Human)-klhw (July 03, 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).

Esperoct – Antihemophilic Factor (Recombinant) GlycoPEGylated (Februry 19, 2019)

You are not currently required to submit final samples or protocols of future lots of Antihemophilic Factor (Recombinant), GlycoPEGylated-exei to the Center for Biologics Evaluation and Research for release by the Director, CBER, under 21 CFR 610.2(a)

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!

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

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

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

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

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

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

stated in FDA market approval letters

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Navigating the complexity of working within the European Union for biopharmaceuticals

European Union

Regulations & Directives

NCA EMA: CHMP

CTA IMPD → MAA

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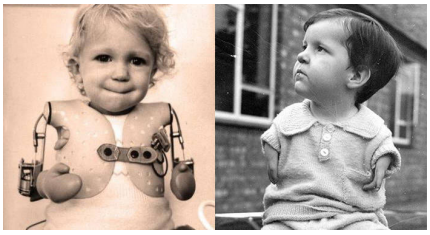
1960's – awakening in Europe for evidence-based medicine authorization

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



1967 – European Commission (EC) established

Proposes new pharmaceutical legislation
Final market approval of EMA recommended medicines

1993 – European Medicines Agency (EMA) established

Scientific evaluation of commercial medicines
Recommends approvals of medicines to EC

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Clinical Development of Biologicals (and Chemical Drugs)

Clinical Trial Directive (2001/20/EC)

National Competent Authorities (NCAs) regulate

(27 Member States – each with a CMC opinion)

Clinical Trial Authorization (CTA)
Investigational Medicinal Product Dossier (IMPD) – CMC
EMA scientific guidance

Clinical Trial Regulation (536/2014)

NCAs still regulate, but assessment of clinical trials is harmonized;
EMA maintains Clinical Trials Information System (CTIS)

'submitted, reviewed, authorized' – single portal entry
CTAs and IMPDs ***EMA scientific guidance***

go-live January 2022
transition until January 2023

Similar to FDA system – upon IND acceptance, clinical trials can begin in all 50 states

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***Market Approval* for Biologics (and Chemical Drugs)**

Centralized Procedure (EU Regulation 2309/93)

Regulated by EMA across all 27 countries within EU

CHMP – Committee for Medicinal Products for Human Use

CAT – Committee for Advanced Therapies

***Mandatory* procedure for *all* biopharmaceuticals**

Recombinant DNA; controlled gene expression; hybridoma and monoclonal antibodies

***ATMPs* gene therapy; somatic cell therapy; engineered tissues**

Biosimilars

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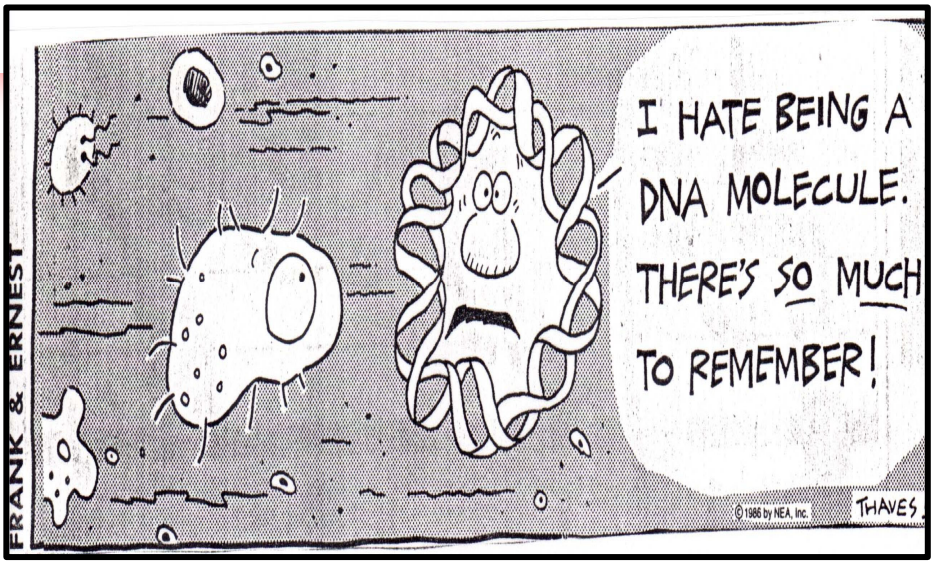
1. CMC Regulatory Compliance is Challenging for Biopharmaceuticals



QUESTIONS ??

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CMC Regulatory Compliance Strategy for Biopharmaceuticals

Course Outline

2. Risk-Managed CMC Regulatory Compliance Strategy

- *The 3 interactive components to protect patients*
- *What the 'minimum CMC regulatory compliance continuum' means for biopharmaceuticals*

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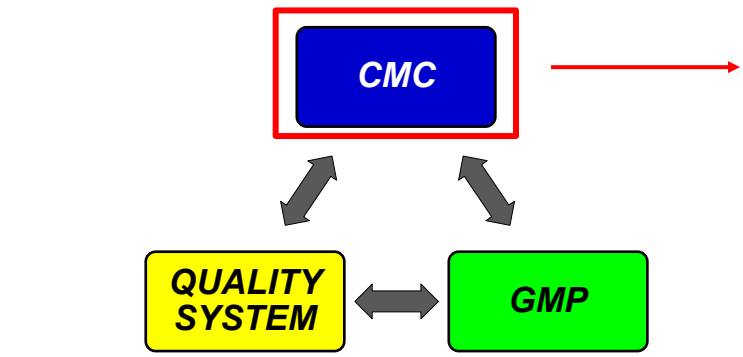
3 interactive components to protect patients

Regulatory authority criteria to be met by Manufacturing & Quality for human medicines



System that ensures regulatory criteria are met by practices carried out by Manufacturing & Quality

Practices carried out by Manufacturing & Quality to meet regulatory criteria

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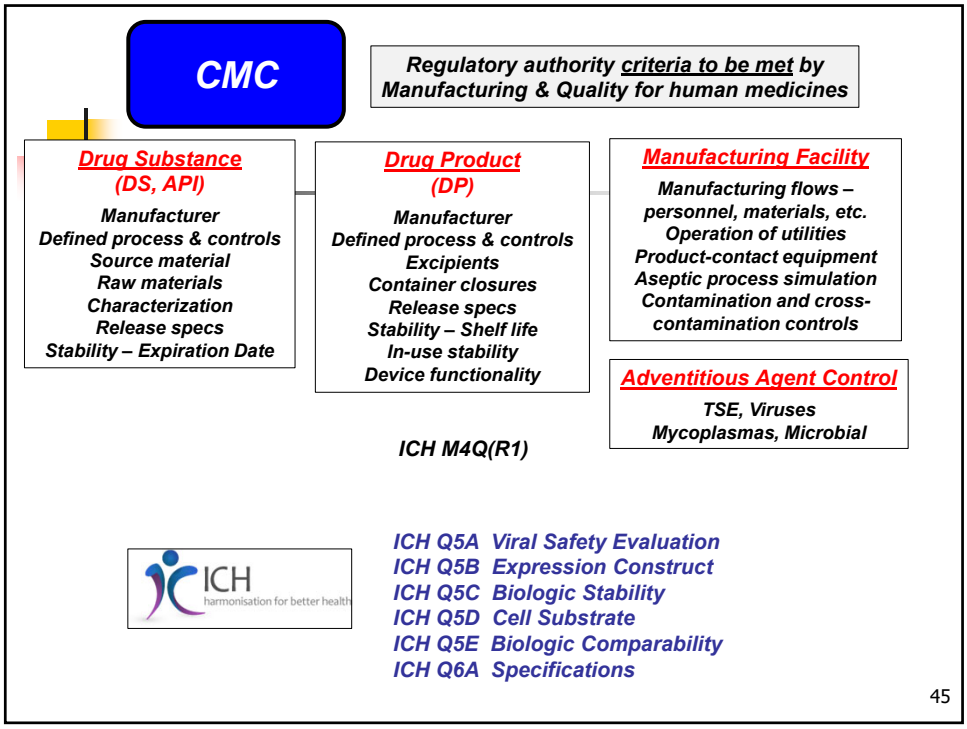
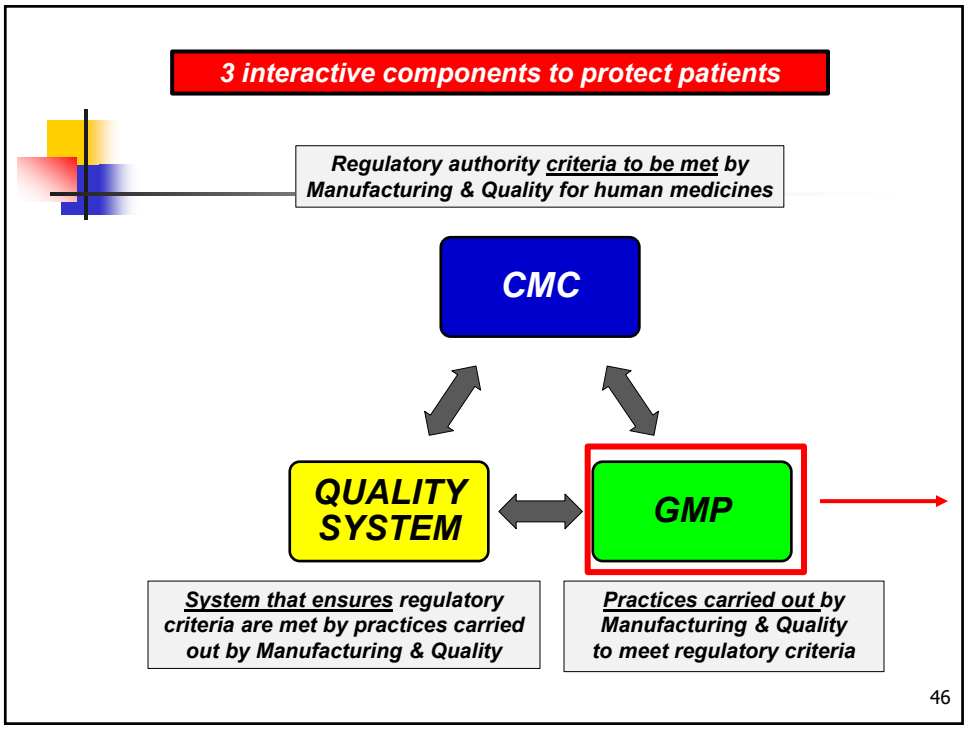

CMC
Regulatory authority criteria to be met by Manufacturing & Quality for human medicines
Drug Substance (DS, API)
Manufacturer
Defined process & controls
Source material
Raw materials
Characterization
Release specs
Stability – Expiration Date
Drug Product (DP)
Manufacturer
Defined process & controls
Excipients
Container closures
Release specs
Stability – Shelf life
In-use stability
Device functionality
Manufacturing Facility
Manufacturing flows – personnel, materials, etc.
Operation of utilities
Product-contact equipment
Aseptic process simulation
Contamination and cross-contamination controls
Adventitious Agent Control
TSE, Viruses
Mycoplasmas, Microbial
ICH M4Q(R1)
ICH Q5A Viral Safety Evaluation
ICH Q5B Expression Construct
ICH Q5C Biologic Stability
ICH Q5D Cell Substrate
ICH Q5E Biologic Comparability
ICH Q6A Specifications
45


3 interactive components to protect patients
Regulatory authority criteria to be met by Manufacturing & Quality for human medicines
CMC
QUALITY SYSTEM
GMP
System that ensures regulatory criteria are met by practices carried out by Manufacturing & Quality
Practices carried out by Manufacturing & Quality to meet regulatory criteria
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Code of Federal Regulation (CFR) Title 21
Parts 210, 211, 600-680

Part 210: *Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General*

Part 211: *Current Good Manufacturing Practice for Finished Pharmaceuticals*

Part 600-680: *Biologics*

210.1 – Status of current good manufacturing practice regulations

'contains the minimum current good manufacturing practice'

210.2 – Applicability of current good manufacturing practice regulations

'211 as pertain to a drug … 600 through 680 as pertain to a biological product'

(applies to both chemical drugs and biologicals)

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2008

CGMP for Phase 1 Investigational Drugs

This guidance is intended to assist in applying current good manufacturing practice (CGMP) required under section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) in the manufacture of most investigational new drugs (IND) used in phase 1 clinical trials.[2] These drugs, which include biological drugs, are exempt from complying with 21 CFR part 211 under 21 CFR 210.2(c) (referred to as phase 1 investigational drugs).

The manufacturing process is critical to ensure the correct composition, quality, and safety of biological and biotechnology products. For these products, it can be difficult to distinguish changes in quality attributes, or predict the impact of observed changes in quality attributes on safety. This is especially true for phase 1 clinical trials where knowledge and understanding of a phase 1 investigational drug is limited and where comprehensive product characterization is often unavailable, especially for products that are difficult to characterize. Therefore, it is critical to carefully control and record the manufacturing process in conjunction with appropriate testing to reproduce a comparable phase 1 investigational drug as may be necessary. Properly

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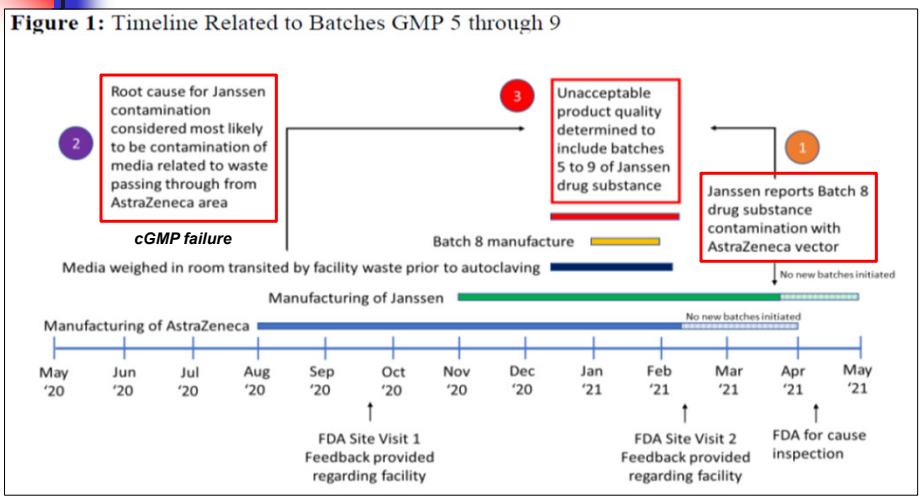
Patients are endangered when cGMPs are <u>not</u> followed!

Emergent BioSolutions – contract manufacturer for COVID-19 J&J adenovirus vaccine and for AZ adenovirus vaccine



FDA tells J&J to scrap 60 million vaccine doses made at troubled plant

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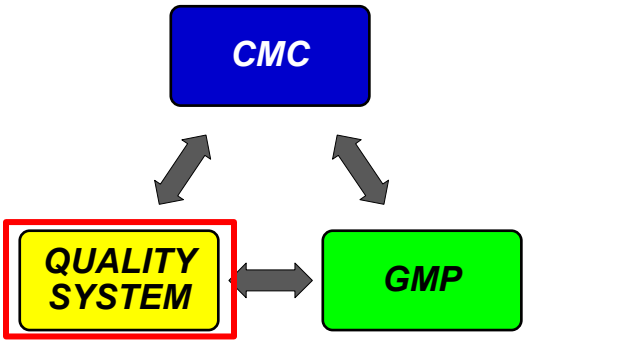
3 interactive components to protect patients

Regulatory authority <u>criteria to be met</u> by Manufacturing & Quality for human medicines



<u>System that ensures</u> regulatory criteria are met by practices carried out by Manufacturing & Quality

<u>Practices carried out by</u> Manufacturing & Quality to meet regulatory criteria

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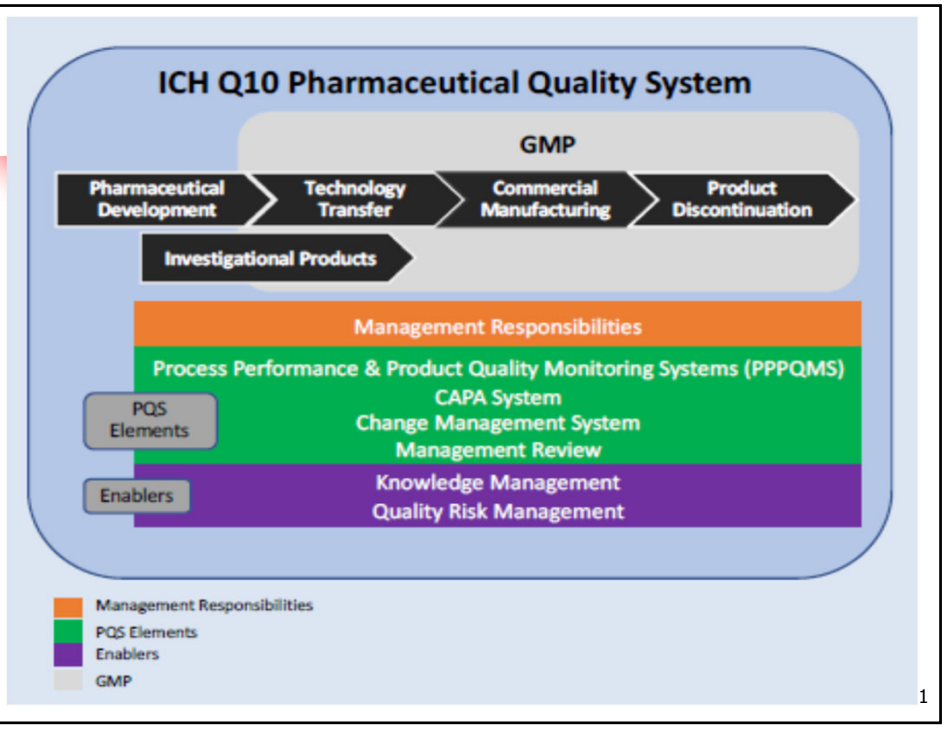

1

ICH harmonisation for better health

Two Strategic Risk-Based Quality Approach Guidelines

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

Quality by Design (QbD):

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

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

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

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

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2) ICH Q9 Quality Risk Management (QRM) 2006

Quality Risk Management:

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

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

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

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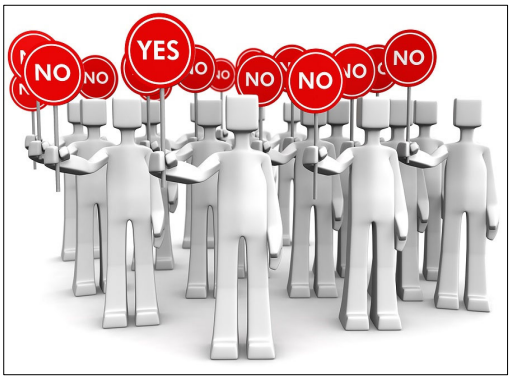
The weakest link with QRM

Selection of the multi-discipline team (Development, Manufacturing, Quality Control, Quality Assurance, Compliance, Regulatory Affairs, etc.) to decide the consensus on each level of risk assignment



- ***wrong people involved***
  - *non-competent*
  - *inexperienced*
- ***insufficient time***
  - *'you have just a week to finish it'*
  - *3 pm on Friday afternoon*
- ***wrong environment***
  - *fatigue*
  - *herd-mentality*

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

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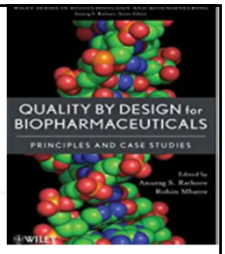
Quality by Design (QbD)



- **QTPP** – Quality Target Product Profile
- **CQA** – Critical Quality Attributes
- **CPP** – Critical Process Parameters
- **CS** – Control Strategy

Quality Risk Management (QRM)

'MINIMUM CMC regulatory compliance CONTINUUM'

"minimum" – different levels of CMC regulatory compliance at different clinical stages

"continuum" – increasing levels of CMC regulatory compliance as clinical development advances

illustrated →

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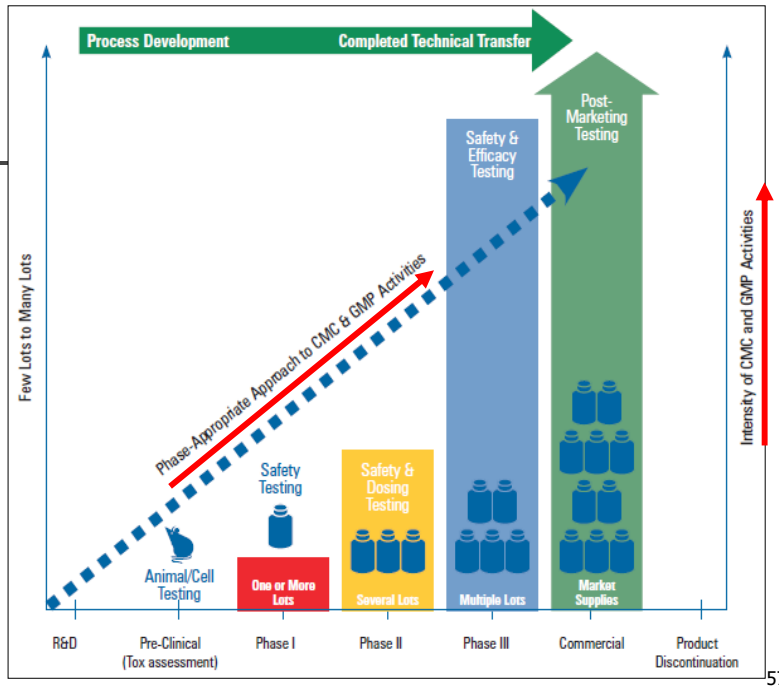
PDA
Parenteral Drug Association

Technical Report No. 56

2016



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'MINIMUM CMC regulatory compliance CONTINUUM'

a risk-based approach that provides necessary flexibility

***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.

U.S. FOOD & DRUG ADMINISTRATION

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

– *Early clinical stage focus* → *product safety for patient*

– *Later clinical stage focus* → *product safety for patient*
+ manufacturing process consistency to achieve the necessary quality biologic product

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'MINIMUM CMC regulatory compliance CONTINUUM'

a risk-based approach that protects patients

> ***"The safety and well-being of trial subjects (be they patients or healthy volunteers) should always be the priority and special consideration should be given to characterising risk and putting in place appropriate strategies to minimise risk."***

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

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

- ***A risk-based approach focuses CMC regulatory compliance 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 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 in early clinical study phases, especially when product understanding and resources may be limited***

'good regulatory sense and good business sense'

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'MINIMUM CMC regulatory compliance CONTINUUM'

a risk-based approach that is acknowledged by regulatory authorities

Classroom Work Problem

REFERENCE 1

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

24 June 2021
EMA/CHMP/BWP/534898/2008 rev. 2

Read the EMA guidance: Where in the IMPD CMC submission are phrases used such as:

- ***'based on a limited number'***
- ***'inherently preliminary'***
- ***'acknowledged that during early clinical development'***
- ***'complete information may not be available'***
- ***'continuously being improved and optimised'?***

→ ***fill in table***

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REFERENCE 1

(~15 minutes)

'MINIMUM CMC regulatory compliance CONTINUUM'

acknowledged by regulatory authorities

IMPD CMC Section		EMA CMC Guideline for Biologic IMPS
S.2.2	Description of Manufacturing Process and Process Controls	
S.2.4	Control of Critical Steps	
S.2.5	Process Validation	
S.2.6	Manufacturing Process Development	
S.4.1 P.5.1	Specifications	
S.4.3	Validation of Analytical Procedures	
S.4.5	Justification of Specification	
S.7	Stability	

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CMC Regulatory Compliance Strategy for Biopharmaceuticals

Course Outline

3. Applied Risk-Managed CMC Regulatory Compliance Strategy

- CMC strategy applied across the manufacturing process from starting material → protein production → purification → formulation → drug product → administered drug product

Case examples and references are from public sources
(manufacturers do not voluntarily reveal their manufacturing details or problems;
but FDA and EMA will after market approval,
and the company frequently has to in SEC filings)

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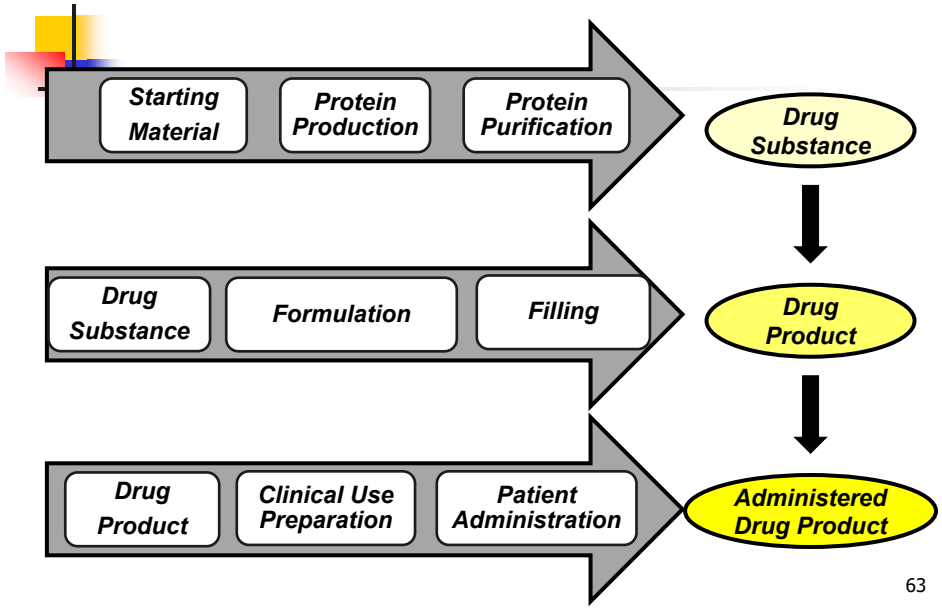
Applied Risk-Management Across the Manufacturing Process



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Classroom Work Problem

REFERENCE 1

'minimum CMC regulatory compliance continuum'

acknowledged by regulatory authorities

IMPD CMC Section		EMA Guidaline on Biologic IMPs
S.2.2	Description of Manufacturing Process and Process Controls	Since early development control limits are normally based on a limited number of development batches, they are inherently preliminary. During development, as additional process knowledge is gained, further details of IPCs should be provided and acceptance criteria reviewed.
S.2.4	Control of Critical Steps	It is acknowledged that due to limited data at an early stage of development (phase I/II) complete information may not be available.
S.2.5	Process Validation	Process validation data should be collected throughout development, although they are not required to be submitted in the IMPD.
S.2.6	Manufacturing Process Development	Manufacturing processes and their control strategies are continuously being improved and optimised, especially during the development phase and early phases of clinical trials.
S.4.1 P.5.1	Specifications	As the acceptance criteria are normally based on a limited number of development batches and batches used in non-clinical and clinical studies, they are by their nature inherently preliminary and may need to be reviewed and adjusted during further development. Additional information for phase III clinical trials As knowledge and experience increases …

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IMPD CMC Section		EMA Guideline on Biologic IMPs
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 should be provided
S.4.5	Justification of Specification	It is acknowledged that during clinical development, the acceptance criteria may be wider and may not reflect process capability. However, for those quality attributes that may impact patient safety, the limits should be carefully considered taking into account available knowledge (e.g. process capability, product type, dose, duration of dosing etc.).
S.7	Stability	Progressive requirements will need to be applied to reflect the amount of available data and emerging knowledge about the stability of the active substance during the different phases of clinical development. By phase III the applicant should have a comprehensive understanding of the stability profile of the active substance.

2. Risk-Managed CMC Regulatory Strategy

QUESTIONS??

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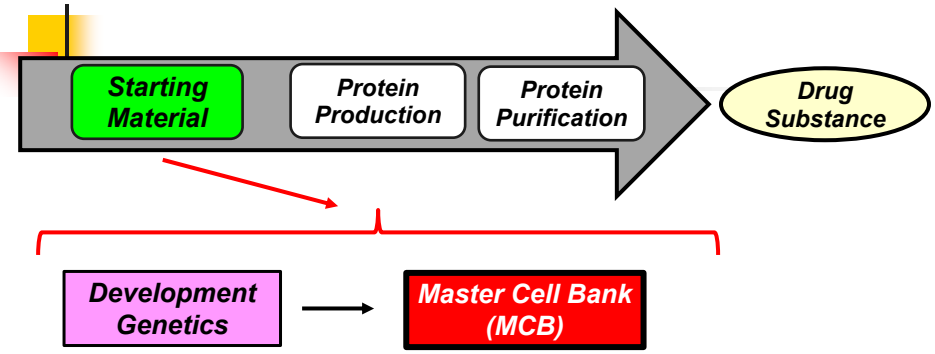
Applied Risk-Management Across the Manufacturing Process



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

'recombinant' contains the genetic capacity to express the protein of interest

→ (7-12 month process) →

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Starting Materials (ICH Q11)

for chemical drugs

A starting material should be a substance of defined chemical properties and structure. Non-isolated intermediates are usually not considered appropriate starting materials;

A starting material is incorporated as a significant structural fragment into the structure of the drug substance. "Significant structural fragment" in this context is intended to distinguish starting materials from reagents, solvents, or other raw materials. Commonly available chemicals used to create salts, esters or other simple derivatives should be considered reagents.

for recombinant proteins and monoclonal antibodies

Cell banks are the starting point for manufacture of biotechnological drug substances and some biological drug substances. In some regions, these are referred to as source materials; in others, starting materials. Guidance is contained in ICH Q5A, Q5B, and Q5D.

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

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Development Genetics

(Step 1 of 2) Stitching together the genetic components

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

(genes can be further genetic engineered)

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

gene

vector

expression construct

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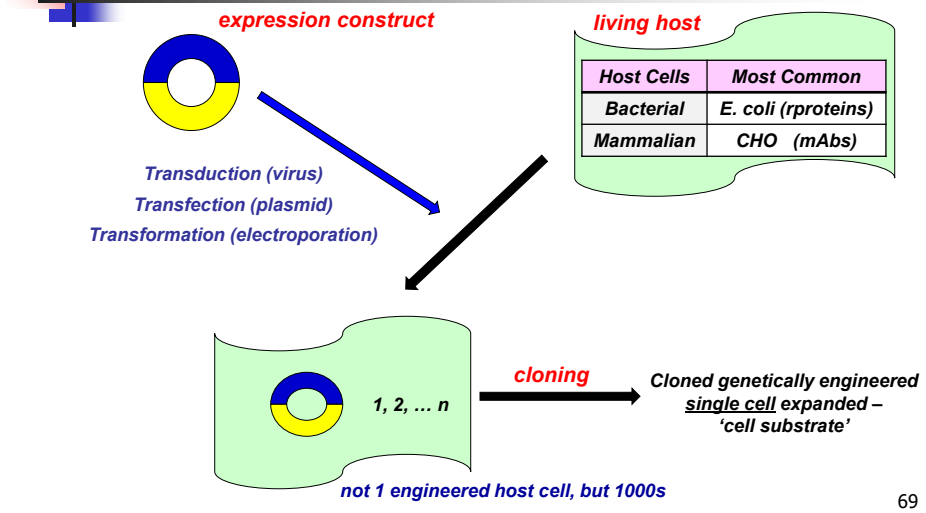
Development Genetics

(Step 2 of 2) Preparing the Cloned Cell Substrate



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Why is 'proof' of clonality so important?

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

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

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

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

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USP <1042> Cell Banking

why 2 rounds of limiting dilution

LIMITING DILUTION CLONING

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

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

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

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

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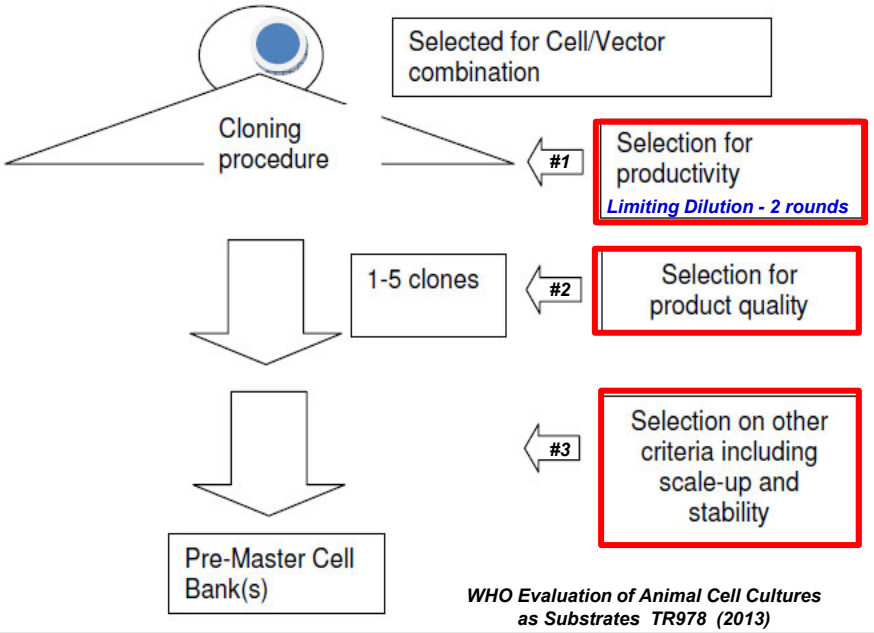
WHO – illustration of three essential screens in clone selection



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

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Development Genetics

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

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

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

cGMP not required, but careful written documentation critical!

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Master 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

↓ ***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

MCB + WCB can provide up to 40,000 batches

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MINIMUM CMC Regulatory Compliance CONTINUUM

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

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

"What's the big deal?"

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

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MINIMUM CMC Regulatory Compliance CONTINUUM

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

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

CMC Details Required

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

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Description in IND/IMPD for clinical development

Source, history and generation of the cell substrate

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

Cell bank system, characterisation and testing

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

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

24 June 2021
EMA/CHMP/BWP/534898/2008 rev. 2

REFERENCE 1

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Description in BLA/MAA for market approval

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

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

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

FDA 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)

REFERENCE 2

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MINIMUM CMC Regulatory Compliance CONTINUUM

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

Regulatory authority focus to enter clinical development	***Regulatory authority focus to enter market approval***
CMC Details Required	
brief description IND/IMPD	***detailed description in BLA/MAA***
Level of CMC Regulatory Review	
limited, single CMC reviewer patient safety focus	***thorough, CMC team reviewers patient safety focus + manufacturing consistency*** →

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Level of CMC review of IND/IMPD for clinical development

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

FDA CDER Manual of Policy and Procedures (MAPP): MAPP 6030.9 – Good Review Practice: Good Review Management Principles and Practices for Effective IND Development and Review (April 2013)

regulatory authority CMC reviewers do not catch everything

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Patient Safety Focus

Absence of adventitious agents of concern and …

- ***Prions – TSEs***
  - *Prevented through risk minimization strategy in choices for raw materials used to prepare bank (e.g., avoiding animal- or human-derived materials)*
- ***Viruses* – insect/animal/human cell lines***
  - ***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*

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Patient Safety Focus

… and correct identity of genetic components …

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

ICH Q5B
ICH Q5D

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Patient Safety Focus

R. Novak, CDER, WCBP 2017

… and clonality

Reviewer Considerations for Clonality at the IND stage

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

Considerations at the BLA stage

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

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Augmentation of the Control Strategy

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

R. Novak, CDER, WCBP 2017

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MINIMUM CMC Regulatory Compliance *CONTINUUM*

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

Regulatory authority focus to enter clinical development	*Regulatory authority focus to enter market approval*
CMC Details Required	
brief description IND/IMPD	*detailed description in BLA/MAA*
Level of CMC Regulatory Review	
limited, single CMC reviewer patient safety focus	*thorough, CMC team reviewers patient safety focus + manufacturing consistency*
Other CMC Expectations	
-----	*for commercial manufacturing* →

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CMC requirements for commercial manufacturing

assurance of continued supply

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

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

ICH Q5D

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

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

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CMC requirements for commercial manufacturing

assurance of long-term stability

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

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

ICH Q5D

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

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

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So how frequent should the MCB be tested for stability?

One answer

- ***There is no regulatory authority guidance on the frequency of stability testing for a MCB, so consultants have typically recommended every 4-5 years***
- ***However, the FDA indicated their preference on the MCB frequency of stability testing in a communication to Genentech during the market approval of the CHO-produced monoclonal antibody, Perjeta:***

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

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

88

CMC requirements for commercial manufacturing

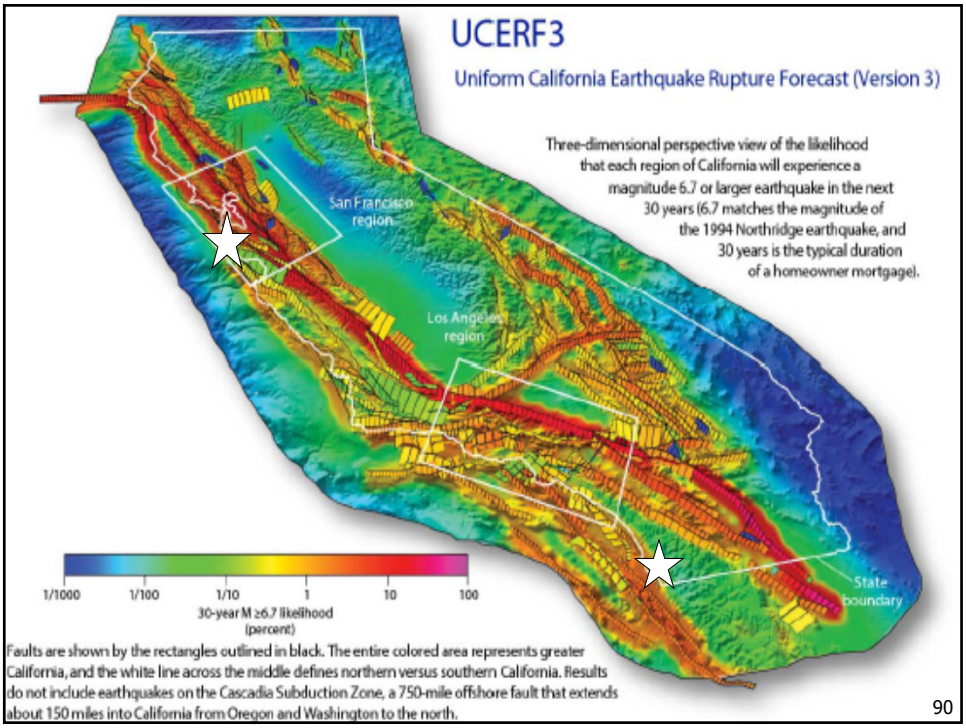
secure catastrophic event plan

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

ICH Q5D

What catastrophic event might happen where your MCB is stored?

89



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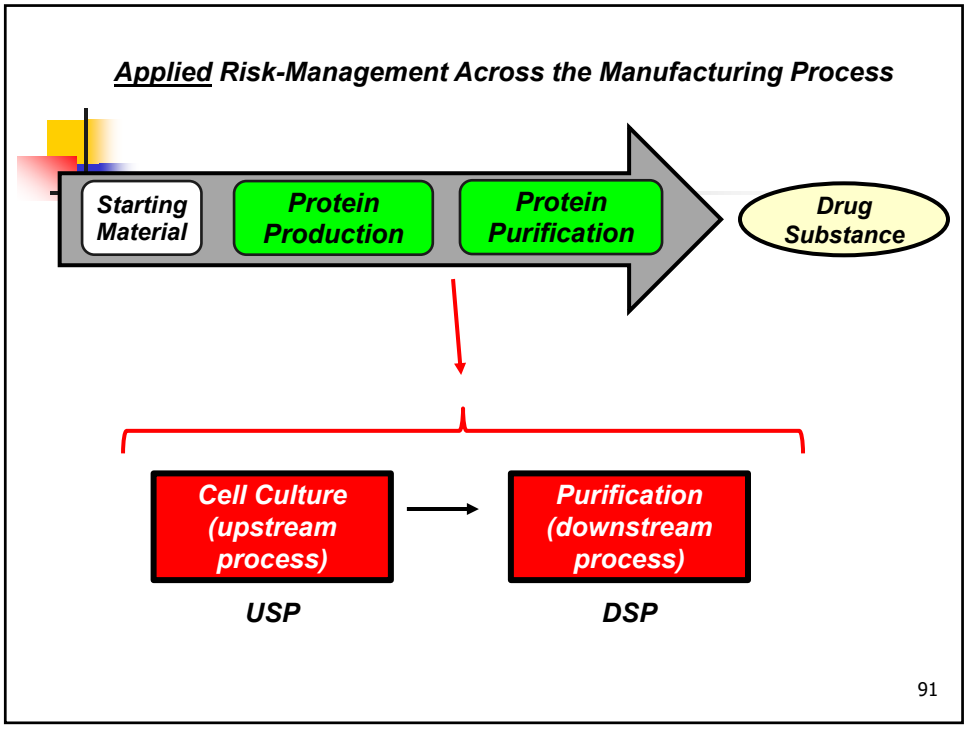

Applied Risk-Management Across the Manufacturing Process
Starting Material
Protein Production
Protein Purification
Drug Substance
Cell Culture (upstream process)
Purification (downstream process)
USP
DSP
91


Genentech 4 min

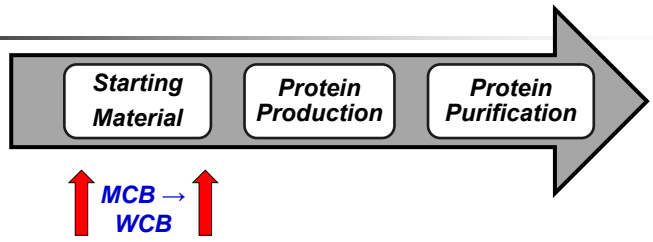
2016

Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

ICH consensus guidance adopted by FDA (and EMA) because 21 CFR 210-211 applies only to 'finished pharmaceuticals'

93

4 Major CMC regulatory compliance issues for recombinant protein/mAb DS manufacturing processes



94

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

Regulatory authority 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.

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

24 June 2021
EMA/CHMP/BWP/534898/2008 rev. 2

REFERENCE 1

Caution is advised with a new WCB during clinical development

(FDA – CMC amendment – no prior approval NCA – 'substantial' – prior approval)

95

Heightened regulatory authority concern at the commercial stage

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

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

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

USP <1042>

96

Problems with WCBs are discovered during BLA/MAA review

Pfizer

WCB problem 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.

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

97

Problems with WCBs are discovered during pre-approval inspections

Genentech

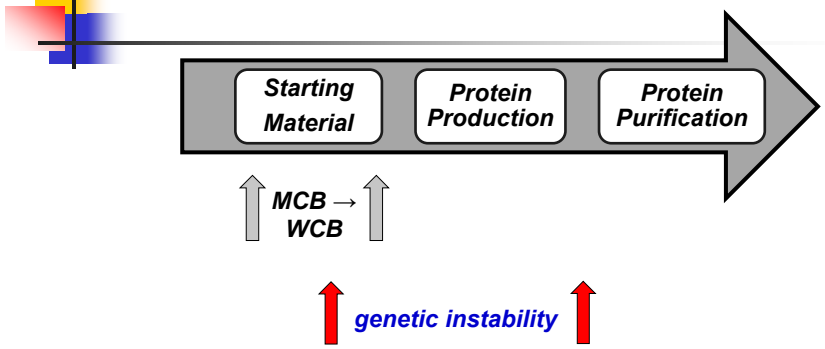
In addition, while inspecting the facility,
we discovered that the Sponsor was experiencing serious issues with the thaw and subsequent propagation of cells from WCB__ used to manufacture pertuzumab.
At the time of inspection, the root cause investigation was ongoing and no root cause had been identified, although data suggested instability of WCB … The 483 items cited on this inspection could generally be classified as VAI (voluntarily action indicated), but the deviation and follow up data supplied from the firm related to their inability to successfully thaw and grow cultures from their working cell bank lead us to concur with the recommendation to withhold on this application by Division of Monoclonal Antibodies.

FDA Drugs – Search Drugs@FDA: FDA Approved Drug Products: Perjeta (Pertuzumab) – Approval History, Letters, Reviews and Related Documents – Chemistry Review – Product Quality Review Data Sheet (May 31, 2012)

more on this story when we get to process validation

98

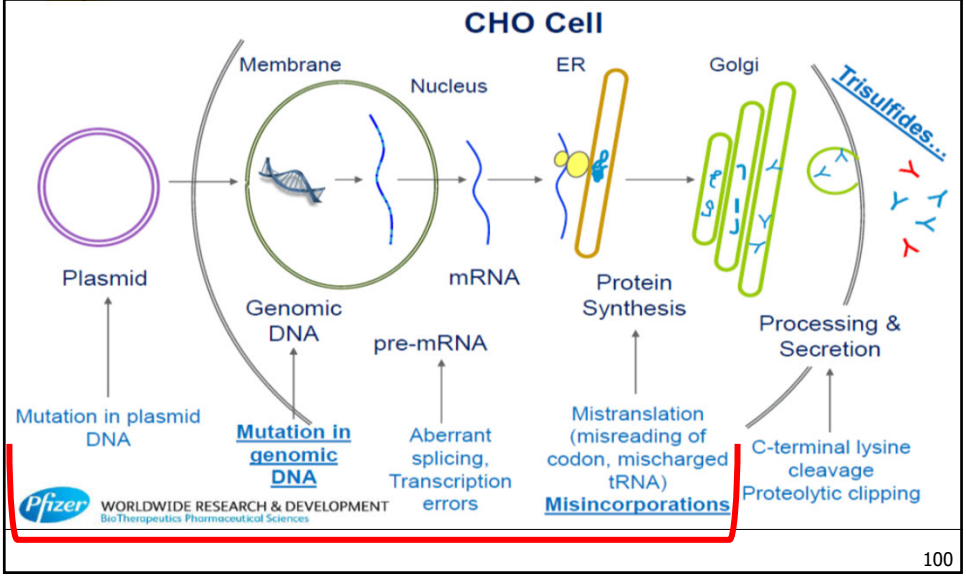
4 Major CMC regulatory compliance issues for recombinant protein/mAb DS manufacturing processes



99

Genetic Instability

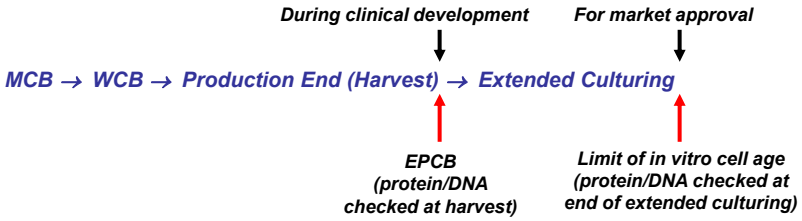
A reality that occurs with all living systems!



100

Evaluation of genetic stability

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



→ population doublings, cell generations, elapsed culturing time →

ICH Q5B/Q5D

- *Confirmation of <u>no change of expressed protein</u> amino acid sequence*
- *Confirmation of <u>no change in genetic DNA/RNA</u> nucleic acid sequence*
- *Confirmation of <u>absence of latent virus induction</u> (insect/mammalian/human cells)*
  (e.g., shingles and chickenpox in humans – especially as we age)

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USP <1042> Cell Banking

LIVCA for inclusion in BLA/MAA submission

5.1 Genetic Characterization

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

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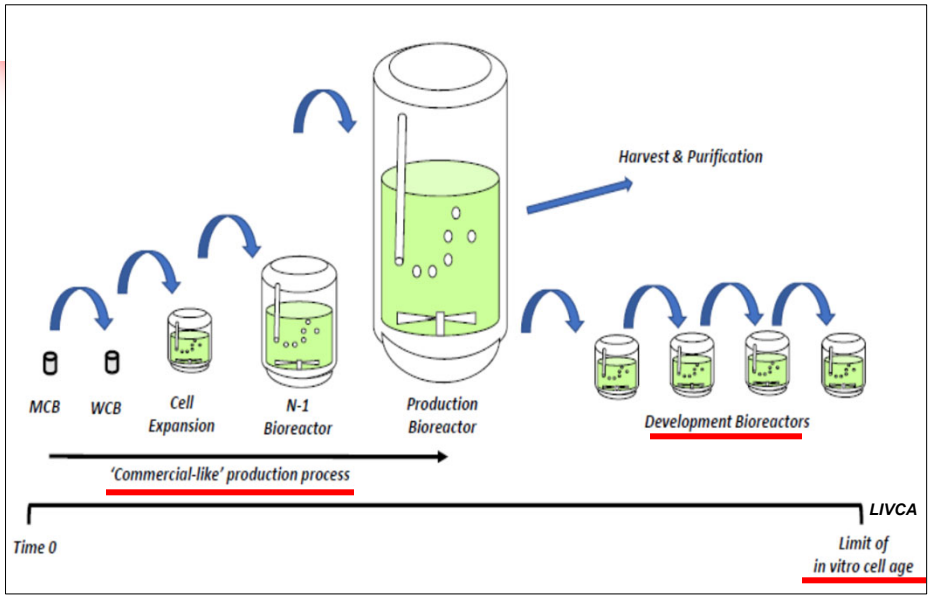
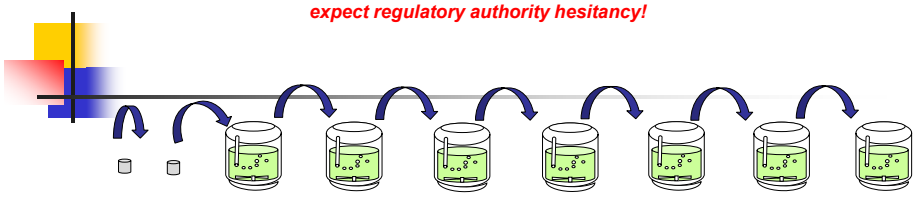
***Traditional* & *Expected* approach to LIVCA determination**



103

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

expect regulatory authority hesitancy!



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

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

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

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

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

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

104

Genetic instability can result in protein sequence variants (SVs)!

Biopharmaceutical Industry Practices for Sequence Variant Analyses of Recombinant Protein Therapeutics

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

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

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

According to the industry survey →

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

105

According to the industry survey –

What if protein sequence variants are detected?

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

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

Case Example

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

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

Samsung Biosimilar to Avastin (Genentech)

106

Genetic instability is observed in commercial mAbs!

Case Example

Copy number loss

Inflectra MAb (Infliximab Biosimilar) EPAR Hospira 2013

Sp2/0 murine cells

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

CQAs → no impact
KPPs → yield lowered

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Case Example

Chromosomal gene translocation ('jumping genes') –

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.

Merck Serono SA

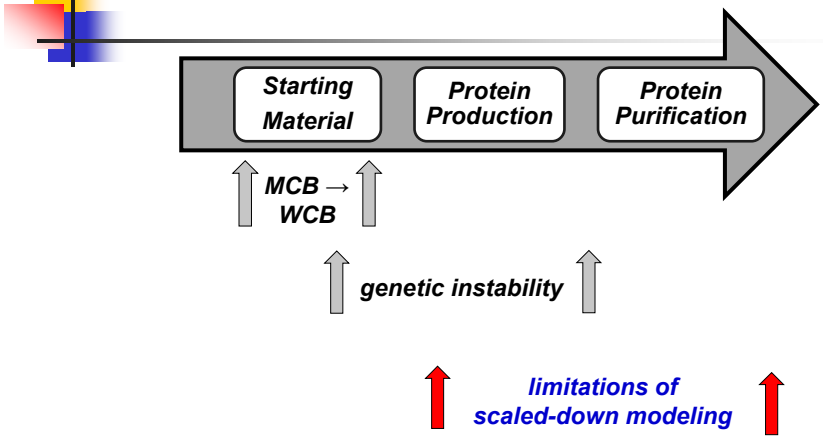
Reciprocal Translocation Observed in End-of-Production Cells of a Commercial CHO-Based Process

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

CQAs → no impact
KPPs → no impact

108

4 Major CMC regulatory compliance issues for recombinant protein/mAb DS manufacturing processes



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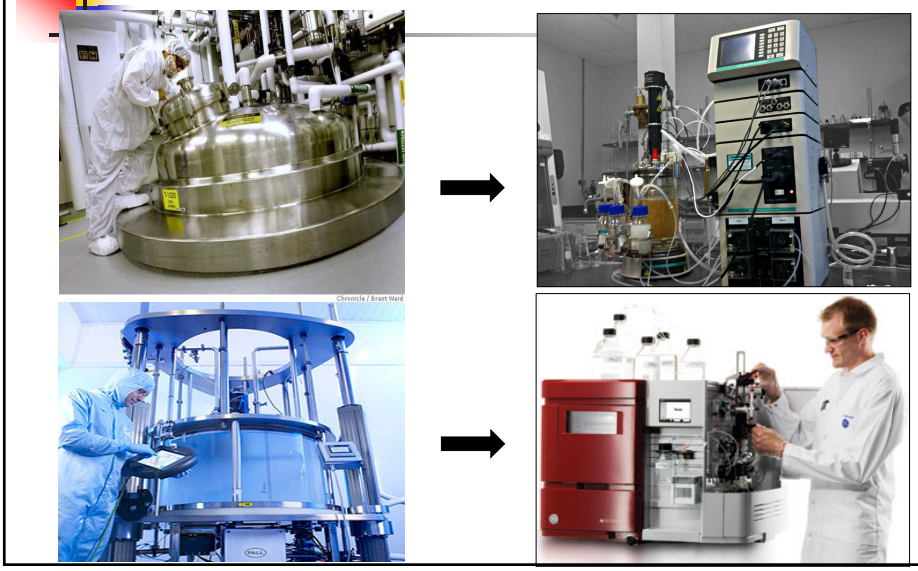
Limitations of Scaled-Down Modeling

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



110

Limitations of Full-Scale Manufacturing 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 tying up a commercial manufacturing facility*

111

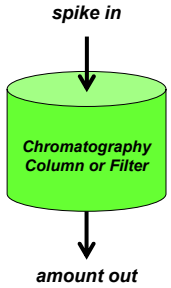
Scaled-down models are absolutely necessary for biologics!

UPSTREAM PROCESS

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

DOWNSTREAM PROCESS

- *Identification of purification CPPs (DOE)*
- *Process hold times*
- *Clearance studies*
  - *Virus evaluation (low pH, chromatography, nanofiltration)*
  - *Process-related impurities (host cell DNA and proteins, Protein A leachables)*
  - *Product-related molecular variants (oxidation, deamidation, aggregates)*
- *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 compared to the commercial scale manufacturing process!

The contribution of data from small-scale studies to the overall validation package will depend upon demonstration that the small-scale model is an appropriate representation of the proposed commercial-scale. Data should be provided demonstrating that the model is scalable and representative of the proposed commercial process. Successful demonstration of the suitability of the small-scale model can enable manufacturers to propose process validation with reduced dependence on testing of commercial-scale batches. Data derived from commercial-scale batches should confirm results obtained from small-scale studies used to generate data in support of process validation. Scientific grounds, or reference to guidelines which do not require or specifically exclude such studies, can be an appropriate justification to conduct certain studies only at small-scale (e.g., viral removal).

ICH Q11

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

114

Expect that the regulatory authorities will review and challenge, if necessary, the design of the scaled-down models provided in the market application

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

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

FDA Chem Review of BLA (May 30, 2014)

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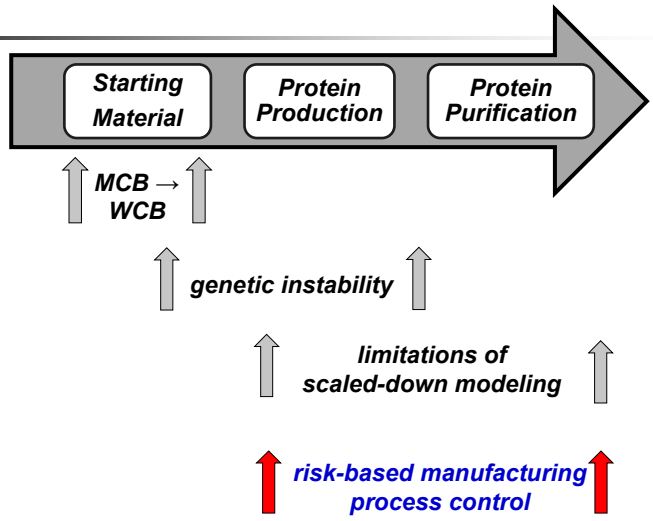
4 Major CMC regulatory compliance issues for recombinant protein/mAb DS manufacturing processes



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Adequate Risk-Based Control

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

	FDA	EMA
Stage 1	Process Design	Process Characterization
	Goal: develop the manufacturing process that can consistently deliver a defined product that meets its quality attributes (clinical development and scale-up activities)	
Stage 2	Process Qualification	Process Verification
	Goal: confirm that the final manufacturing process can achieve the desired CQAs (process validation activities and PPQ batches for market approval)	
Stage 3	Continued Process Verification	Ongoing Process Verification
	Goal: ongoing assurance of the controlled commercial 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 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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Adequate Risk-Based Control

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

	FDA	EMA
Stage 1	Process Design	Process Characterization
	Goal: develop the manufacturing process that can consistently deliver a defined product that meets its quality attributes (clinical development and scale-up activities)	
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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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Pre-BLA submission meetings: FDA, to stress to a company the importance, sometimes attaches to the meeting minutes, a "hot topic" list of frequently encountered deficiencies in biologic process validation

REFERENCE 3

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-BLA
Meeting Date and Time:	Friday, April 17, 2020; 9:00 AM – 10:00 AM (ET)
Meeting Location:	Teleconference

ADC Therapeutics
ADCT-402
Zynlonta (loncastuximab tesirine)

CTD Module 1: Complete Control Strategy (pp12-13)

CTD Module 3.2.S: Drug Substance

- ***3.2.S.2.4 Controls of Critical Steps***
- ***3.2.S.2.5 Process Validation/Evaluation (pp14-15)***
- ***3.2.S.4 Control of Drug Substance***

CTD Module 3.2.P: Drug Product

- ***3.2.P.3.4 Controls of Critical Steps (pp 15-16)***
- ***3.2.P.3.5 Process Validation/Evaluation (pp 16)***
- ***3.2.P.8 Stability (In-Use) (Q2)***

CTD Module 3.2R: PV reports (Q1)

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REFERENCE 3

Module 3 CMC - Drug Substance
3.2.S.2.5 Process Validation/Evaluation

Drug Substance Process Validation FDA Expectations for BLA
Bioburden and endotoxin data obtained during manufacture of three process qualification (PPQ) lots (3.2.S.2.5)
Microbial data from three successful product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5)
Chromatography resin and UF/DF membrane lifetime study protocols and acceptance criteria for bioburden and endotoxin samples. During the lifetime studies, bioburden and endotoxin samples should be taken at the end of storage prior to sanitization (3.2.S.2.5)
Information and summary results from the shipping validation studies (3.2.S.2.5)

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Biologic process validation missteps unfortunately occur!

Case Example

Portola Pharmaceuticals
Recombinant coagulation factor Xa

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

FDA meeting minutes Complete Response Letter discussion

We acknowledge that 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.

(2 year delay in BLA approval, 2018)

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Biologic process validation missteps unfortunately occur!

Case Example

Genentech
Perjeta (pertuzumab)

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

A pre-approval inspection (PAI) for pertuzumab drug substance manufacture was performed at the Vacaville (VV), CA facility from March 20 to March 28, 2012 by BMT reviewer Bo Chi (lead), BMT trainee Qing Zhou, product reviewers Kathryn King and Laurie Graham and an inspector from the San Francisco District, Lance DeSouza. VV is responsible for the manufacture of pertuzumab drug substance and for DS QC testing. A form 483 was issued at the end of this inspection. Observations included: 1) The environment of [redacted] (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 [redacted] (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 [redacted] (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 [redacted] (b)(4) WCB [redacted] (b)(4) is under the

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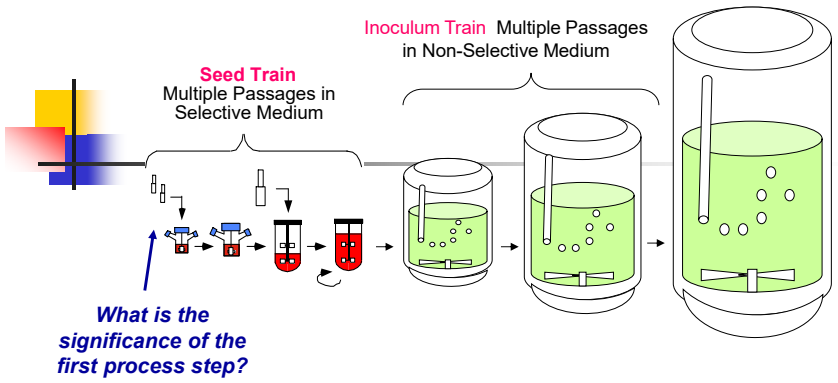

Summary Review for Regulatory Action

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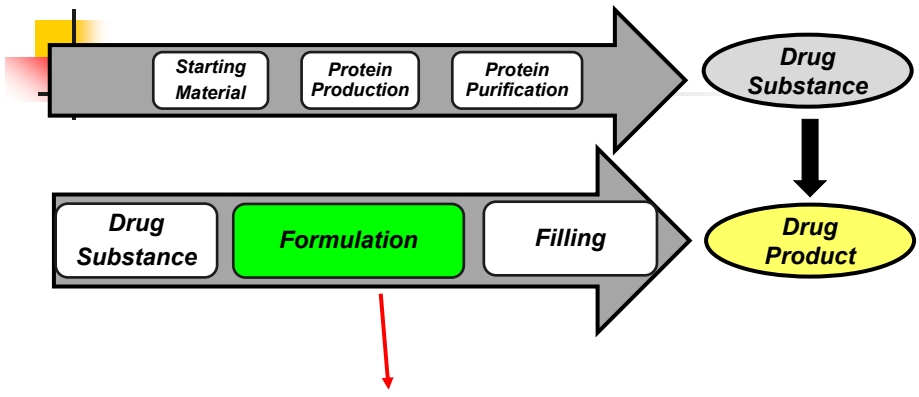
***Applied* Risk-Management Across the Manufacturing Process**



biologic formulation changes are considered 'high risk', but they can be managed

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Biological drug products are formulated with excipients

each excipient present should be justifiable

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)*

127

Sometimes 'novel excipients' are absolutely required!

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

Novo Nordisk

Ozempic, SC Injectable Recombinant GLP-1 Peptide

Formulation: sodium phosphate, propylene glycol, phenol

Rybelsus, Oral Tablet Recombinant GLP-1 Peptide

Formulation: SNAC, povidone K90, magnesium stearate, cellulose

EMA 2020

Novel Excipient: SNAC

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

SNAC – required a 2 year tox study!

CTD also 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 are frequently necessary with increasing protein concentrations

Roche Rituxan (commercial mAb)

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

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Formulation changes even occur with biosimilars

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

Humira (adalimumab)				
INNOVATOR	***BIOSIMILAR***			
Abbvie Humira (FDA, 2002)	***Amgen Amjevita (FDA, 2016)***	***Samsung Hadlima (FDA, 2019)***	***Pfizer Abrilada (FDA, 2019)***	***Mylan Hulio (FDA, 2020)***
Expression System CHO				
Strength: 50 mg/mL Pre-filled syringe				
Formulation				
Mannitol Polysorbate 80 Sodium phosphate Sodium citrate Sodium chloride	***Sucrose Polysorbate 80 Sodium acetate***	***Sorbitol Polysorbate 20 Sodium citrate L-histidine***	***Sucrose Polysorbate 80 L-histidine L-methionine EDTA***	***Sorbitol Polysorbate 80 Sodium glutamate L-methionine***

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Biologic formulation changes are considered 'high risk'

***not all** biologic formulation changes are successful!*

Dash of EDTA!

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

- *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, who sold it off to company B, which finally sold it off to Bayer*
  - *How effective do you think was the CMC 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*
  - *Analytical testing 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*

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SYNCOPE

- *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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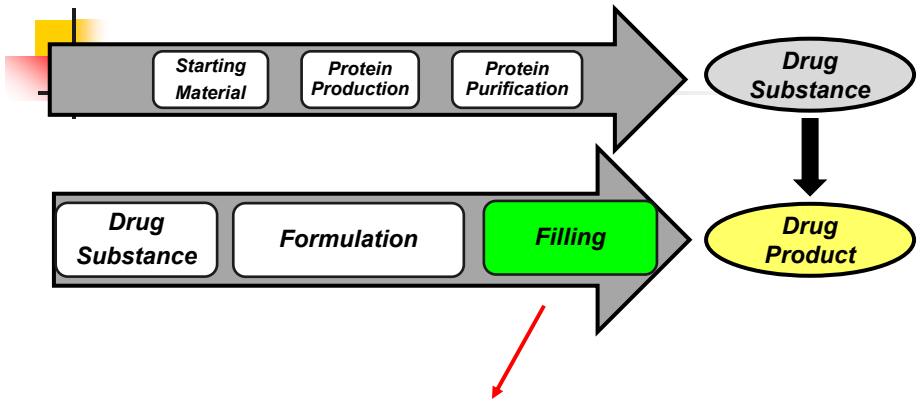
Applied Risk-Management Across the Manufacturing Process



- aseptic processing –critical to do it right
- sterile filtration – not an option
- concern for container closure interactions

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Critical Importance of Aseptic Filling for Biologics

aseptic processing – validated from FIH onwards

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

- Conducting aseptic manipulation in an aseptic workstation (e.g., laminar air flow workbench, biosafety cabinets, or barrier isolator system) under laminar airflow conditions that meet Class A, ISO 5. You should perform all manipulations of sterile products and materials under aseptic conditions.
- Conducting a process simulation using bacterial growth media to demonstrate that the aseptic processing/controls and production environment are capable of producing a sterile drug
-

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

U.S. FOOD & DRUG ADMINISTRATION

Guidance for Industry
CGMP for Phase 1 Investigational Drugs

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

Good reference on how to do Aseptic Process Simulation

PDA

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

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Sterile Filtration of the Formulated Bulk Drug Solution

best practice: 2 x 0.22 µ filters in series

The integrity of the sterilised filter should be verified by testing before use unless specifically justified and validated, and should be verified by on line testing immediately after use. Nominal pore sizes of 0.22 µm or less are acceptable without further justification, in accordance with Ph. Eur.

For routine commercial manufacturing, bioburden testing should be performed on the bulk solution immediately before sterile filtration.

In most situations, a limit of NMT 10 CFU/100 ml (TAMC) would be acceptable for bioburden testing. If a pre-filter is added as a precaution only and not because the unfiltered bulk solution has a higher bioburden, this limit is applicable also before the pre-filter and is strongly recommended from a GMP point of view. A bioburden limit of higher than 10 CFU/100 ml before pre-filtration may be acceptable if this is due to starting material known to have inherent microbial contamination. In such cases, it should be demonstrated that the first filter is capable of achieving a bioburden of NMT 10 CFU/100 ml prior to the last filtration. Bioburden should be tested in a bulk sample of 100 ml in order to ensure the sensitivity of the method. Other testing regimes to control bioburden at the defined level should be justified.

The maximum time between the start of bulk solution preparation and sterile filtration should be stated, minimised and appropriately supported by data. Filtration times longer than 24 hours should be justified.

Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container

6 March 2019
EMA/CHMP/CVMP/QWP/850374/2015

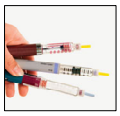
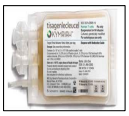
135

Container Closures for Biologicals

heightened concern 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, recombinant)***

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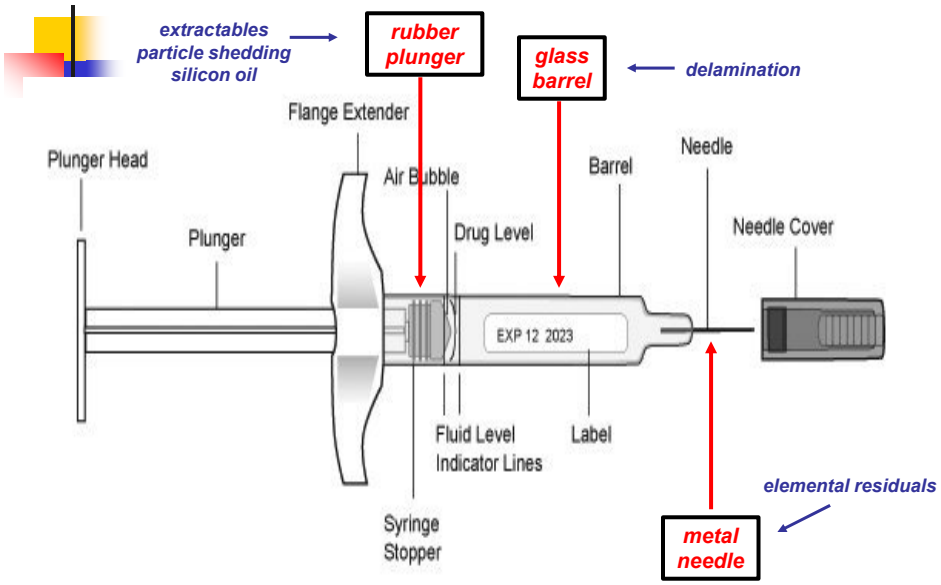
Product-contact surfaces of the container closures



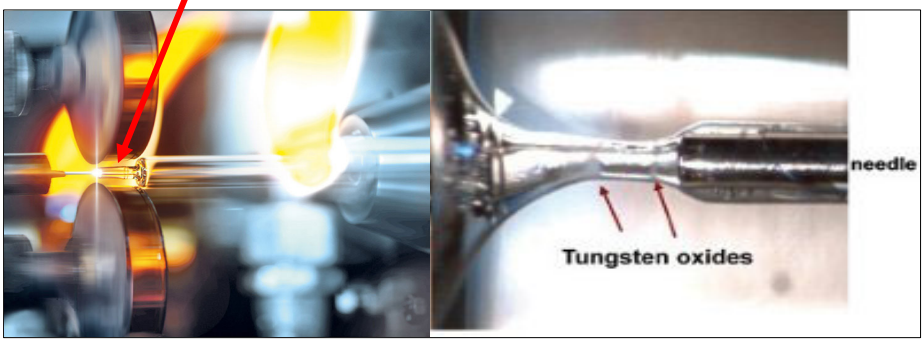
137

Impact of container closure on biologic!

Pre-filled Syringes – discovery of tungsten oxide residuals

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

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



PDA J Pharm Sci and Tech **2013**, *67* 670-679
Access the most recent version at doi:10.5731/pdajpst.2013.00941
Department of Drug Product Development, Amgen Inc.,

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

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Impact of biologic on container closure!

Glass Vials – discovery of glass delamination

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 every glass vial of Epogen manufactured since 1982!

Patient safety concern

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

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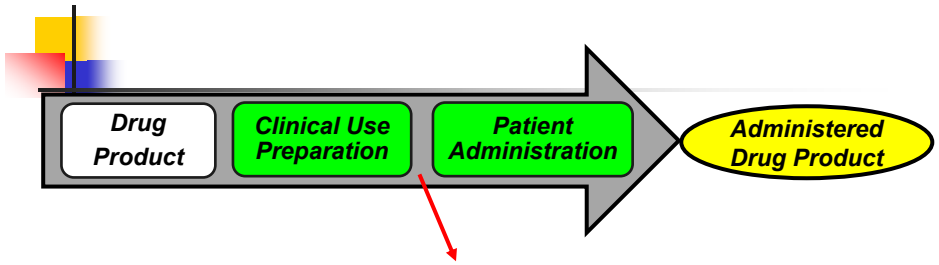
Applied Risk-Management Across the Manufacturing Process



Dilution	Holding Time	Delivery
Compatibility with Diluents Loss due to Surface Contact	Physicochemical Stability Microbial Stability (2-8°C, 25°C)	% Recovery (from vial to vein)

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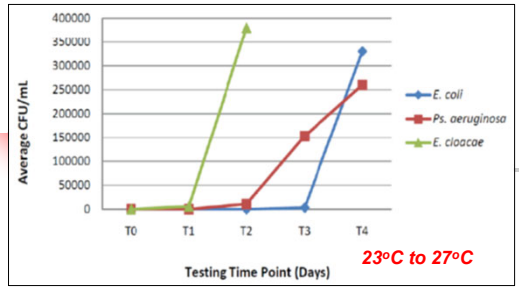
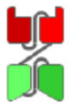


23°C to 27°C

BLINCYTO



Storage times over 4 hours typically must be supported by microbial data!

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

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

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

blinatumomab

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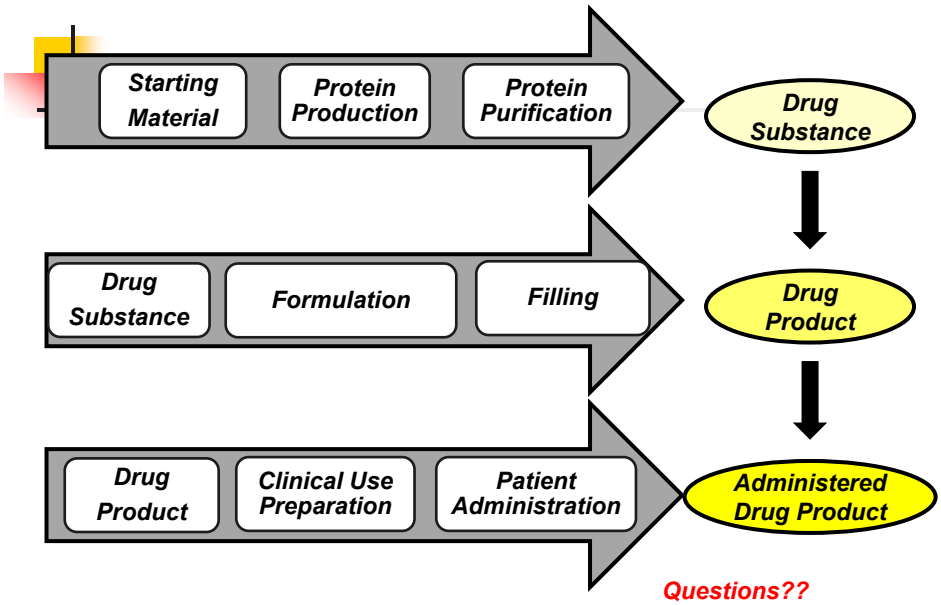
3. *Applied* Risk-Management Across the Manufacturing Process



Questions??

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CMC Regulatory Compliance Strategy for Biopharmaceuticals

Course Outline

4. **Demonstrating Biologic Comparability After Manufacturing Process Changes**

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

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

but <u>every change carries risk</u> that has to be effectively managed!

- ***Improvements in the biological 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 biological product quality***
  - *Improved chromatography to reduce residual impurities*
  - *Higher quality critical raw material to reduce impurities*
  - *Exchange to more sensitive QC analytical techniques (e.g., SDS-PAGE → CE-SDS; IEF → cIEF)*

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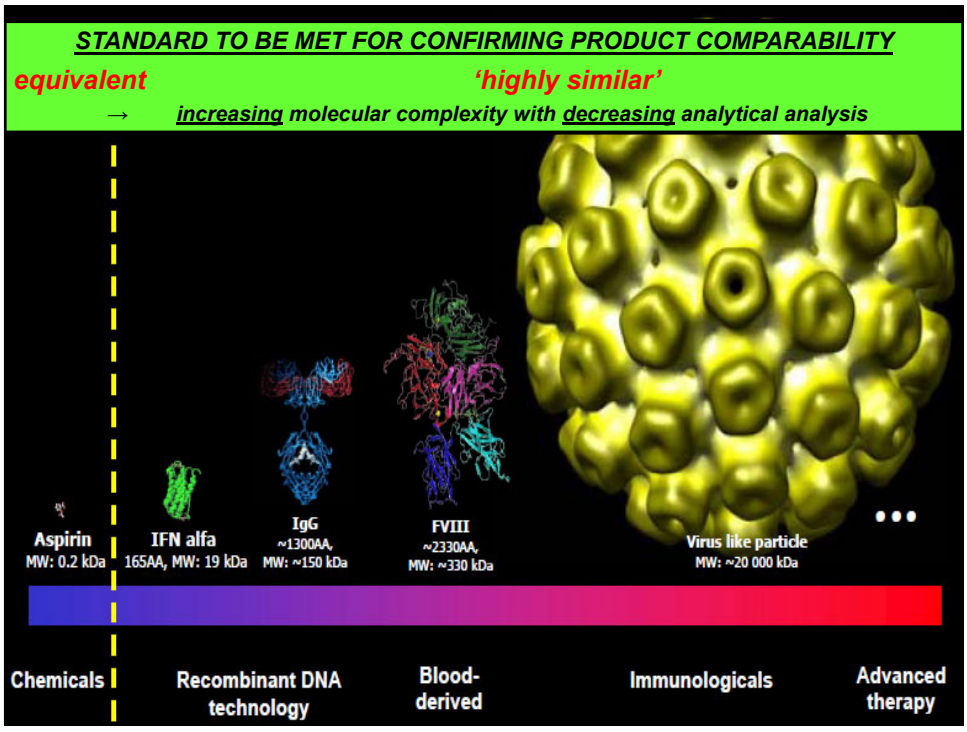
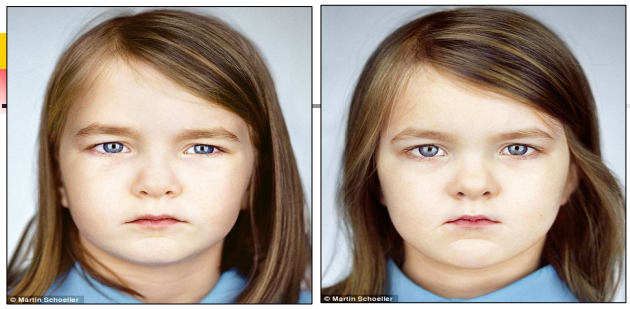


Same standard for ALL biologicals: "highly similar" (ICH Q5E)



'not identical'

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

IS SUBJECTIVE!

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

- ***Particularly challenging for advanced therapy manufacturing***

Questions and answers
Comparability considerations for Advanced Therapy Medicinal Products

6 December 2019
EMA/CAT/499821/2019

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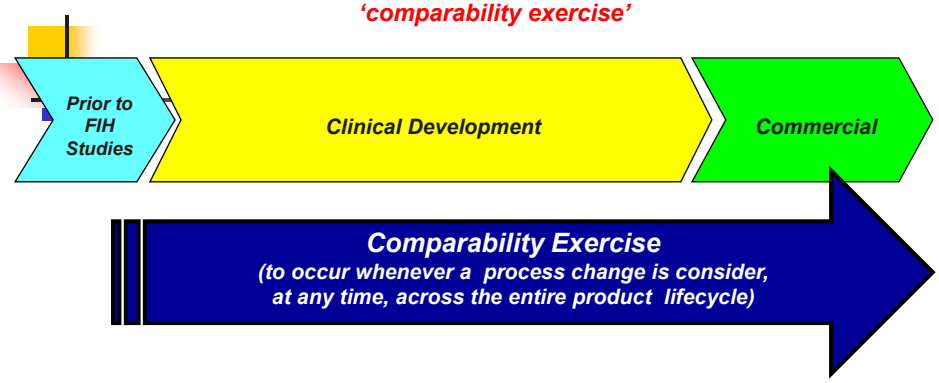
Risk/Benefit assessment due to a manufacturing process change

'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 process change worth the risk to impacting the biological product?

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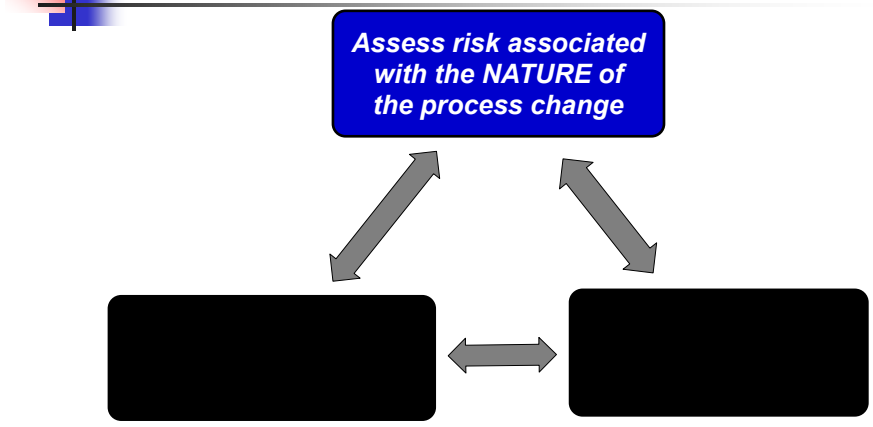
3 key design elements of an effective risk-managed comparability exercise



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Nature of the Process Change

(type of change, location of change, criticality of process step)

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

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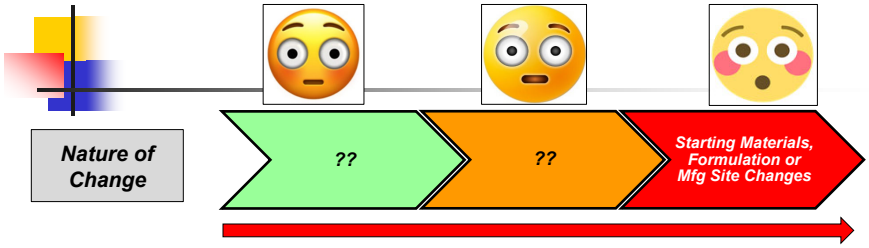
ICH Q5E: A Risk-Based Approach to Product Comparability



increasing risk concern due to the nature of the process change

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

ICH Q5E

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Regulatory authority guidance on assessing risk due to nature of change!

during Clinical Development

Regulatory Authority Perceived Risk Level	Examples of Biologic Process Changes
Substantial Modification (EU NCA prior-approval) Significant (FDA informed by CMC Amendment)	– Addition/replacement of manufacturing site/testing site – Change in source material (e.g., new MCB) – Change in upstream production scale – Addition or removal of a purification step – 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) – Any process change that impacts the impurity profile, microbial contamination, viral safety, or TSE
Non-substantial Modification (EU NCA not reported) Minor (FDA Annual Report)	– Anything that is not significant or non-substantial

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

U.S. FOOD & DRUG ADMINISTRATION

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

24 June 2021
EMA/CHMP/BWP/534898/2008 rev. 2

Ref 1 last page

21 CFR 312.31 and 312.33

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Regulatory authority guidance on assessing risk due to nature of 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

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CAUTION

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

Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products

Food and Drug Administration
Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research
1997

Inclusion	Exclusion
BLAs rproteins mAbs biosimilars	all other BLAs

CMC Postapproval Manufacturing Changes for Specified Biological Products To Be Documented in Annual Reports
Guidance for Industry

Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
2017

Inclusion	Exclusion
BLAs rproteins mAbs biosimilars	all other BLAs

Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products

Food and Drug Administration
Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research
2021

Inclusion	Exclusion
BLAs Advanced Therapy Vaccines	BLAs rproteins mAbs biosimilars

Postapproval Changes to Drug Substances
Guidance for Industry

Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
2018

Inclusion	Exclusion
NDAs ANDAs	all BLAs

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Get the assigned risk level wrong – incur the wrath of the FDA!

ask 3 consultants, get 3 different answers

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

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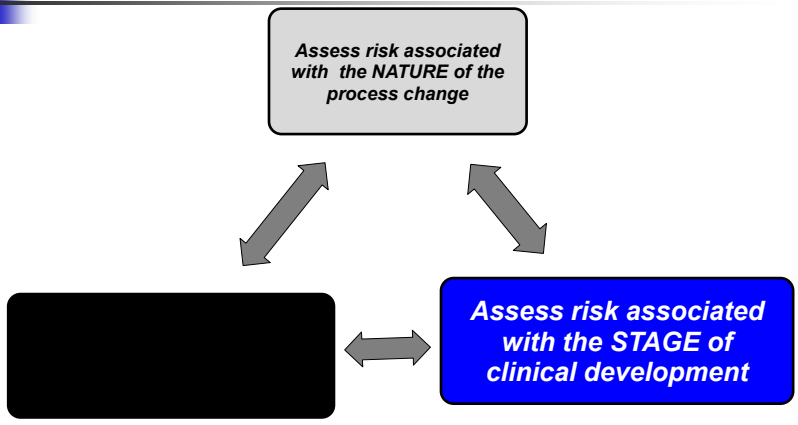
3 key design elements of an effective risk-managed comparability exercise



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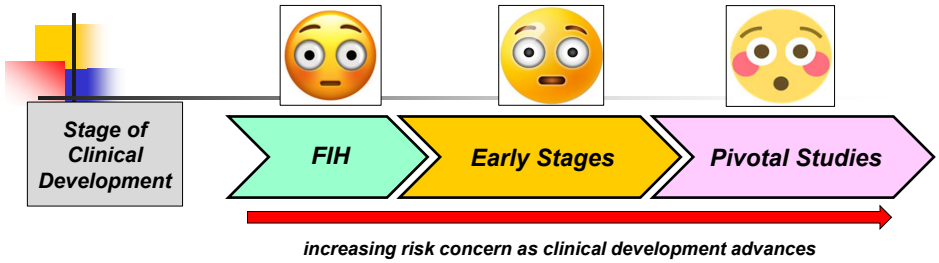
ICH Q5E: A Risk-Based Approach to Product Comparability



Where changes are introduced in development before nonclinical studies, the issue of assessing comparability is not generally raised because the manufacturer subsequently conducts nonclinical and clinical studies using the post-change product as part of the development process. During early phases of nonclinical and clinical studies, comparability testing is generally not as extensive as for an approved product. As knowledge and information accumulate, and the analytical tools develop, the comparability exercise should utilise available information and will generally become more comprehensive. Where process changes are introduced in late stages of development and no additional clinical studies are planned to support the marketing authorisation, the comparability exercise should be as comprehensive and thorough as one conducted for an approved product. Some outcomes of the comparability studies on quality attributes can lead to additional nonclinical or clinical studies. ***ICH Q5E***

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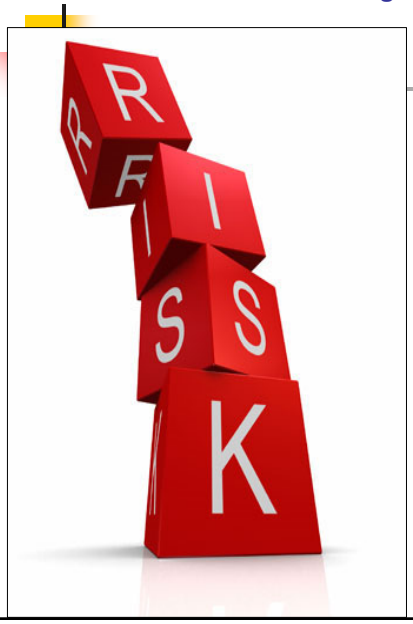
Stage of Clinical Development



- ***Each stage of clinical development carries its own level of potential risk from a manufacturing process change***
- ***Early stage clinical development – lower risk level since biological product used primarily to assess toxicity and potential medical benefit ('adequate comparability')***
- ***Late stage clinical development – higher risk level since biological product used to gather pivotal efficacy and safety data which must meet predefined statistical thresholds ('thorough, comprehensive comparability')***

ICH Q5E

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

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

Suitability of bridging data package between Selexys and Novartis materials

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

Does the Agency agree with this approach?

Selexys based in Oklahoma, USA ***Novartis based in Switzerland***

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MEMORANDUM OF MEETING MINUTES

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

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

FDA Response to Question 7:

Based on the preliminary data provided in the meeting packages, the proposed commercial crizanlizumab product manufactured at Novartis differs from the Selexys material in [redacted] 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.

ADAKVEO® (crizanlizumab-tmca)

FDA market approved November 2019 – manufactured in Switzerland by Novartis

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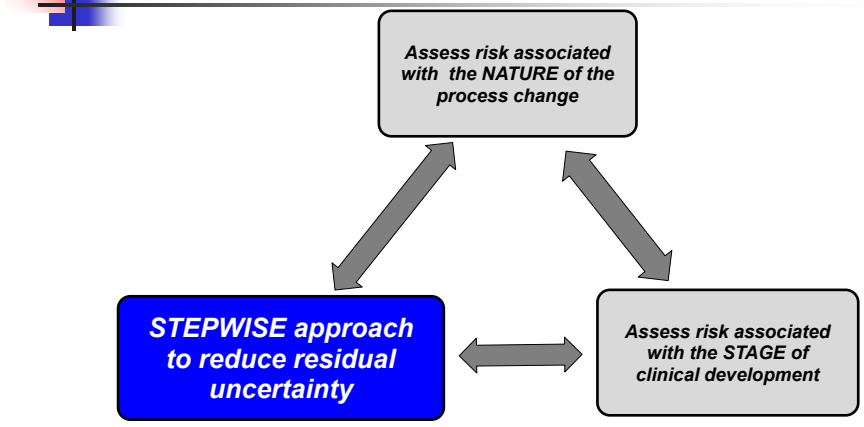
3 key design elements of an effective risk-managed comparability exercise



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ICH Q5E: A Risk-Based Approach to Product Comparability

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

Step 2 (if residual uncertainty remains) animal nonclinical studies

Step 1 – analytical/functional studies

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

ICH Q5E

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Step 1 — Analytical/Functional Studies

Composed of 4 main studies *ICH Q5E*

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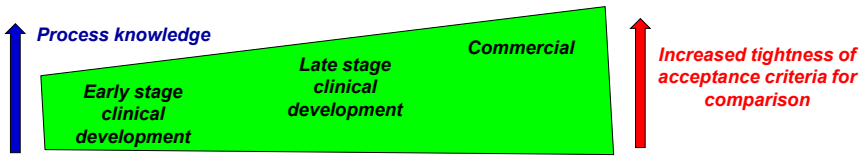
1) Consistency batches (spec comparison before and after change)

as process knowledge increases, this comparison takes on more strength

- ***Specifications … should focus on those molecular and biological characteristics found to be useful in ensuring the safety and efficacy of the product.*** *ICH Q6B*
- ***Acceptance criteria should be established and justified based on data obtained from lots used in preclinical and/or clinical studies, data from lots used for demonstration of manufacturing consistency and data from stability studies, and relevant development data*** *ICH Q6B*
- ***Specifications … should be based on risk to clinical performance, not what can be achieved by process*** *Janet Woodcock (former CDER Director)*



2) Comprehensive physicochemical characterization comparability (for a mAb)

Characterization by LC/MS Monoclonal Antibody 8 min *Waters*

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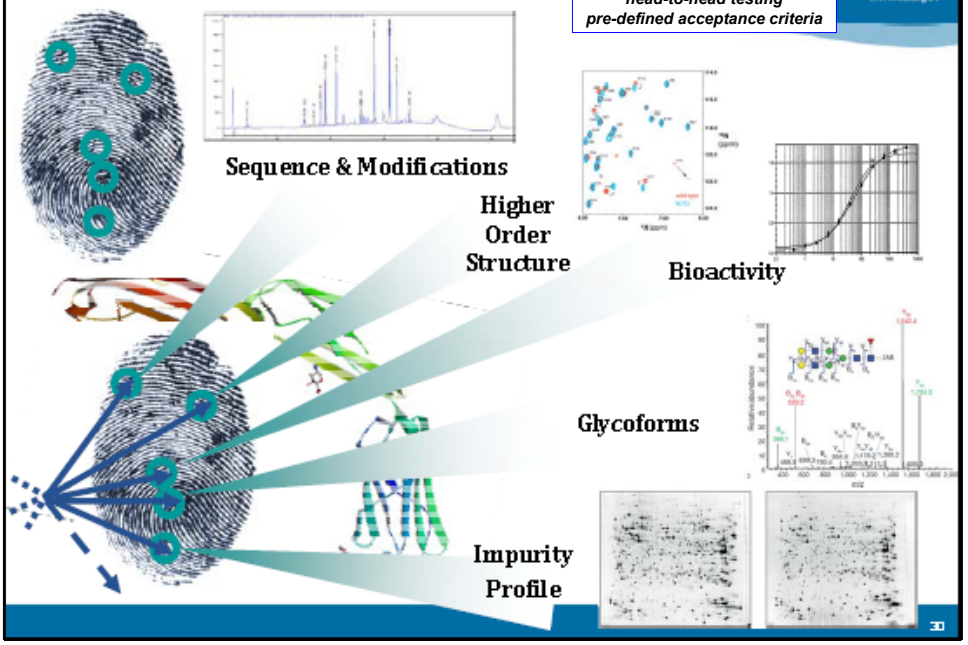
Fingerprinting

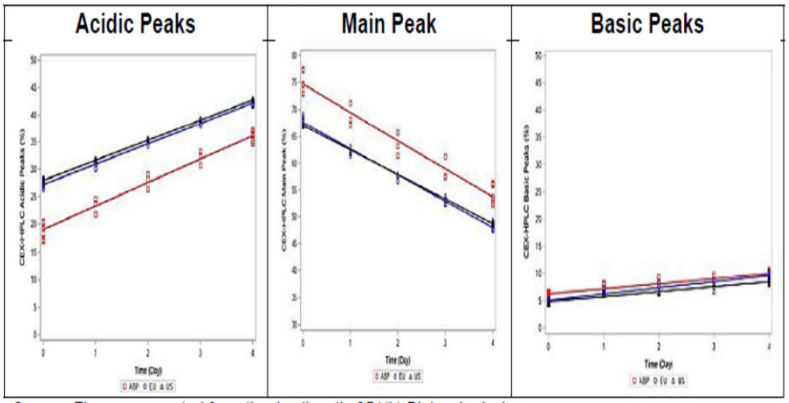
U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

head-to-head testing
pre-defined acceptance criteria



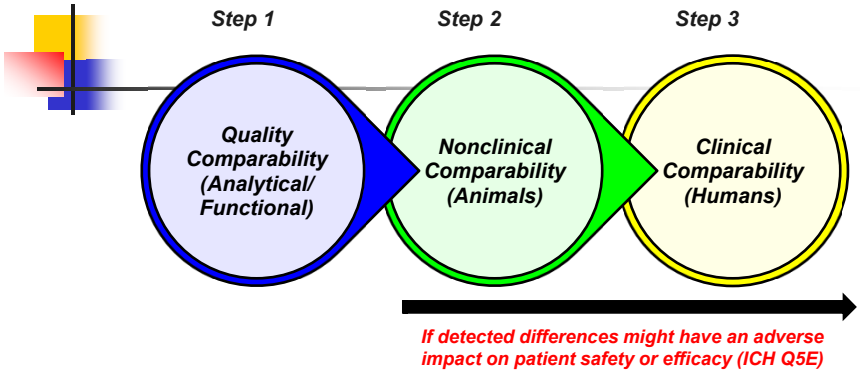
3) ***Accelerated and Stress stability slope comparison (differences in rate of molecular variant change)*** ***pre-defined acceptance criteria***

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

When are Steps 2 and/or 3 necessary for comparability?



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

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

Case Example: EMA MAA Review

EMA – consistency batches only – not sufficient for market approval

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

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

but … full Step 1 added during MAA review

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

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 MAA Review

Process changes to recombinant protein – not Step 1 comparable

After process changes: product is purer and more potent …

Process optimisation from Process 1 (clinical) to Process 2 (commercial) comprises changes in both upstream and downstream process. All performed process changes have been explained and sufficiently assessed with regard to their impact on the product quality.

Comparability of Processes

Besides an initial comparability study comprising comparative analytical testing, comparative characterisation and stability studies, an additional, extensive comparability study has been performed at the active substance level. The studies revealed the main difference between Process 1 and Process 2 imlifidase active substances. Commercial Process 2 imlifidase active substance is considerably purer and has a higher biological activity.

Extensive comparability tests have been also performed at the finished product level covering evaluation of the changes in the composition, dosage form and manufacturing. As expected, the finished products of process 1 and process 2 are not fully comparable. The impurity profile with respect to the inactive variant is different and the biological activities are not comparable.

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… but Step 2 and 3 were comparable

In summary, due to the observed differences at quality level, that process 2 material is purer and 2-times more potent than process 1 material, an impact on safety and efficacy profile could not be excluded. Additional toxicological studies demonstrate comparability between process 1 and process 2 imlifidase. *In vitro* PD data and results of a new PK/PD study using process 2 material show that IgG degradation *in vitro* (using human plasma) and *in vivo* is largely comparable. Because of these findings and due to the fact that imlifidase is highly specific for degrading IgG and no off-target effects have been identified or can be expected, it is concluded that the clinical performance of the products from two different processes is expected to be similar.

Idefirix imlifidase
expressed in *E. coli* as a recombinant protein

13 July 2020
EMA/372587/2020 Rev 1

Hansa Biopharma

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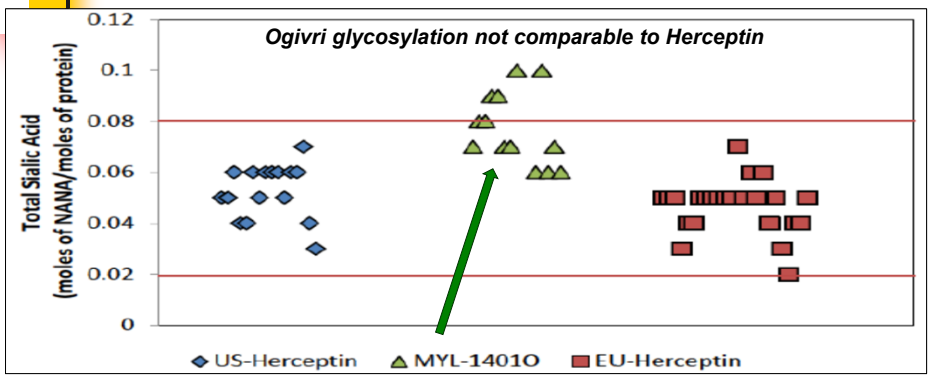
Case Example: FDA Biosimilar BLA Review

residual uncertainly about glycosylation differences (Step 1) 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

Mylan

2017 FDA Advisory Committee Meeting

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Demonstrating '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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CMC Regulatory Compliance Strategy for Biopharmaceuticals

Prior to FIH Studies → ***Clinical Development Phases Phases 1-3 or expedited*** → ***Commercial***

Course Overall Outline

- ✓ ***CMC Regulatory Compliance is Challenging for Biopharmaceuticals***
  - ***Increasing diversity of biologics matched with regulatory authority systems (FDA/EMA) in place to control these evolving manufacturing processes and products***
- ✓ ***Risk-Managed CMC Regulatory Compliance Strategy***
  - ***3 interactive components in place to protect patients; the 'minimum CMC regulatory compliance continuum' is most important for biopharmaceuticals***
- ✓ ***Applied Risk-Managed CMC Regulatory Compliance Strategy***
  - ***A risk-based CMC strategy can be applied across the manufacturing process from starting materials → production → purification → formulation → drug product → administered drug product***
- ✓ ***Demonstrating Comparability After Manufacturing Process Changes***
  - ***3 key design elements for an effective risk-managed comparability exercise***

Thank You!

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