Caution

FDA: '3 Run Rule' is Gone!

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

No. ***Neither the CGMP regulations nor FDA policy specifies a minimum number of batches to validate a manufacturing process. The current industry guidance on APIs (see ICH Q7A for APIs) also does not specify a specific number of batches for process validation. FDA recognizes that validating a manufacturing process, or a change to a process, cannot be reduced to so simplistic a formula as the completion of three successful full scale batches.***

The manufacturer is expected to have a sound rationale for its choices in this regard. The agency encourages the use of science based approaches to process validation."

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

ICH: '3 Run Rule' is Gone!

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

ICH Q11

So how many consecutive production batches will your company run for your biologic process validation studies?

***Timing* for completion of process validation**

***MAJOR* difference between chemical drugs and biologics!**

Process validation can include the collection and evaluation of data, from the process design stage throughout production, that establish scientific evidence that a process is capable of consistently delivering a quality drug substance.

The drug substance manufacturing process should be validated before commercial distribution of resulting drug product. For biotechnological processes, or for aseptic processing and sterilisation process steps for drug substances, the data provided in support of process validation is included as part of the marketing application (3.2.S.2.5). For non-sterile chemical entity drug substance processes, results of process validation studies are not normally included in the dossier.

ICH Q11

Biologics – *Process validation must be completed with results reported in the submitted market application dossier!*

Validation Studies for the Cell Growth and Harvesting Process.

A description and documentation of the validation studies which identify critical parameters to be used as in-process controls, to ensure the success of routine production should be submitted. Reference may be made to the flow diagram(s) as appropriate.

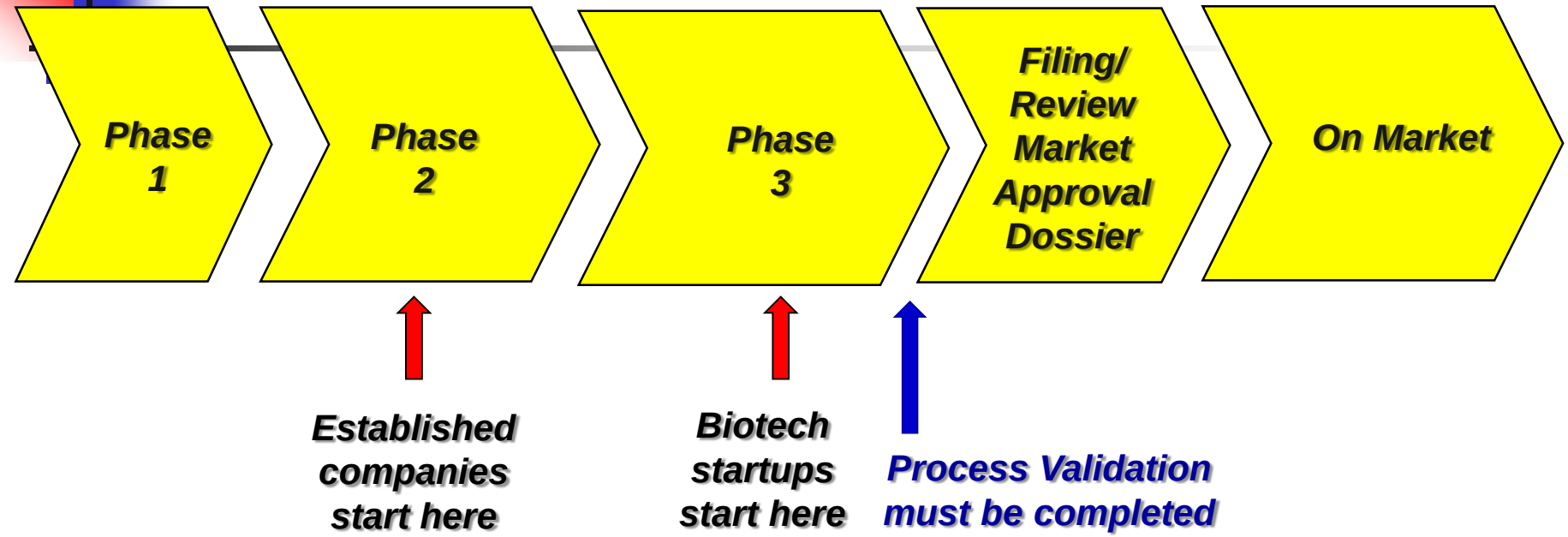
Validation Studies for the Purification Process.

A description and documentation of the validation of the purification process to demonstrate adequate removal of extraneous substances such as chemicals used for purification, column contaminants, endotoxin, antibiotics, residual host proteins, DNA, and viruses, where appropriate, should be provided. (See

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

Center for Biologics Evaluation and Research (CBER)
Center for Drug Evaluation and Research (CDER)
August 1996

Timing differences for starting biologic process validation!



Earlier Process Validation Start

Pro – Once burnt, never again!

Con – Investment in $$ and resources for validation may either need to be repeated if the process changes or lost if the product fails clinical

Later Process Validation

Pro – Conserved $$ and resources for validation at later date

Con – Risk of surprises during process validation, and possible product approval delays

Biologic process validation missteps!

3 Case Examples

- **Recombinant protein produced by CHO cells**
  - Incomplete process validation was submitted – resulted in a Complete Response Letter (CRL) and a delay of 18 months in FDA market approval
- **Monoclonal antibody produced by CHO cells**
  - The submitted process validation was insufficient and lacked validation protocols and reports – resulted in a 'major' amendment and added 3 months onto FDA review
- **Genetically engineered CAR T-cells**
  - Did not follow process validation guidance provided by the FDA during the pre-BLA meeting – repeated PV, no delay in market approval

FDA review of Andexxa (recombinant Factor Xa)

CHO produced recombinant protein

We acknowledge that ANDEXAA is a breakthrough therapy developed for an indication that addresses an urgent unmet medical need. As such, FDA is committed to working with Portola to advance your manufacturing program…The data you provided in your responses to the Form FDA 483 issued on do not adequately address the deficiencies in the validation of the ANDEXXA manufacturing process that were identified during the Pre-License Inspection (PLI) of the facility. The ANDEXXA process is not validated to assure reasonable control of sources of variability that could affect production output and to assure that the process is capable of consistently delivering a product of well-defined quality… Complete the validation studies for the clearance of all impurities and submit the final study reports to demonstrate identification and control of these impurities. This is needed to assure process consistency and establish a process control strategy which will ensure the quality of the commercially manufactured product… Please note that impurity clearance studies are considered critical to the process qualification stage of process validation (reference is made to the 2011 FDA Guidance on Process Validation) and therefore prior to submission to FDA these studies should be reviewed and approved by your quality assurance unit to document the use of sound scientific methodology and principles with adequate data to support the conclusions.

BLA submitted Dec 2015; CRL Aug 2016; FDA market approval May 2018

FDA review of Cosentyx (secukinumab)

CHO produced monoclonal antibody

Novartis

BLA submitted October 2013

FDA CMC Review

This BLA initially included little information regarding control of the manufacturing process. For example, non-critical attributes and key operating parameters were not included, it appeared that in-process limits could be changed without notification, development of the drug substance manufacturing process was not described and no data were provided, insufficient validation data were provided, validation protocols for (b) (4) were not included, and insufficient information regarding (b) (4) was provided, which could affect the acceptability of some aspects of the control strategy. In addition, critical quality attributes (CQAs) were not specifically identified.

CMC data that needed to be provided resulted in a 'major' amendment, extending the review timetable by 3 months

FDA market approved January 2015

FDA review of Kymriah (CAR T-Cells)
Genetically engineered cells

Novartis ***FDA Mid-Cycle Meeting*** ***May 2017***

Manufacturing process validation for Tisagenlecleucel - Based on the ongoing CMC review and results of the PLI at the Morris Plains NJ manufacturing facility, the following major CMC issues need to be resolved for approval of the BLA.

a. The product lots used for the process validation studies were manufactured before the validation protocol was formally approved by the Novartis quality unit and before the commercial process was established. This was not a prospectively designed validation study and is inconsistent with what FDA recommended during the pre-BLA meeting discussion.

b. Clinical batch records rather than commercial batch records were used for manufacture of lots used in the process validation study. FDA notes that there were multiple differences between the clinical batch record used at the time of the PV and the proposed commercial batch records.

c. Novartis did not run any batches with leukapheresis materials that contained high levels of monocytes as advised by the FDA during the pre-BLA discussion.

d. FDA questioned the acceptance criteria for critical process parameters (CPP) and key process parameters (KPP) used in the process performance qualification (PPQ) studies. Some of the CPP and KPP ranges are quite wide, and were based on data not submitted in the BLA. These ranges are sufficiently broad such that they would not help define a validated and controlled commercial manufacturing process. During the discussion with Novartis during the inspection, the FDA recommended that the acceptable ranges for CPPs and KPPs should be revised to reflect the accumulated manufacturing data and experience. FDA indicated that a simple 3 times the standard deviation may not be a suitable approach given the wide ranges of the available data.

e. Some unit operation holding times were not defined (e.g. (b) (4) , volume reduction, beads wash).

Novartis repeated process validation – no delay in market approval (August 2017)

Question

Can a biopharmaceutical manufacturing process be considered 'validated' if 1 manufacturing process step is out of control?

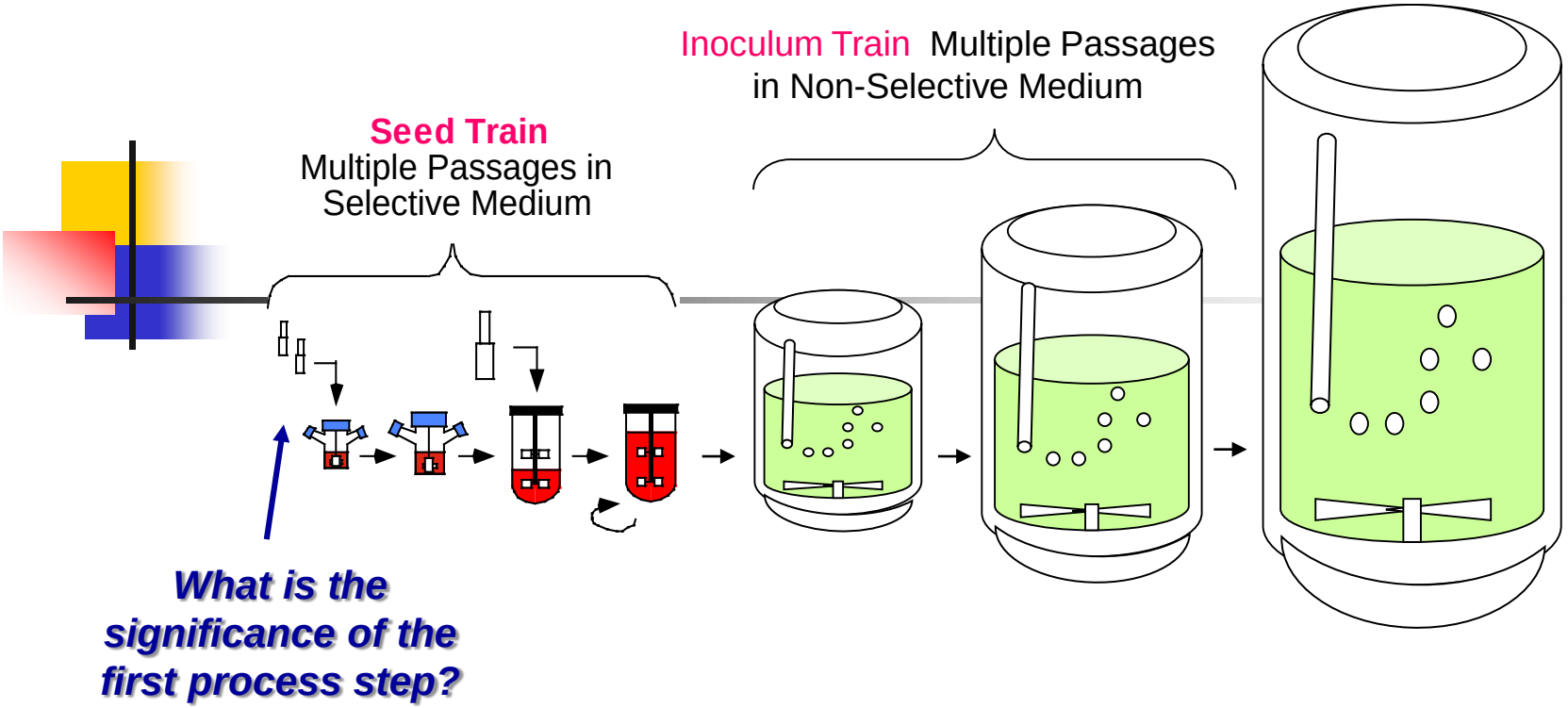
FDA CMC Experts say 'NO!"

Kathryn King (Traditional Elements Reviewer)
Laurie Graham (Quality by Design Reviewer)

Concerns about the validation of the manufacturing process, discovered during the pre-approval inspection of the DS manufacture

Genentech **PERJETA™ (pertuzumab)**

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



Summary Review for Regulatory Action

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

CHEMISTRY REVIEW(S)

The Division of Monoclonal Antibodies (DMA), Office of Biotechnology Products, OPS, CDER, does not currently recommend approval of STN 125409 for Pertuzumab manufactured by Genentech. The data submitted in this application are inadequate to support the conclusion that the manufacture of Pertuzumab is well controlled and consistently leads to a product that is pure and potent.

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.

Last minute FDA higher up intervention – Telecon June 07, 2012, one day before PDUFA clock and market approval

Genentech

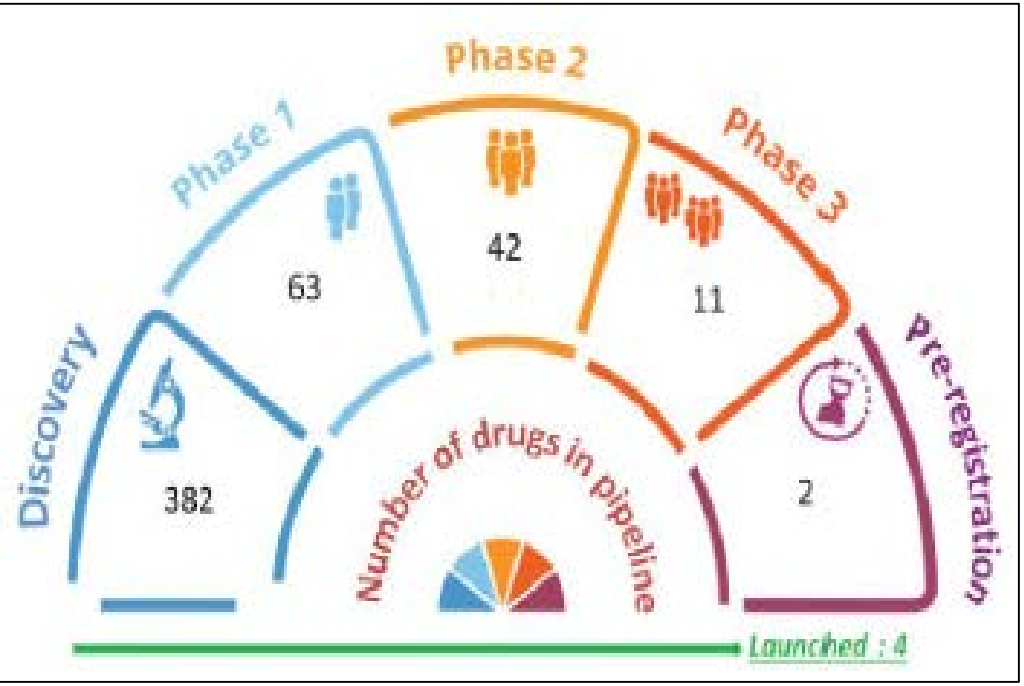
Josephine, Ing, Sr. Scientist, Regulatory Affairs
Mark "Kip" Benyunes, Senior Group Medical Director, Product Development Oncology Clinical Science
Dietmar Berger, Vice President, Clinical Development, Hematology/Oncology
Ian Clark, Chief Executive Officer, Genentech and Head of North American Commercial Operations
Michael Doherty, Senior Vice President, Global Head Product Development Regulatory
Liz Homans, Vice President, HER2 Franchise, Global Product Strategy
Sandra Horning, Senior Vice President, Global Head Clinical Development Hematology/Oncology
Josephine Ing, Regulatory Program Director, Product Development Regulatory
Karen Jones, Global Head Oncology, Product Development Regulatory
Lynne Krummen, Senior Director, Pharma Technical Regulatory
Theresa Martinez, Lifecycle Leader, Global Product Strategy
Teresa Perney, Director, Product Development Regulatory
Michelle Rohrer, Vice President, US Regulatory Affairs, Product Development Regulatory
Mary Sliwkowski, Vice President, Regulatory Chemistry Manufacturing and Controls and Information Systems
Pascal Soriot, Chief Operating Officer, Roche Pharmaceuticals Division
Patrick Yang, Executive Vice President, Head Global Technical Operations

FDA

Janet Woodcock, Director, CDER
Richard Pazdur, Director, OHOP *(Office of Hematology/ Oncology Products)*
Robert Justice, Director, DOP1 *(Division of Oncology Products)*
Amna Ibrahim, Deputy Director, DOP1
Patricia Cortazar, Clinical Team Leader
Gideon Blumenthal, Clinical Reviewer
Nancy Scher, Clinical Reviewer (Safety)
Kathryn Fedenko, Deputy Director Safety
Denise Esposito, Deputy Director, ORP
Maryll Toufanian, Associate Chief Counsel for Drugs, OCC
David Joy, Regulatory Counsel, ORP/DRPI
Elizabeth Giaquinto, Project Manager, OEP
Mary Beth Clarke, Acting Director, OEP *(Office of Pharmaceutical Science)*
Helen Winkle, Director, OPS
Steven Kozlowski, Director, OPB *(Office of Biotechnology Products)*
Patrick Swann, Deputy Division Director, DMA
Kathryn King, Biologist, DMA
Patricia Hughes, Team Leader, Microbiology Product Quality, OC/OMPQ/BMAB
Bo Chi, Ph.D., CMC Microbiology Reviewer, OC/OMPQ/DGMPA/BMAB
Steven Lynn, Director (Acting), OMPQ
Ilisa Bernstein, Deputy Director, OC
Tara Gooen, LCDR, Acting Chief, OC/OMPQ/DGMPA
Mahesh Ramanadham, LT., Acting Team Leader, OC/OMPQ/DGMPA
Tamy Kim, Associate Director of Regulatory Affairs (Acting), IO/OHOP
Alice Kacuba, Chief Project Management Staff, DOP1
Amy Tilley, Regulatory Project Manager, DOP1

Conjugating the produced and purified biopharmaceutical API

Antibody	**Linker**	**PEG**
Antibody	**Linker**	**Radiolabel**
Antibody	**Linker**	**Chemical Drug**



Antibody-Drug Conjugates (ADCs)

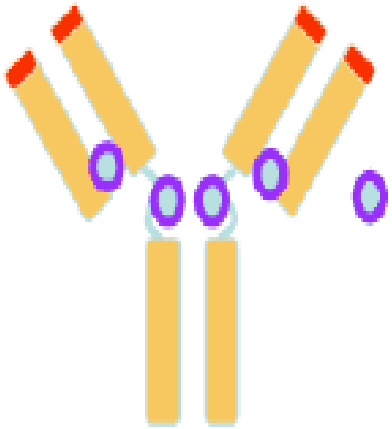
Pharmaceutical Outsourcing
September/October 2018

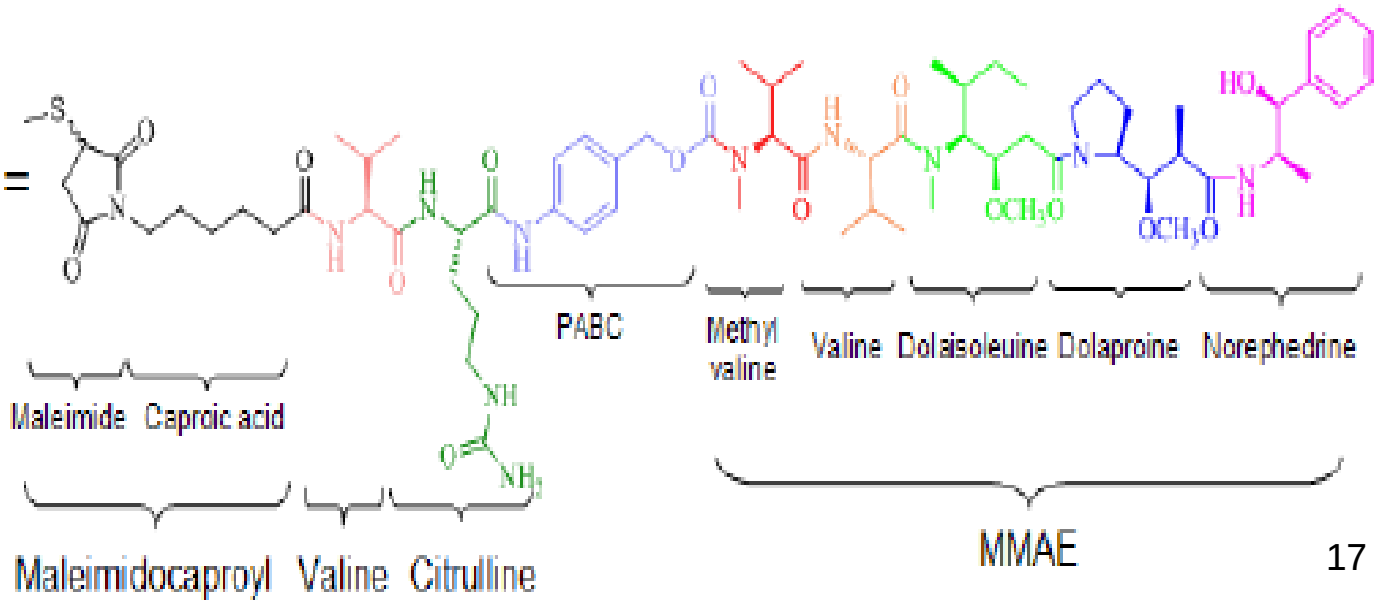
Illustration of a commercial Antibody-Drug Conjugate (ADC)

ADCETRIS (brentuximab vedotin)

Antibody	***Linker***		***Chemical Drug***
cAC10 anti-CD30 antibody	Attachment group	Protease-cleavable linker	MMAE cytotoxic drug

(~ 4 MMAE molecules/mAb molecule)





Increased complexity with ADCs

1) ADCs require addressing BIOLOGIC mAb CMC concerns

- API becomes a starting material

2) ADCs require addressing CHEMICAL DRUG CMC concerns

- Manufacture of highly cytotoxic chemical drugs (toxins)
  - Worker safety
  - Residual organic solvents (ICH Q3C)
  - Residual elemental impurities (ICH Q3D)
  - Mutagenic impurities (ICH M7)
- Both the toxin and the chemical linker need to be manufactured and tested under appropriate and adequate GMP-like control
- Typically, the toxin and chemical linker are chemically combined before attachment to the mAb; it becomes the second starting material

***TOXINS* currently incorporated into commercial ADCs**

Calicheamicin

MYLOTARG
BESPONSA

- Most potent naturally occurring hydrophobic antibiotic cytotoxin
  - Approximately 1000-fold more active than doxorubicin against xenograft tumors
- Binds to the minor groove in DNA, resulting in double stranded DNA breakage and cell death

Maytansine

KADCYLA

- Potent anti-mitotic macrolide with clinical activity in broad range of tumors
  - Synthetic maytansine analogs, DM1 and DM4
- Inhibits mitosis by interfering with microtubule assembly

Auristatin

ADCETRIS

- Highly potent fully synthetic analog of natural product, dolastatin-10
  - MMAE (membrane permeable)
  - MMAF (membrane impermeable)
- Inhibits mitosis by interfering with microtubule assembly

Duocarmycin

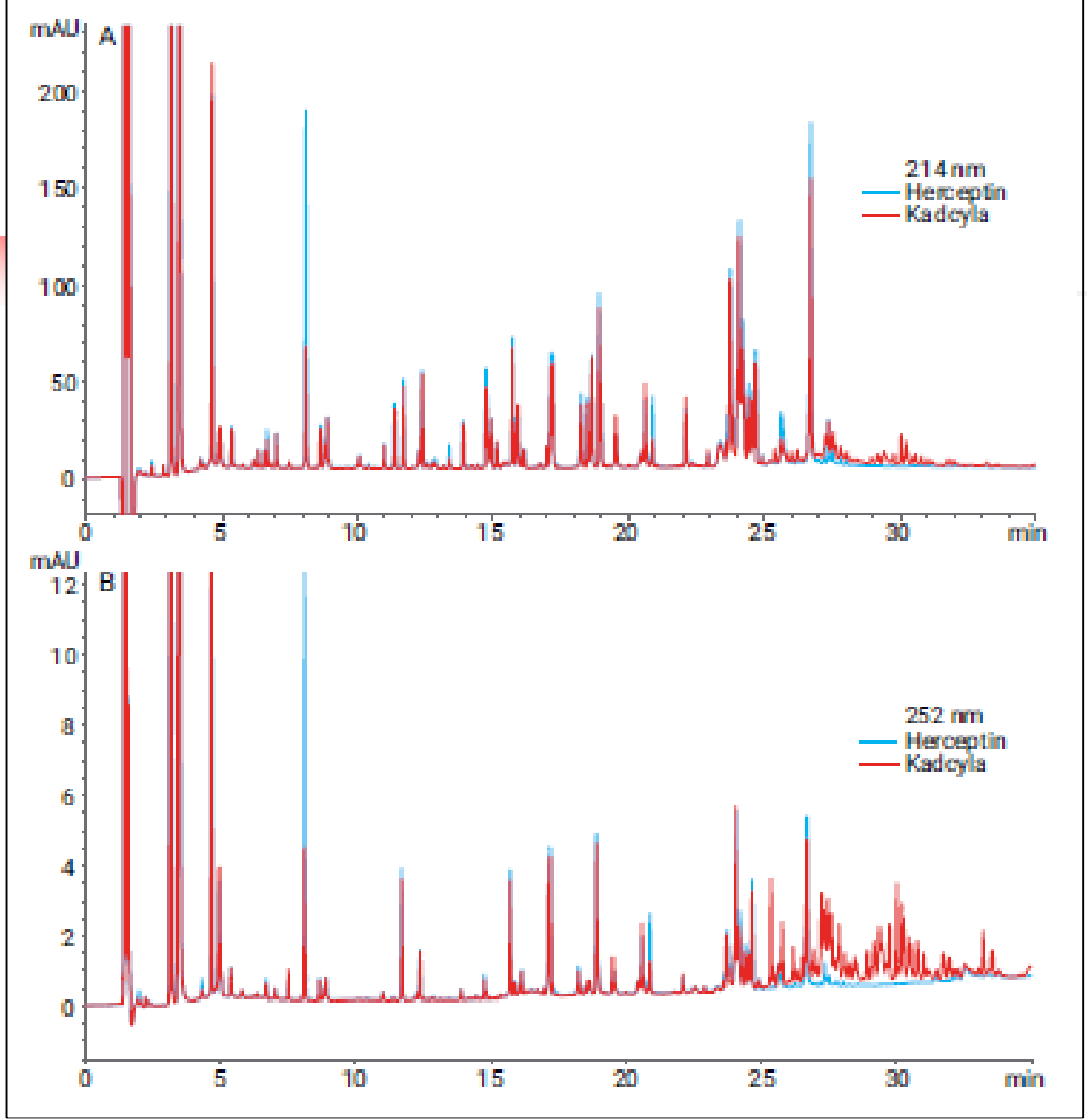
- DNA alkylating agent, picomolar activity
- Binds to DNA minor groove, resulting in DNA alkylation and cell death

Pyrrolobenzodiazepine (PBD)

- Class of naturally occurring anti-tumor antibiotic found in Streptomyces, sub-nano/picomolar activity
- Binds to DNA minor groove, PBD dimers cross-link opposing DNA strands producing highly lethal lesions

3) ADCs require addressing ADC CMC concerns

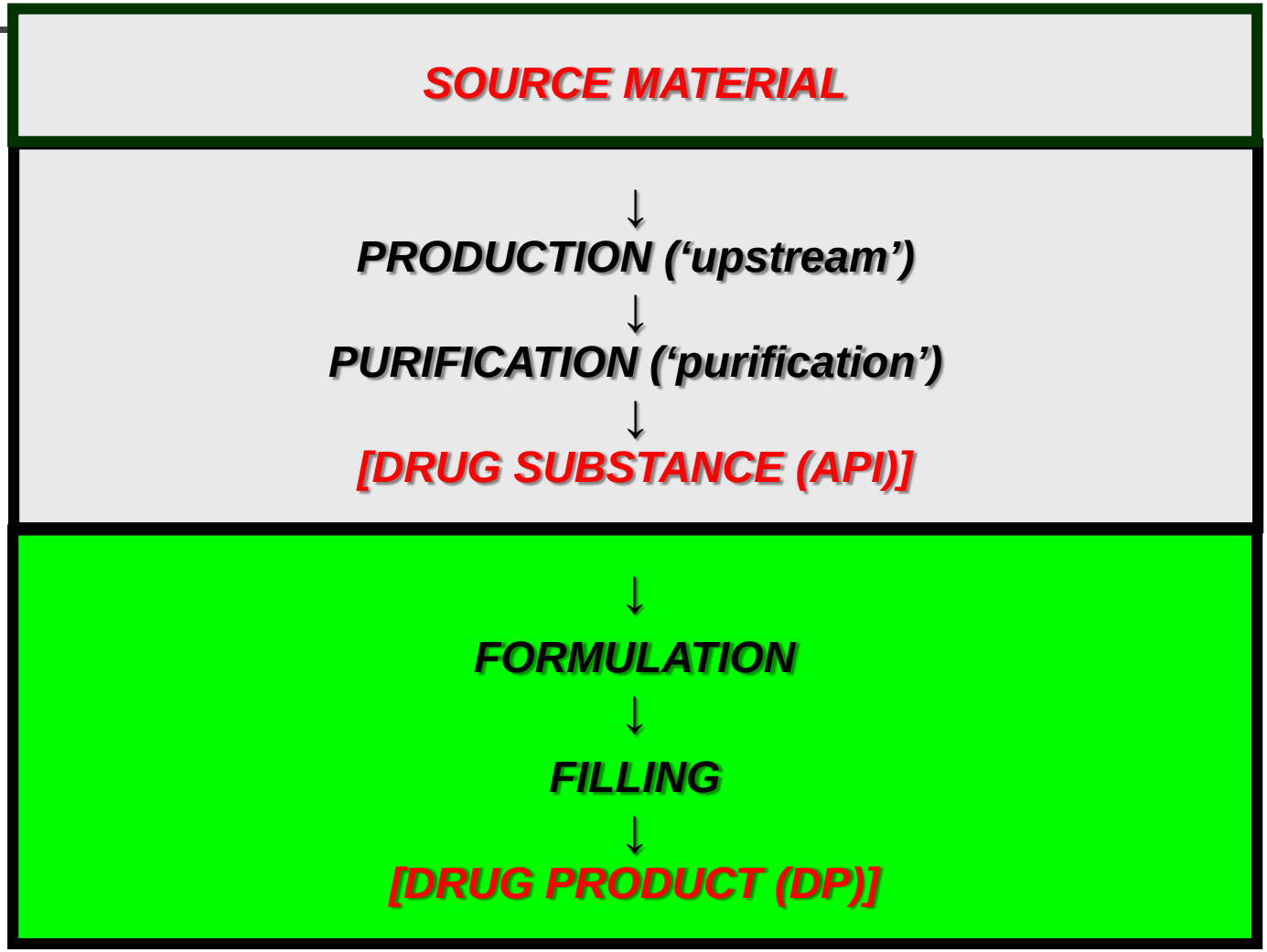
- **Assuring ADC lot-to-lot manufacturing consistency**
  - **Adequate and appropriate control of the chemical reaction conjugation process ensuring consistency of the number of toxin molecules per mAb molecule**
  - **Residual free toxin (and unconjugated mAb)**
- **Assuring ADC lot-to-lot stability**
  - **Linker instability (e.g., hydrolysis)**
  - **Toxin instability (e.g., oxidation)**
  - **mAb instability (e.g., aggregation)**



Increased peptide complexity after conjugation

Basic Manufacturing Process Flow Diagram

Application of CMC Risk-Managed Control Strategy



Comparison of drug product manufacturing for biopharmaceuticals

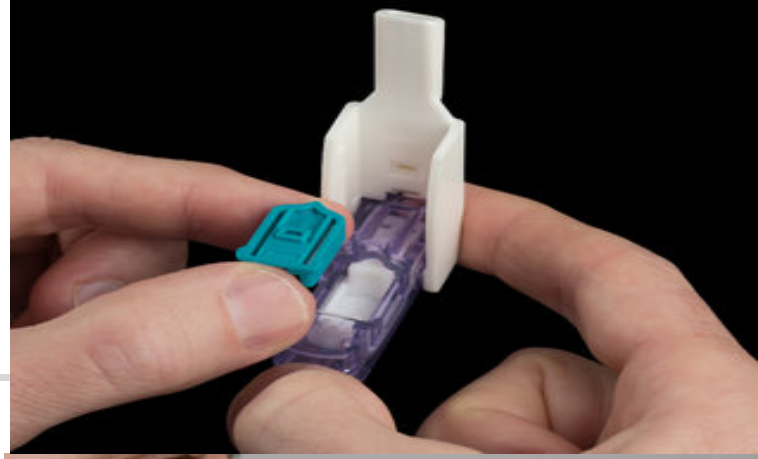
	Recombinant Protein/ Monoclonal Antibody	Genetically Engineered Virus	Genetically Engineered Cell
API	Purified protein ↓ [possible chemical modification]	Purified Virus	Washed Cells
↓ Formulation	Addition of selected excipients	Addition of selected excipients	Addition of selected excipients
↓ Sterilization	Sterile filtration	Sterile filtration	
↓ Aseptic Filling into Container Closure Units	Aseptic filling into chosen container closure unit (typically, glass vials or prefilled syringes) ↓ DP	Aseptic filling into chosen container closure unit (glass vials) ↓ DP	Aseptic filling into chosen container closure unit (plastic patient bags) ↓ DP

Biologics are formulated with excipients

but every excipient present needs to be justified

- ***Minimization of molecular variant formation***
- ***Stability of bioactivity/functionality***
- ***Solubility of product***
- ***Bulking agent (if lyophilized)***
- ***Cryoprotectant (if frozen)***
- ***Antimicrobial preservative***
- ***….***

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



Novel Excipient in Afrezza

Human Insulin formulated with FDKP

Central to the functionality of Afrezza is the excipient fumaryl diketopiperazine (FDKP)

FDKP imparted the critical 0.5-5.8 micron particle size for inhalation

Anything bigger than that impacts in the back of the throat
Anything smaller than that is exhaled

FDKP treated as a novel excipient: 2 yr tox study!

Illustration of the required formulation development studies required for market approval

22 June 2017
EMA/CHMP/559383/2017

Formulation development

In the developmental stage, formulation development studies were performed to confirm the effects of pH, buffer, excipient, and protein concentration on the stability of Imraldi finished product. The formulation development studies and the results were presented. From the results of the developmental studies above, the following conclusions were drawn for optimised Imraldi formulation. Finished product formulation robustness study was done to assess the formulation robustness of Imraldi finished product with variation of protein concentration, pH, L-histidine concentration and sorbitol concentration. Additionally, optimal formulation composition range was identified through this study. Results of the developmental robustness study showed that the Imraldi finished product formulation is robust within range of protein concentration, pH, and L-histidine concentration. The overall results of the formulation robustness study indicate that the formulation may be sufficiently robust at the proposed storage conditions, and that the protein concentration and pH are important factors to ensure acceptable quality of the finished product throughout the shelf-life.

Study done on same formulation as Humira

Commercial biologic formulations are being successfully changed!

Case Example of Market Approved Biologic

(Rituxan/MabThera monoclonal antibody)

Original IV formulation: 10 mg/mL rituximab in sodium chloride, sodium citrate and polysorbate 80

↓

New SC formulation: 120 mg/mL rituximab in L-histidine/ histidine hydrochloride, trehalose, polysorbate 80, L-methionine, and recombinant human hyaluronidase

Case Examples of Market Approved Biosimilars

Sandoz's biosimilar of Neupogen (G-CSF): Changed to glutamate buffer (pH 4.4) in place of acetate buffer (pH 4.0) used by Amgen

Sandoz's biosimilar of Enbrel (anti-TNF): Changed to citrate buffer in place of phosphate buffer used by Amgen

But not all commercial biologic formulation changes are successful!

Dash of EDTA!

- ***Leukine (rh GM-CSF) was originally approved by the FDA in 1991 for Immunex; Immunex also developed a liquid formulation which the FDA approved in 1995 [I was VP Q at the time]***
  - ***Leukine was then passed from company to company when Amgen purchased Immunex, but didn't want Leukine***
- ***In 2006, Bayer, the new owner of Leukine, received FDA approval to add a 'touch' of EDTA to the liquid formulation***
  - ***"EDTA, a chelating agent, approved by the FDA as a preservative in vitamins and baby food, traps metal impurities and thereby extends the shelf life of organic products — making it a logical adjunct to a protein based therapeutic such as Leukine."***

- ***But only 2 years later, in January 2008, Bayer voluntarily withdrew liquid Leukine after post-marketing safety reports indicated an upward trend in adverse events, in particular, that of syncope (fainting)***

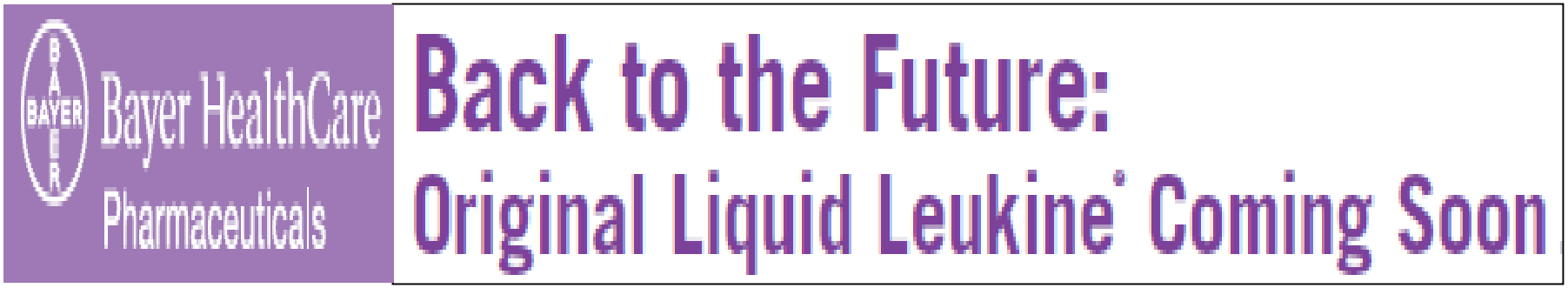
- ***Investigation revealed:***
  - ***"The addition of EDTA appears to increase the absorption rate of GM-CSF, the active ingredient in Leukine, and may result in a temporary increase in plasma concentration of GM-CSF shortly after administration"***

Sometimes it can take months or years in commercial use, before a change in an adverse event profile can be confirmed

(This is the reason why regulatory authorities consider biologic formulation changes to be a 'high risk')

- ***Took Bayer 5 months to take EDTA back out of the liquid formulation – May 2008***
  - ***"FDA has approved Bayer's reintroduction of a formulation of liquid Leukine (sargramostim) that does not contain EDTA"***

A+ to their Marketing Department:



Container Closure

Biologics are typically, but not exclusively, delivered parenterally (i.e., by injection)

Parenteral

- ***Glass vial with rubber stopper***
- ***Pre-filled syringe***
- ***Auto-delivery needle device***
- ***Pre-filled plastic administration bag (cells)***

Inhalation

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

Topical

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

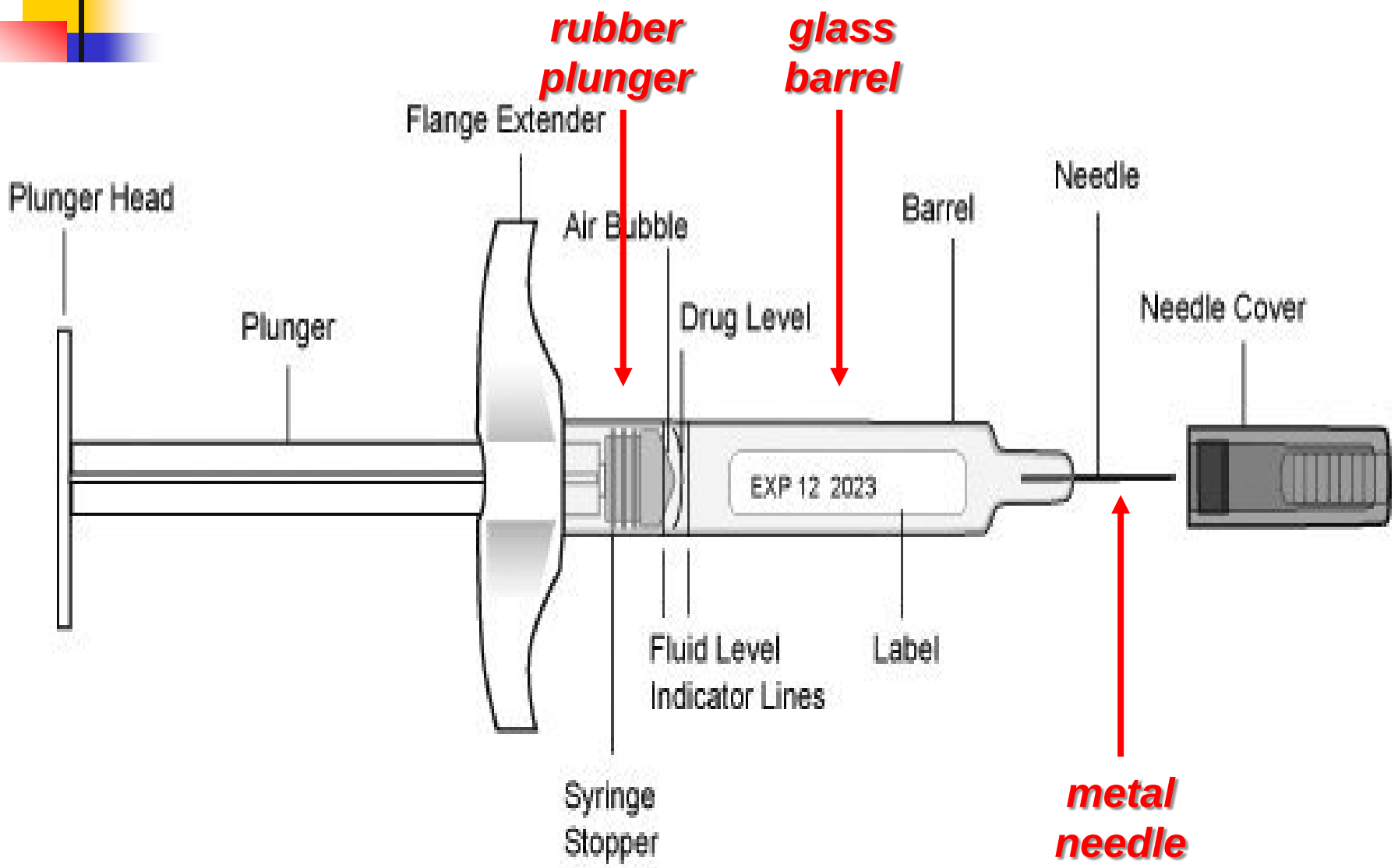
Rectal

Vaginal

Oral

- ***(under development – encapsulated)***

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

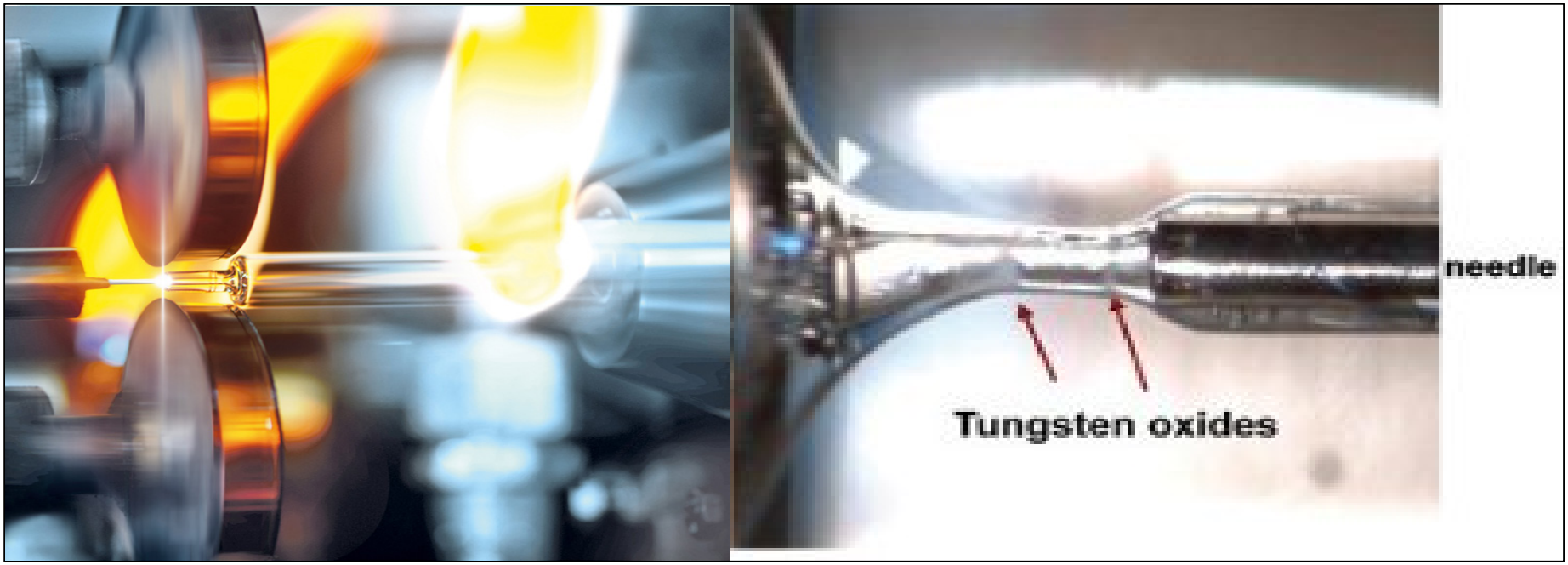


Discovery of tungsten oxides in pre-filled syringes

Tungsten ion accelerates protein aggregation

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

During pin removal, residual tungsten ion can remain



Improved syringe washing processes at the vendors

Incoming batch check for residual tungsten (ICP/MS)

Shocking discovery of glass vial delamination

Micro-Flow Imaging (MFI)

(counting and photographing each type of particle present)

Glass lamellae

Potentially present in <u>every</u> glass vial of Epogen manufactured since 1982!

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

Vial manufacturing process can minimize the problem of delamination – molded process vs tube process (molding uses lower temps than tube)

Avoiding unbuffered solutions and avoiding high pH can minimize glass delamination

Delamination does not occur in pre-filled glass syringes
(vials are formed at ~1400°C, while syringes are formed at ~1200°C)

Container Closures (other than vial-stopper) are DEVICES

device (in addition to biologic) regulations must be met

- ***ISO 10993 Biological evaluation of medical devices***
- ***ISO 11040-4 Prefilled Syringes Part 4: Glass barrels for injectables and sterilized sub assembled syringes ready for filling***
- ***ISO 11608-1 Needle-based injection systems for medical use: Requirements and test methods***
- ***ISO 11608-4 Requirements and test methods for electronic and electromechanical pen injectors***
- ***ISO 11608-6 Needle-based injection systems for medical use: Requirements and test methods – bolus injectors***
- ***ISO13845 Medical devices - Quality management systems***
- ***ISO 14971 Application of risk management to medical devices***
- ***ISO 20069 Device change assessment of combination products for administration of medicinal products***
- ***EU Regulation 2017/745 on medical devices***

Device functionality: both at time of release and throughout the entire shelf life, is critical!

Human engineering studies are most important!

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

Life saving for hyperglycemia

Life saving for anaphylactic shock

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

CMC Regulatory Compliance Strategy For Biopharmaceuticals

Course Outline

4. Major Challenge of Demonstrating Biopharmaceutical Product Comparability After Manufacturing Process Changes

- ✓ *3 essential elements of an effective comparability study*
- ✓ *Value of obtaining a contract with the FDA/EMA for future manufacturing process and test method changes*


Change is inevitable!
Resistance is futile.

There is always more that can be done to make the manufacturing process more robust and the product of higher quality

But every change carries a risk: benefit-risk ratio

- ***Improve consistency of manufacturing***
  - *Tightening cell culture or purification controls*
  - *Chromatography resin improvement*
  - *Move to a commercial-oriented cGMP CMO*
- ***Improve product quality***
  - *Addition of a new chromatographic polishing step*
  - *Tightening of product release specifications*
  - *Higher quality raw material*
- ***Increase manufacturing capacity***
  - *Higher productivity MCB cell line*
  - *Manufacturing site change for scale-up or scale-out*
  - *Switch to continuous manufacturing*

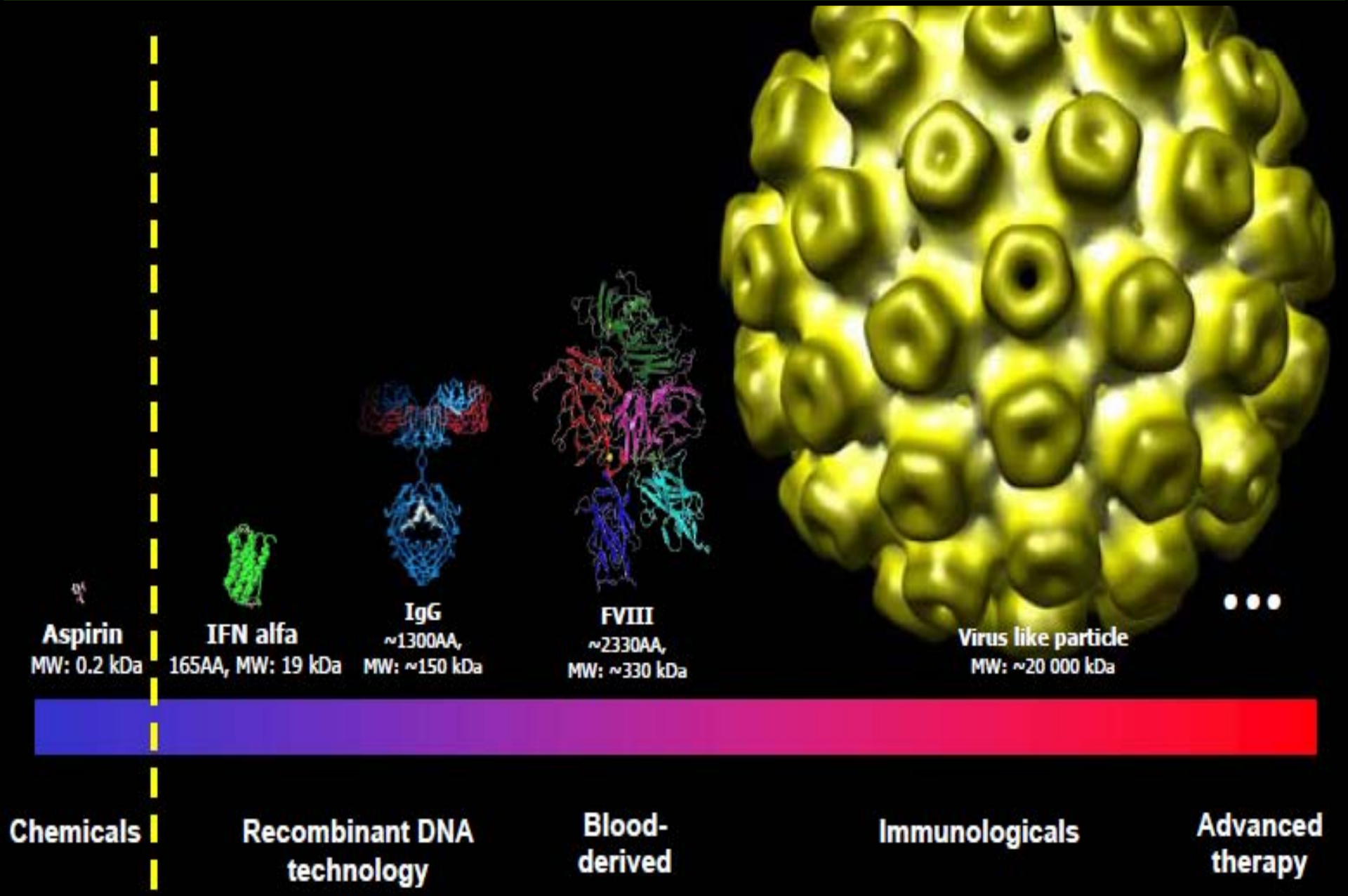
Effectively managing the process change – 2 parts

1) ***Systematically control the change***
   - ***Change control system (cGMP QA)***
   - ***Process revalidation (if already validated)***

2) ***Evaluate impact of change on product***
   - ***Comparability study (post-change to pre-change)***
   - ***Meet the corresponding standard***
     - ***equivalent (chemical drug)***
     - ***highly similar (biologic)***

→ *increasing molecular complexity and decreasing analytical analysis* →

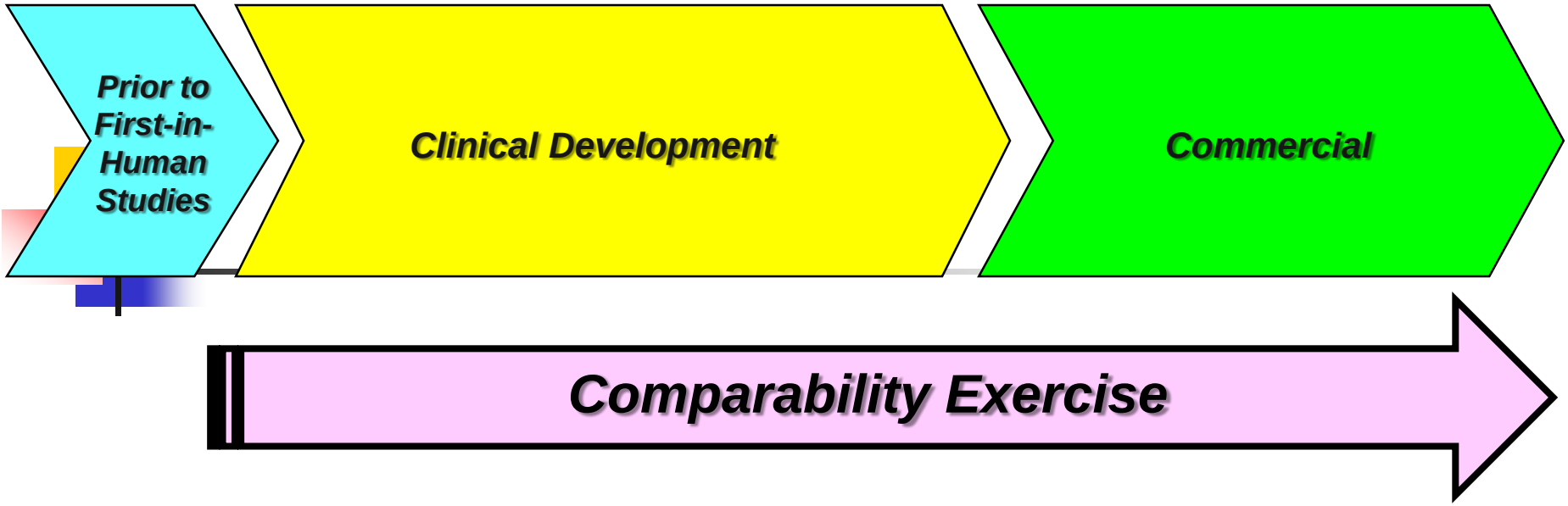
equivalent *'highly similar'*



"Highly Similar"

the standard for <u>all</u> biologic process changes (innovator and biosimilar)

'Not identical' ***'Close, but not exact'*** ***SUBJECTIVE***



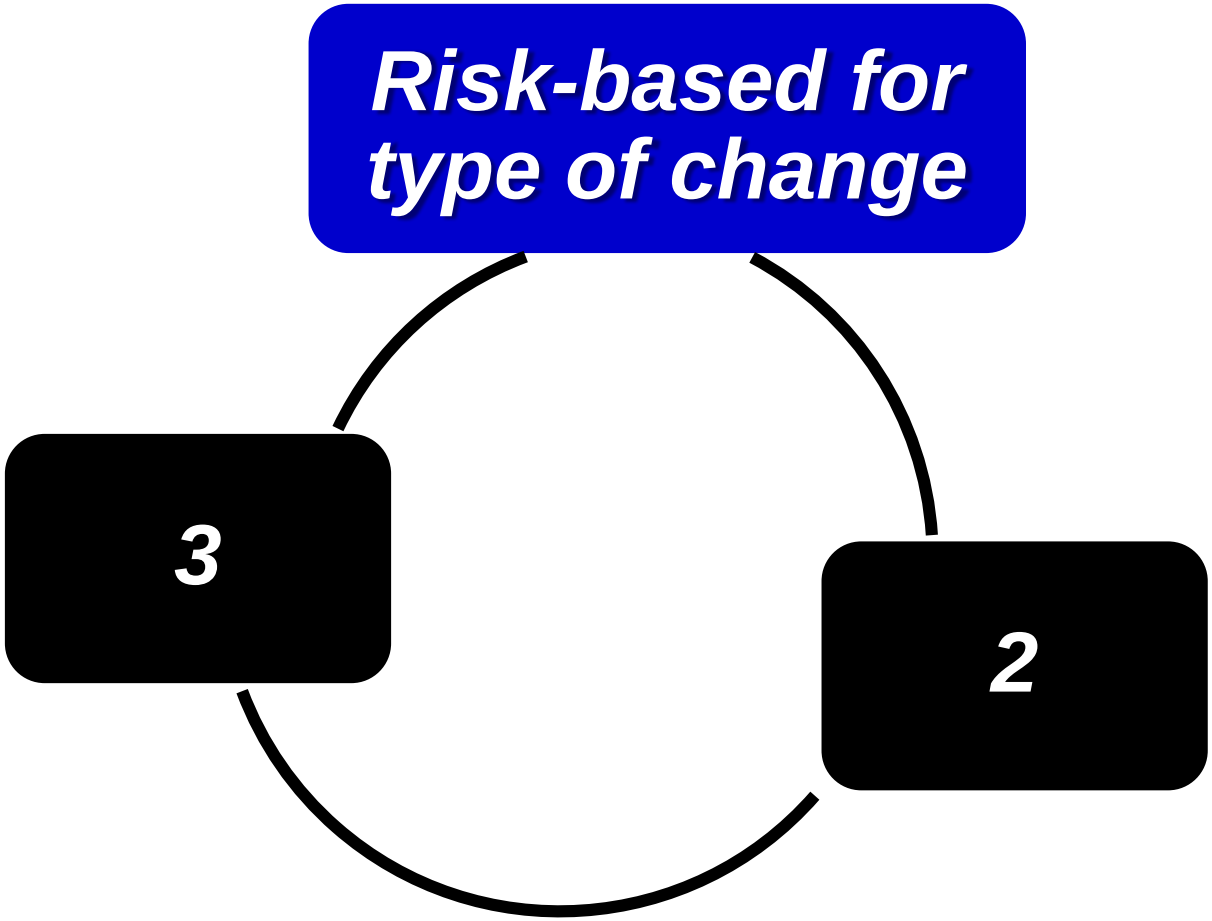
"The goal of the comparability exercise is to ascertain that pre- and post-change drug product is comparable in terms of quality, safety, and efficacy."

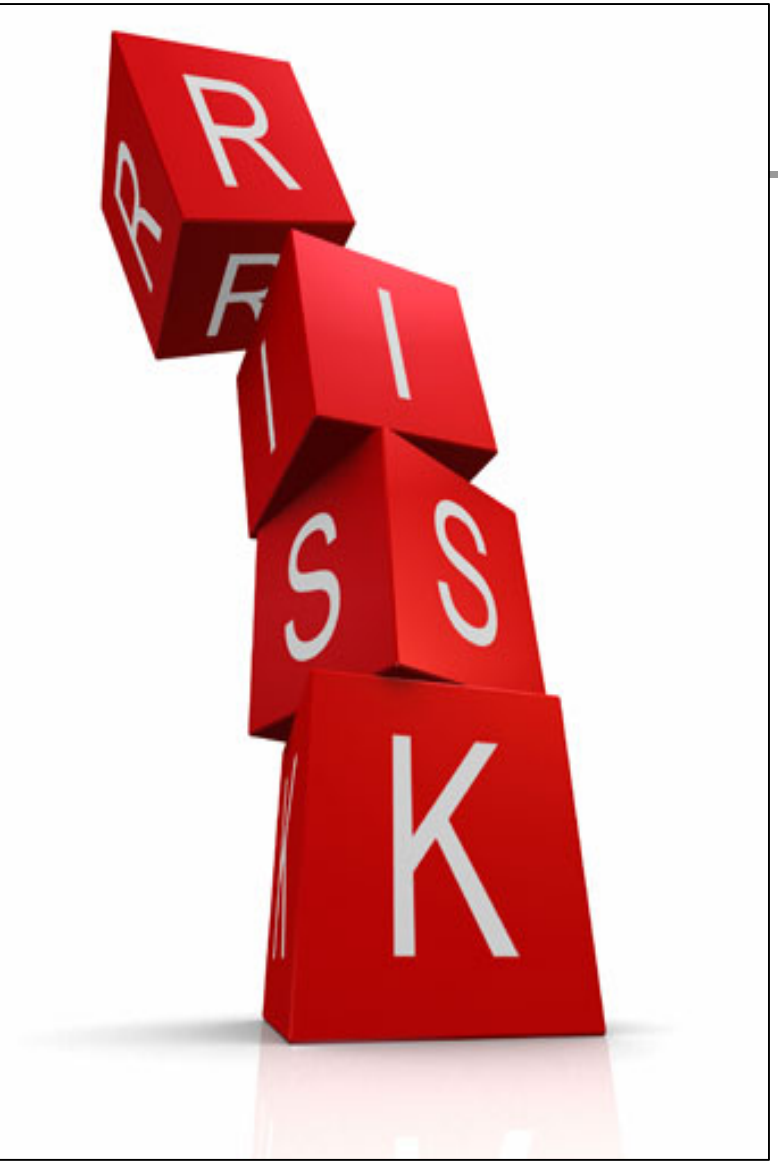
ICH
harmonisation for better health

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

Q5E

3 essential elements of an effective comparability exercise!





Risk-Based Analysis for Type of Change

1) Assess the potential impact of the process change on the quality of the product (e.g., potency, purity, identity)
   - Not all process changes carry the same level of product risk
2) Different levels of risk require different amounts and types of data to support product comparability
3) Different levels of risk require different oversight/approval by regulatory authorities

The level of risk determines the degree of evidence required to support product comparability

The level of risk determines the degree of regulatory oversight/approval

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

The level of risk determines the degree of regulatory oversight/approval

AFTER MARKET APPROVAL

FDA System for Process Changes			
Risk Level	**Major**	**Moderate**	**Minor**
Action Required	**Submit as Prior Approval Supplement (PAS)**	**Submit as Change Being Effective (CBE-30)**	**Submit in Annual Report**

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

EMA System for Process Changes			
Risk Level	**Major**	**Moderate**	**Minor**
Action Required	**Type II Variation (formal approval)**	**Type IB Variation (30 day wait)**	**Type IA Variation (Annual Reporting)**

<u>Same</u> guidance for chemical drugs and biologics

European Medicines Agency post-authorisation procedural advice for users of the centralised procedure

EMA Recommendations – after market approval

APPLICATION FOR VARIATION TO A MARKETING AUTHORISATION

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

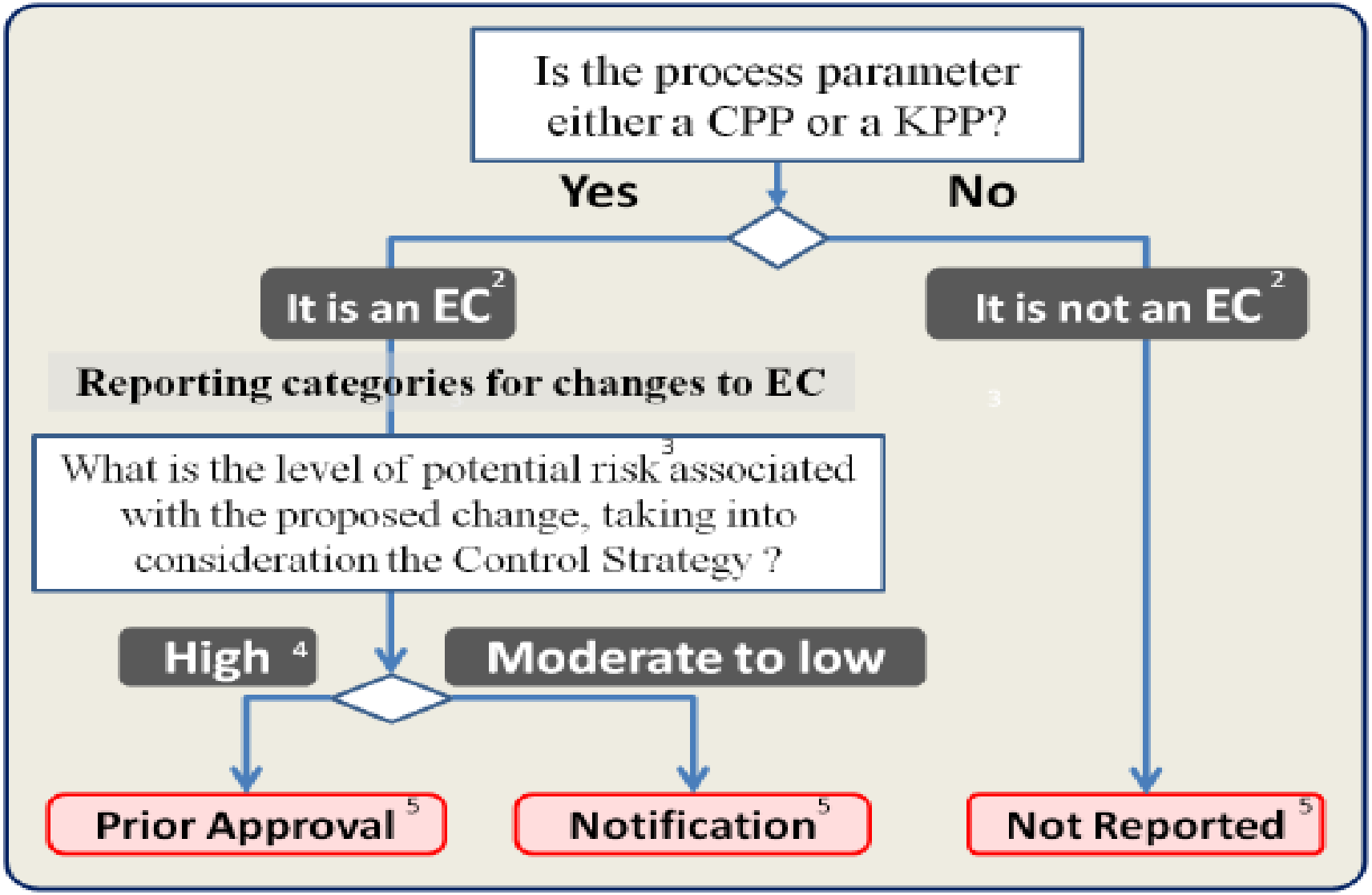
Consistent with FDA PAS for biologics

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

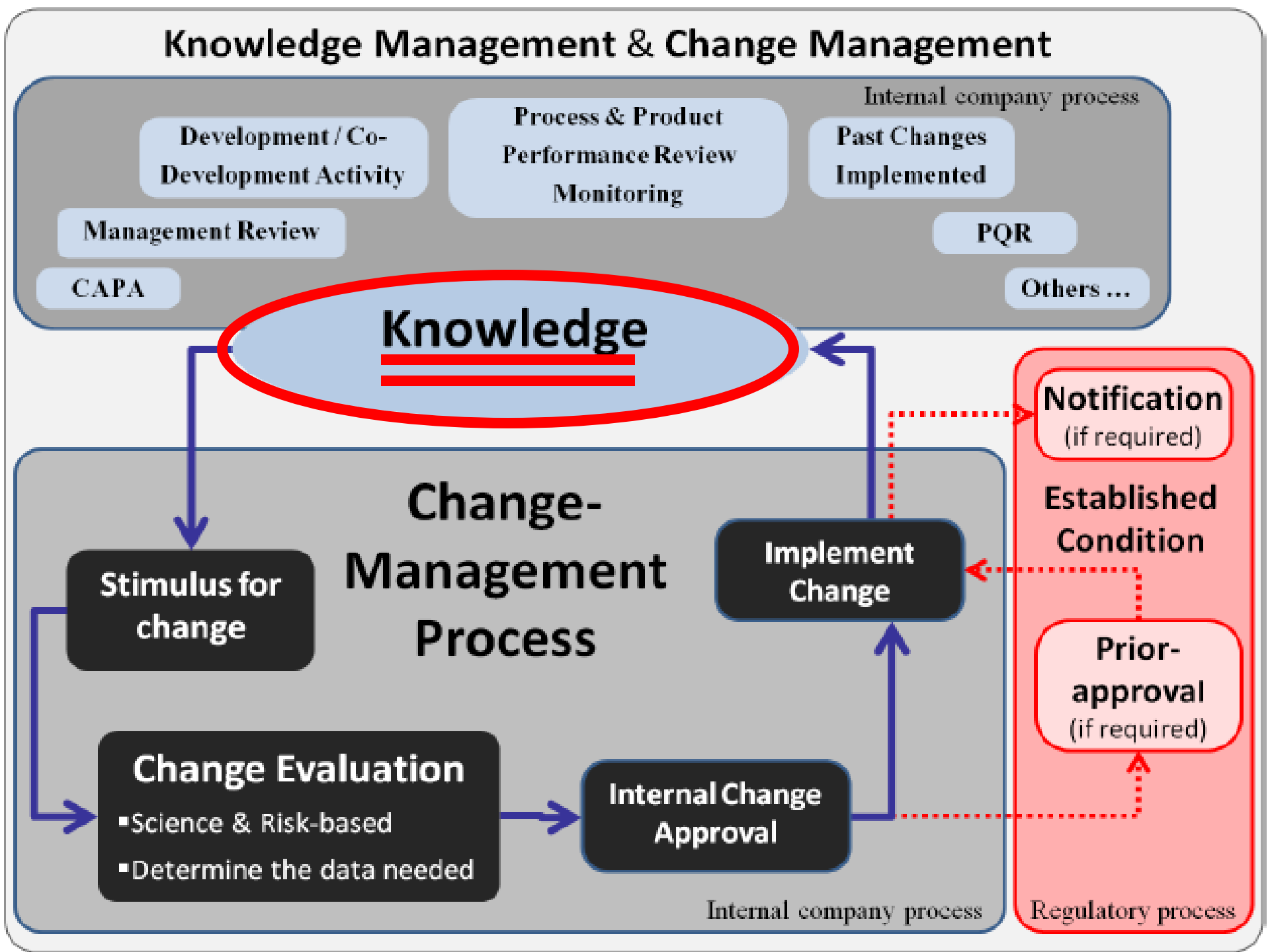
ICH guideline Q12 on technical and regulatory considerations for pharmaceutical product lifecycle management

Step 2b December 2017

Unifying guideline in the works



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


Knowledge Management & Change Management
Internal company process
Development / Co-Development Activity
Process & Product Performance Review Monitoring
Past Changes Implemented
Management Review
PQR
CAPA
Others …
Knowledge
Notification (if required)
Established Condition
Change-Management Process
Stimulus for change
Implement Change
Change Evaluation
▪Science & Risk-based
▪Determine the data needed
Internal Change Approval
Prior-approval (if required)
Internal company process
Regulatory process

The issue with manufacturing process change risk assessment – Get the level of risk wrong and incur the wrath of the FDA!

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

Warning Letter
January 2017

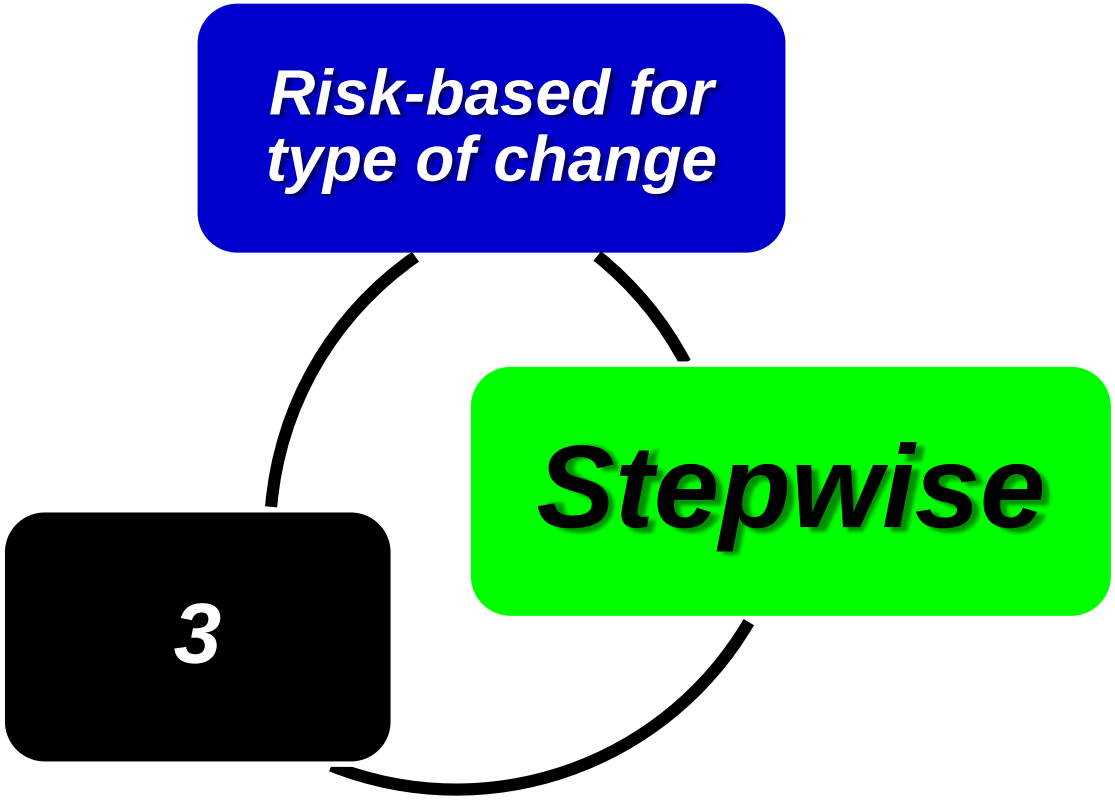
Erwinaze
(Asparaginase)

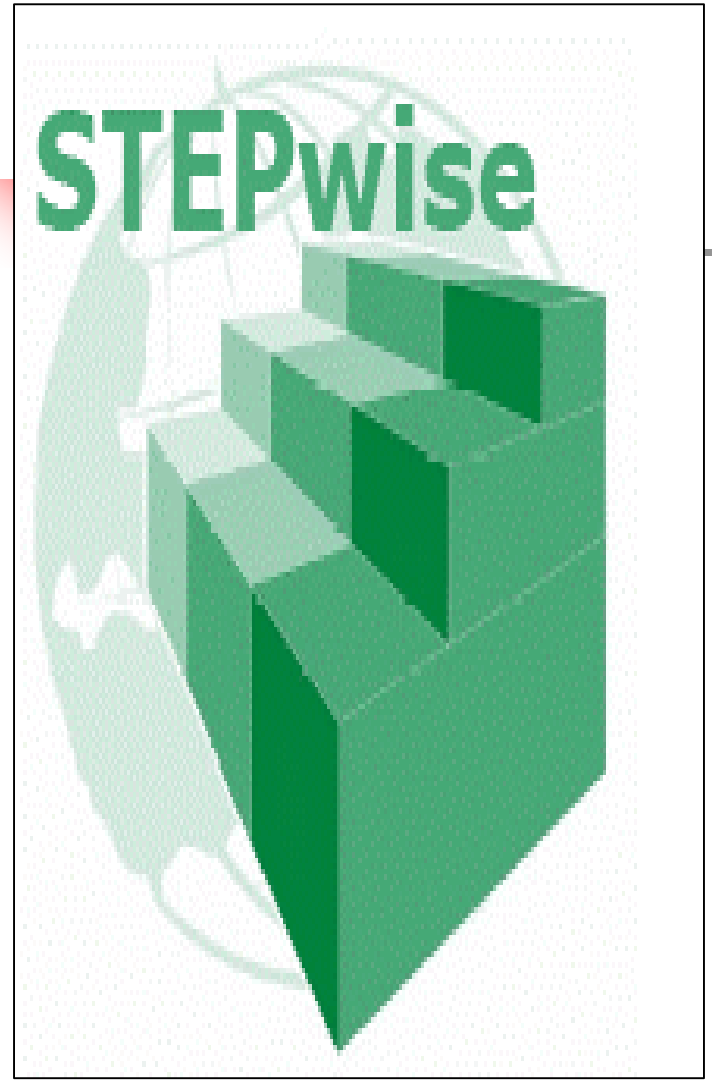
1. Failure to establish and follow change controls to evaluate all changes that could affect the production and control of intermediates or API.

Your firm failed to conduct adequate change controls prior to the use of each working cell bank. For example, your firm has used working cell banks **(b)(4)** for the production of drug substance and drug product batches of Erwinaze®.Your firm previously used only working cell banks **(b)(4)** for production of Erwinaze® drug substance 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

3 *essential elements of an* ***effective*** *comparability exercise!*





Stepwise Reduction of Residual Risk

- *Approach the studies needed to confirm product comparability from a series of distinct steps*
  - *Step 1 (analytical & functional characterization) alone may be sufficient to address quality and regulatory concerns*
  - *<u>If residual risk remains</u>, consider step 2 (nonclinical animal studies)*
  - *<u>If residual risk still remains</u>, consider also step 3 (human clinical studies)*

COMPARABILITY OF BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS SUBJECT TO CHANGES IN THEIR MANUFACTURING PROCESS ICH Q5E

Step 1

• Quality Comparability

Analytical & Functional Testing

much, much more than just meets specs before and after change!

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

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

- **Product characterization (far beyond just 'QC release testing') is critical for the Quality Comparability**
  - Emphasis on 'state-of-the-art' characterization tools
  - Which methods are you using today?

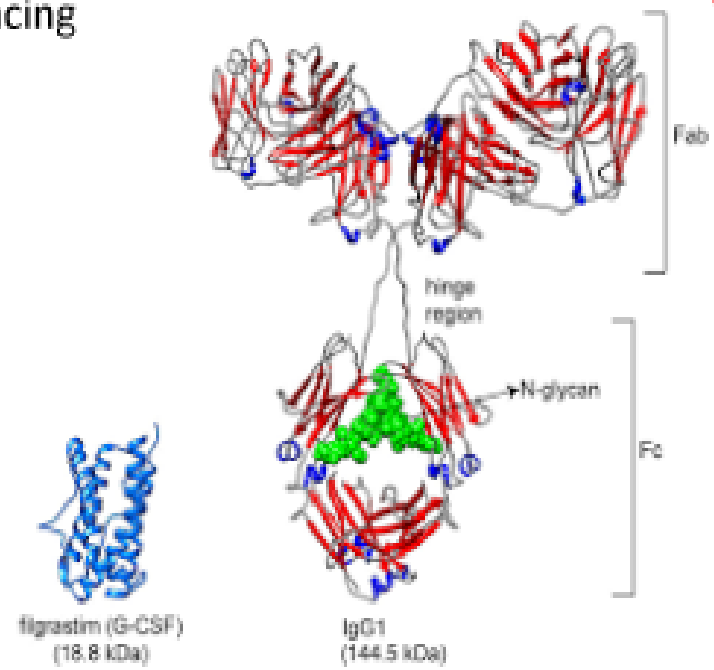
1990s Analytical Tool Box

1° Sequence/PTMs

AA analysis
N- and C-term Sequence
Peptide Mapping and Sequencing
LC-MS/MS (1 sponsor)
MALDI-TOF (BLA)
ESI-MS (BLA)

HOS

CD (1 sponsor)
DSC (BLA)



Japelj et al Sci Reports 2016

Glycan Analysis

Monosaccharide analysis
CE with fluorescence detection (BLA)

Charge/Identity

IEF
IEX
cIEF

Process Related Impurities

Largely focused on bovine proteins
BSA, transferrin, IgG

Size/ Purity

SEC-HPLC
SDS-PAGE R + NR
Coomassie Blue and
Silver Stain
Immunoblotting
CGE (BLA)

Activity

In vitro/ in vivo Bioassays
Binding ELISAs
Flow cytometry
Strength (UV A280)
BCA (1 DS)

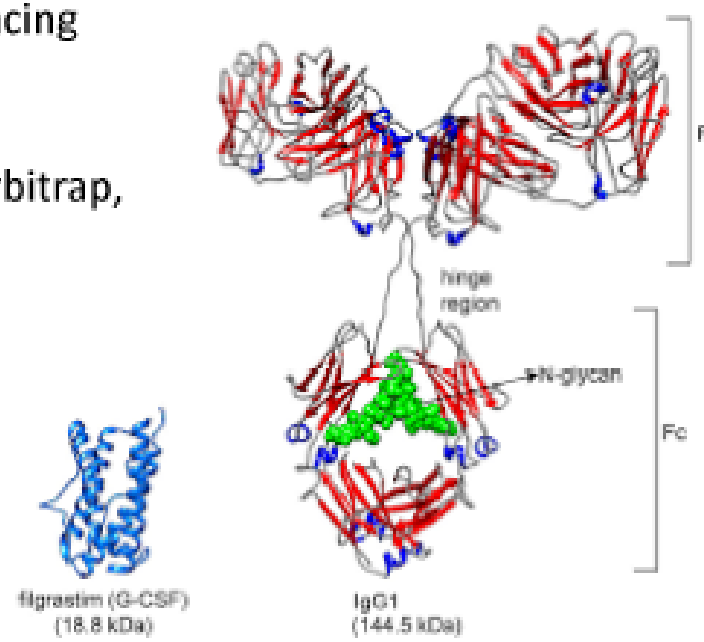
Safety

Bioburden
Sterility
Rabbit Pyrogens
Endotoxin
General Safety

The Current Analytical Tool Box

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

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



Japelj et al Sci Reports 2016

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

Future: MAM Multi-Attribute Method

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

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

Charge
cIEF
icIEF
ICE
IEX- HPLC
CZE

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

Safety
Bioburden
Sterility
Endotoxin
  LAL
  KT

- ***Lessens learned from the biosimilar manufacturers for highlighting the value of extensive product characterization***
  - ***They see differences between their biosimilar and the innovator biopharmaceutical, but they demonstrate that those differences are not clinically meaningful***

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

Category	Analytical Testing and Parameter	Tier - Similarity Assessment Approach	Assessment Criteria	ABP 215 Results	Demonstrated Similarity
Primary Structure	Intact molecular mass: Profile	3 - Qualitative comparison	N/A	Visually similar[3], Figure 32	√
	Intact molecular mass: Molecular weight	2 - Pre-defined limit	Observed mass should be within ± 50 ppm of the theoretical mass for the predominant species	Predominant species all within 50 ppm of the theoretical masses	√
	Reduced and deglycosylated molecular masses of HC and LC: Profile	3 - Qualitative comparison	N/A	Visually similar[3], Figure 33 and Figure 34	√
	Reduced and deglycosylated molecular masses of HC and LC: Molecular weight	2 - Pre-defined limit	Observed mass should be within ± 50 ppm of the theoretical mass	Observed mass was within 50 ppm of the theoretical mass	√
	Reduced peptide map: Profile	3 - Qualitative comparison	N/A	Visually similar[3], Figure 35	√

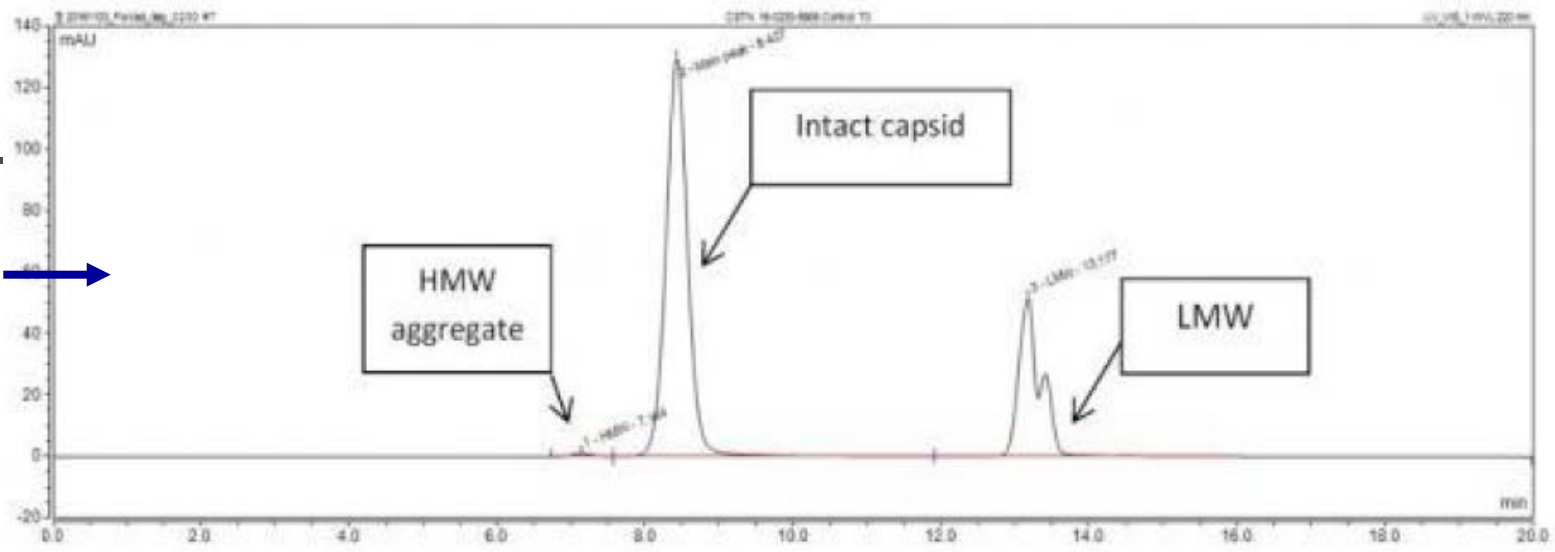
Category	Analytical Testing and Parameter	Tier - Similarity Assessment Approach	Assessment Criteria	ABP 215 Results	Demonstrated Similarity
Primary Structure	Non-reduced peptide map: Profile	3 - Qualitative comparison	N/A	Visually similar[a], Figure 36	√
	Non-reduced peptide map: Disulfide structure	2 - Pre-defined limit	Observed mass of the tryptic peptide fragments should be within ± 200 ppm for peptide mass > 2000 Da, and within ± 1000 ppm for peptide mass < 2000 Da	Observed mass was within ± 200 ppm for peptide mass > 2000 Da, and within ± 1000 ppm for peptide mass < 2000 Da	√
	Glycan map: Profile	3 - Qualitative comparison	N/A	Visually similar[a], Figure 37	Similar profile Minor quantitative differences in specific glycans (Section 3.2.1.1)
	Glycan map: % high mannose	2 - Quality range[b]	LOQ (0.1) to 1.2	1.2 to 2.7	
	Glycan map: % galactosylation	2 - Quality range[b]	1.2 to 26.7	17.1 to 29.4	
	Glycan map: % afucosylation	2 - Quality range[b]	0.9 to 3.5	1.2 to 1.7	√
	Glycan map: % sialylation	3 - Qualitative comparison	N/A	Both ABP 215 and bevacizumab have similarly low levels of sialylation at or near the LOQ (0.1%) of the assay	√

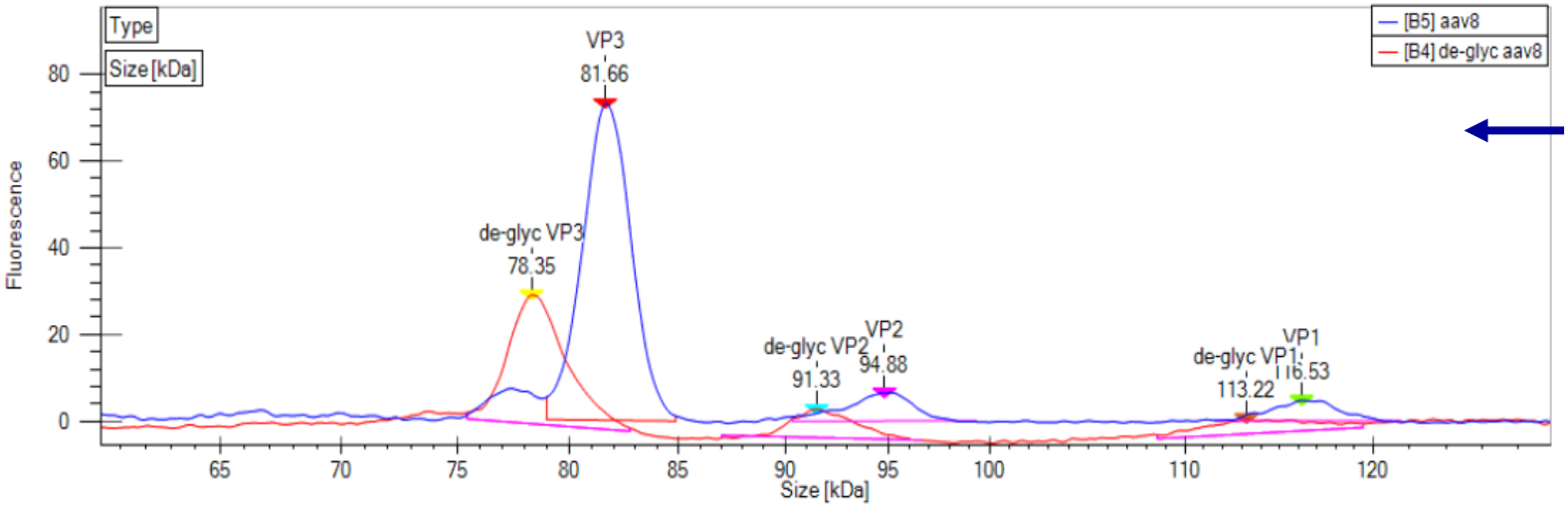
Category	Analytical Testing and Parameter	Tier - Similarity Assessment Approach	Assessment Criteria	ABP 215 Results	Demonstrated Similarity
Product-related Substances and Impurities	SE-HPLC: Profile	3 - Qualitative comparison	N/A	Visually similar[a], Figure 48	Similar profile
	SE-HPLC: HMW	2 - Age adjusted quality range[b]	2.6 to 3.5	2.2 to 3.3	Minor differences in high molecular weight species (Section 3.2.1.4)
	rCE-SDS: Profile	3 - Qualitative comparison	N/A	Visually similar[a], Figure 49	Similar profile
	rCE-SDS: HC+LC	2 - Age adjusted quality range[b]	94.8 to 96.0	96.8 to 97.3	Minor differences in glycan occupancy and fragmented species (Section 3.2.1.4)
	rCE-SDS: NGHC	2 - Age adjusted quality range[b]	1.5 to 2.1	0.6 to 0.8	
	rCE-SDS: LMW + MMW	2 - Age adjusted quality range[b]	1.9 to 2.5	1.6 to 1.9	
	nrCE-SDS: Profile	3 - Qualitative comparison	N/A	Visually similar[a], Figure 50	Similar profile
	nrCE-SDS: Main peak	2 - Quality range[b]	96.5 to 97.5	96.1 to 97.7	Minor differences in partially reduced species (Section 3.2.1.4)
	nrCE-SDS: Pre-peaks	2 - Quality range[b]	2.1 to 2.8	2.0 to 3.8	

Extensive characterization is limited for genetically engineered viruses

Genomic and proteomic characterization possible

AAV viral capsid aggregation (SE-HPLC)





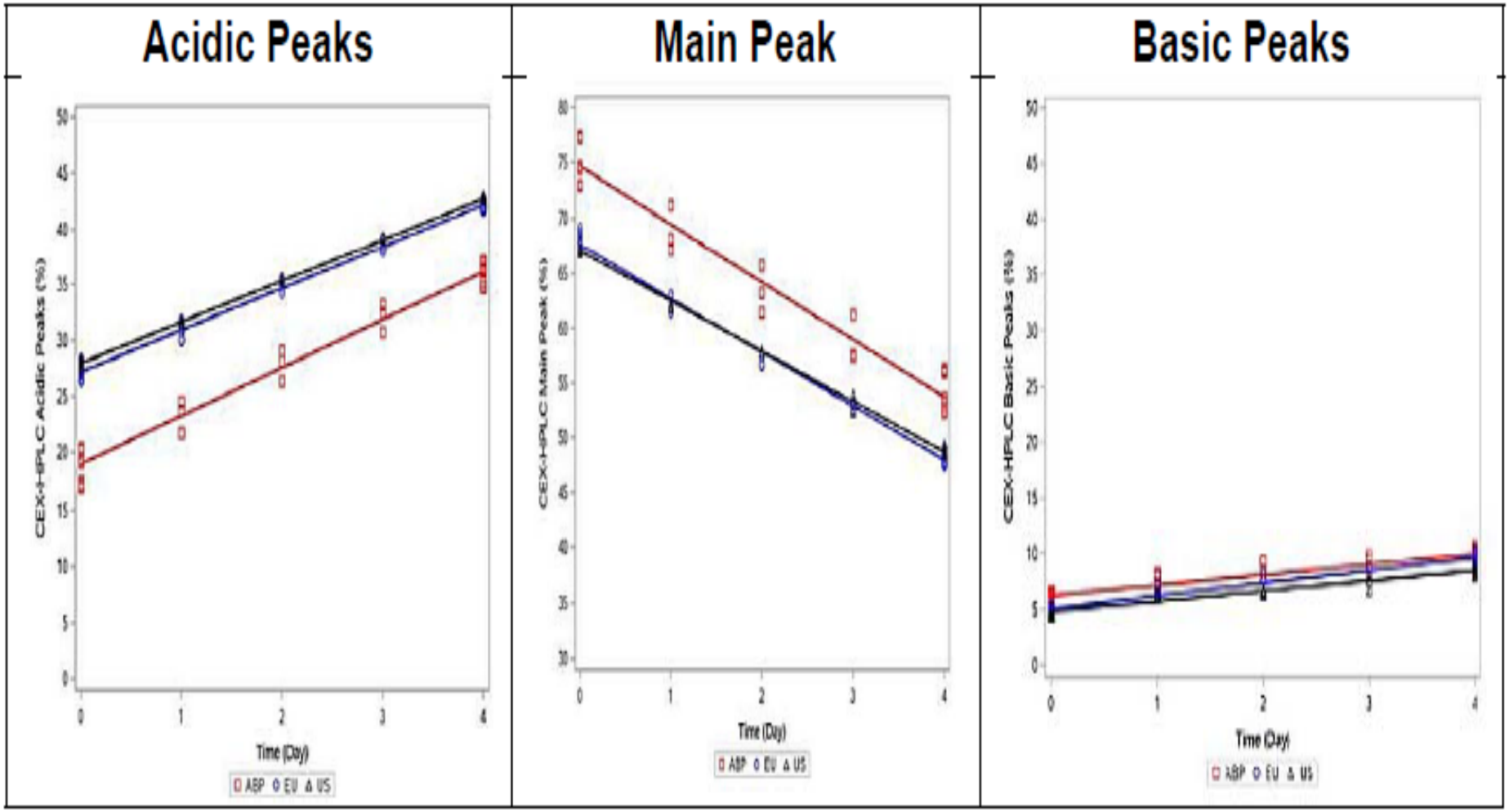
AAV viral capsid glycoprotein composition (CE-SDS)

AAV viral capsid genome content (empty vs full) by Analytical Ultracentrifugation

2) Accelerated and Stress stability slope comparison (potential differences in molecular variant formation)

- ***Stress testing has become a most important part of the Quality Comparability***
  - ***Using 'state-of-the-art' characterization tools***
- ***Look to the biosimilar manufacturers for highlighting the value of stress testing***
  - ***They see differences between their biosimilar and the innovator biopharmaceutical, but they demonstrate that those differences are not clinically meaningful***

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



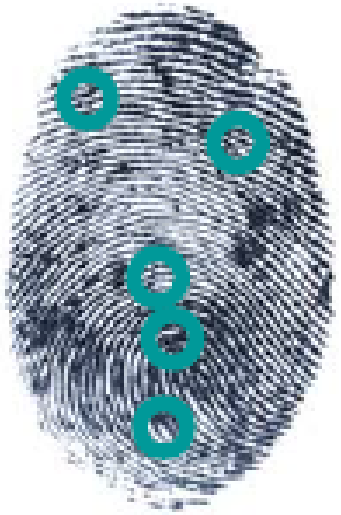
Source: Figures excerpted from the Applicant's 351(k) BLA submission

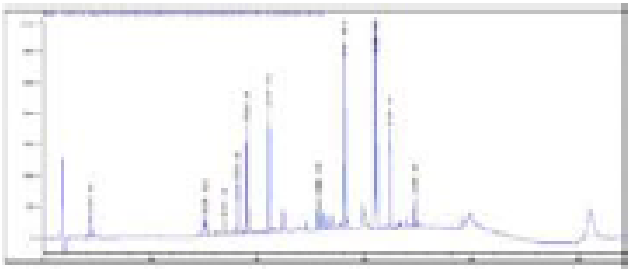
3) *Consistency batches (spec comparison before and after change)*

4) *Historical data analysis (potential "drift" in CQAs)*

- ***Specs are important, but specs are typically set as wide as practically possible (to not reject a good batch)***
  - ***Specs are set based either upon patient safety concerns or demonstrated manufacturing process performance – thus biosimilar manufacturers and innovators will end up with different spec limits/ranges***

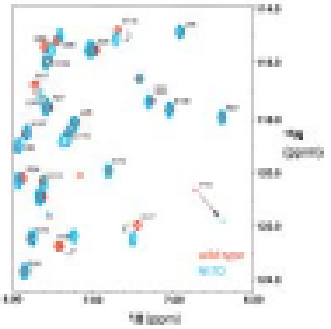
Fingerprinting



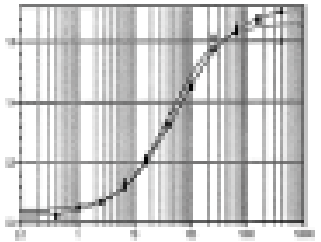


Sequence & Modifications

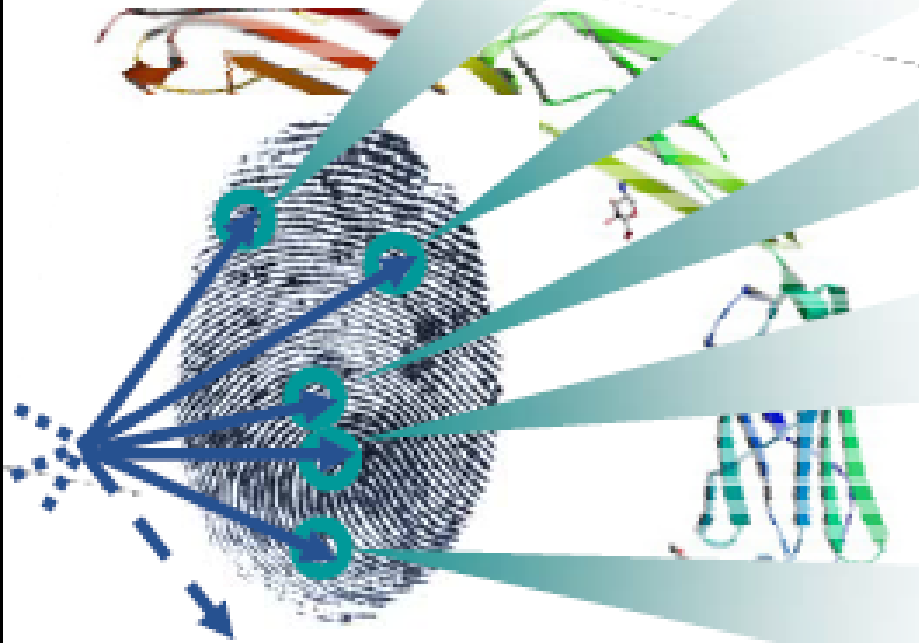
Quality Comparability

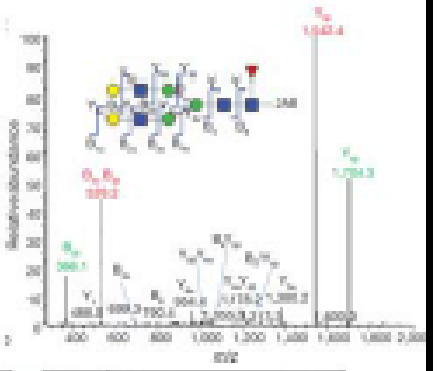


Higher Order Structure

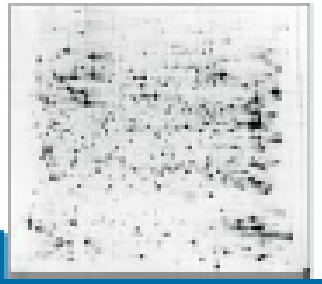


Bioactivity



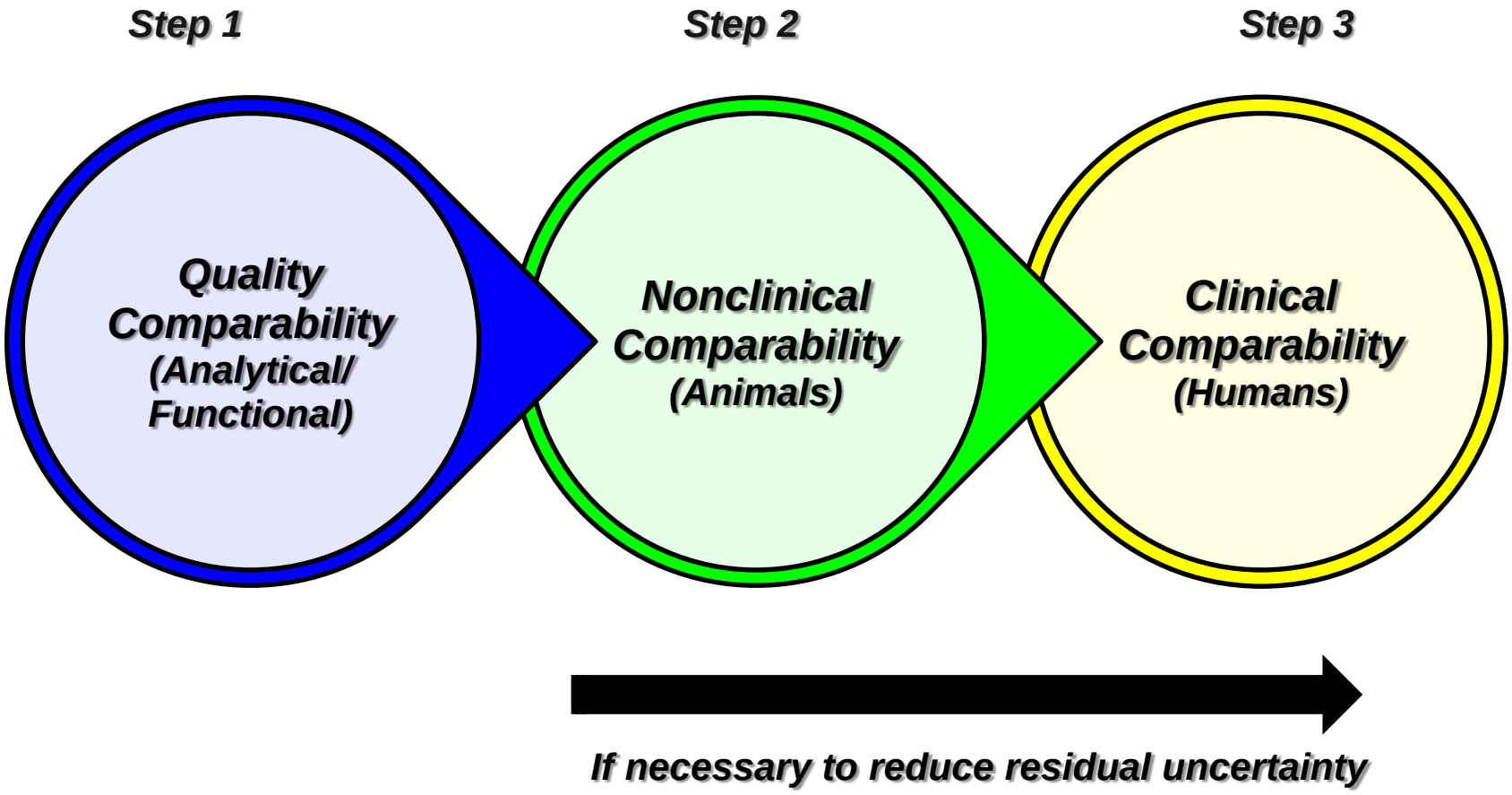


Glycoforms

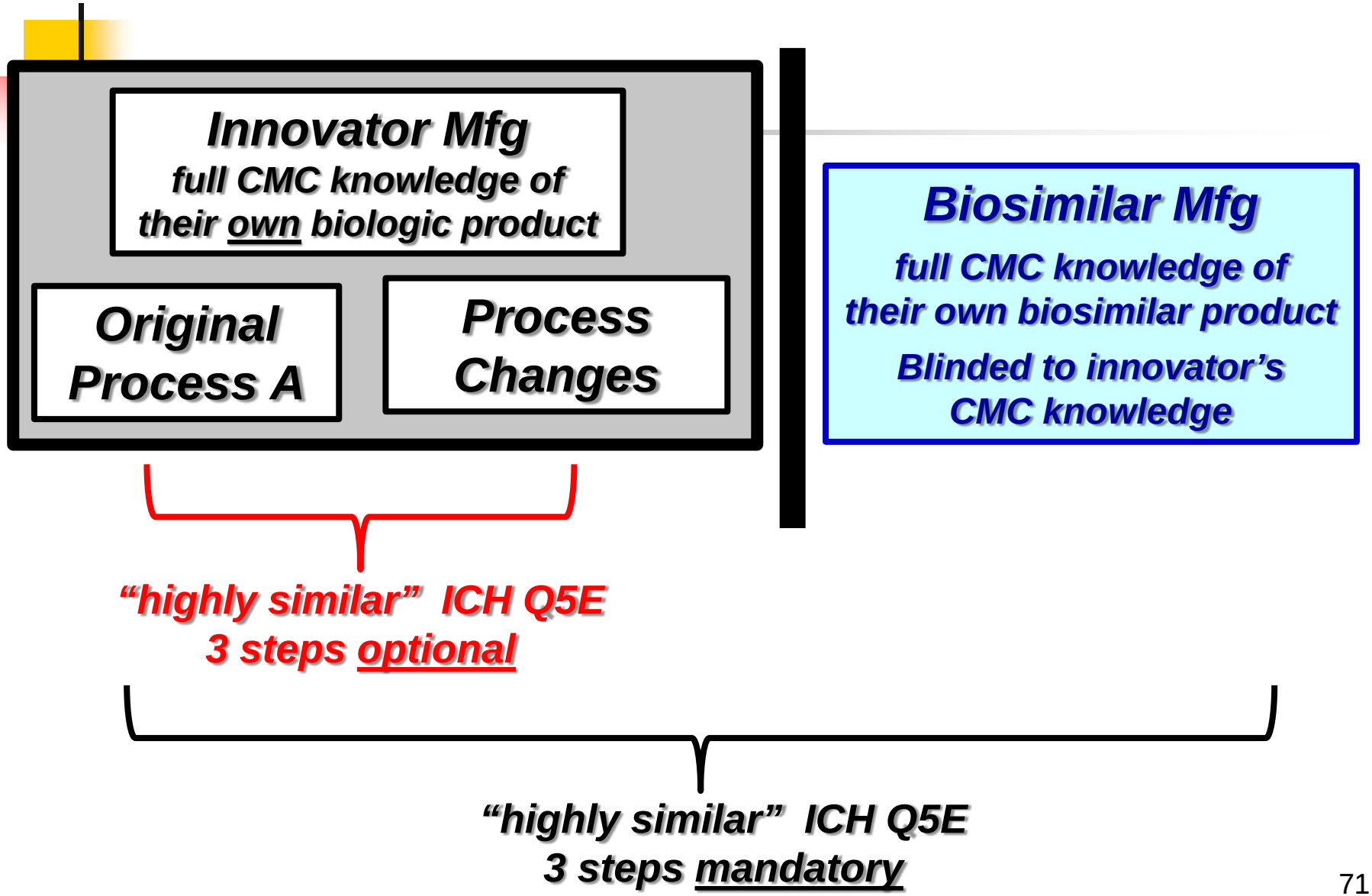


Impurity Profile

Stepwise Reduction of Residual Uncertainty

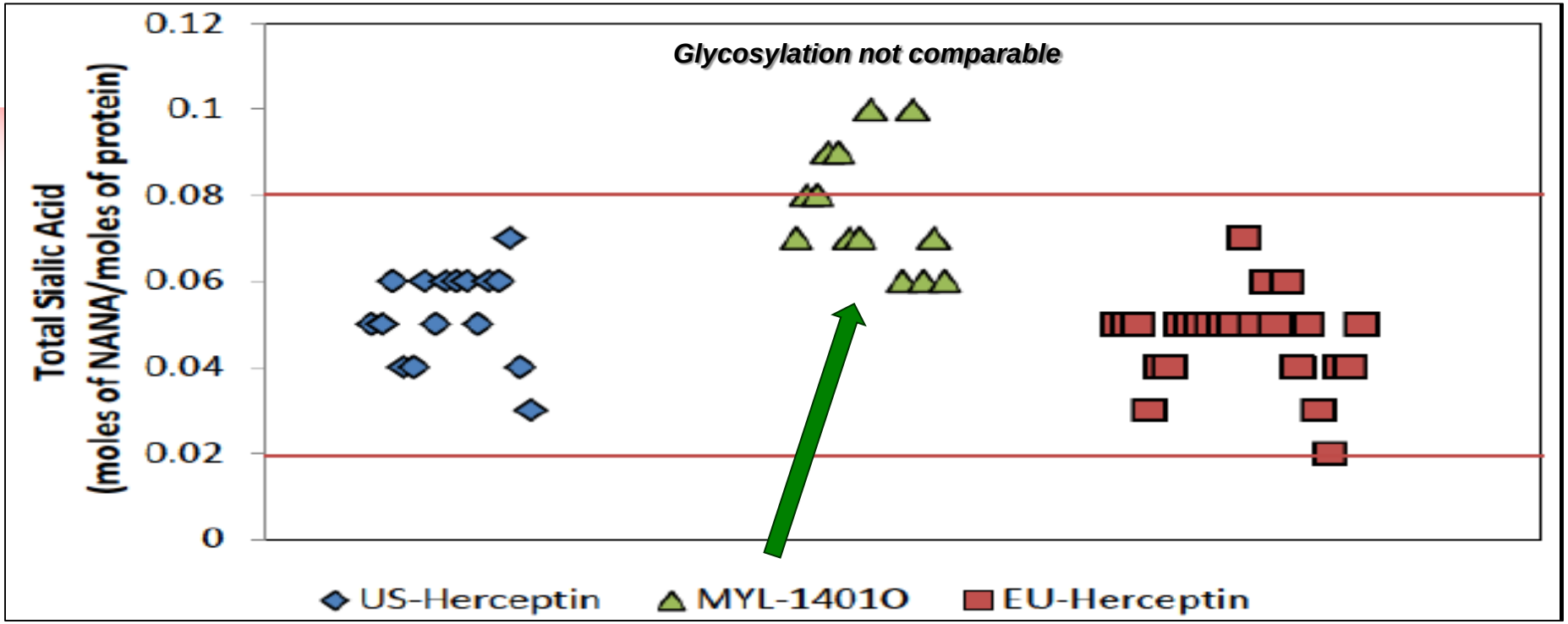


Residual uncertainty drives need for Steps 2 and/or 3



Residual uncertainty addressed for a biosimilar: Ogivri

(Mylan's biosimilar to Genentech's monoclonal antibody Herceptin)

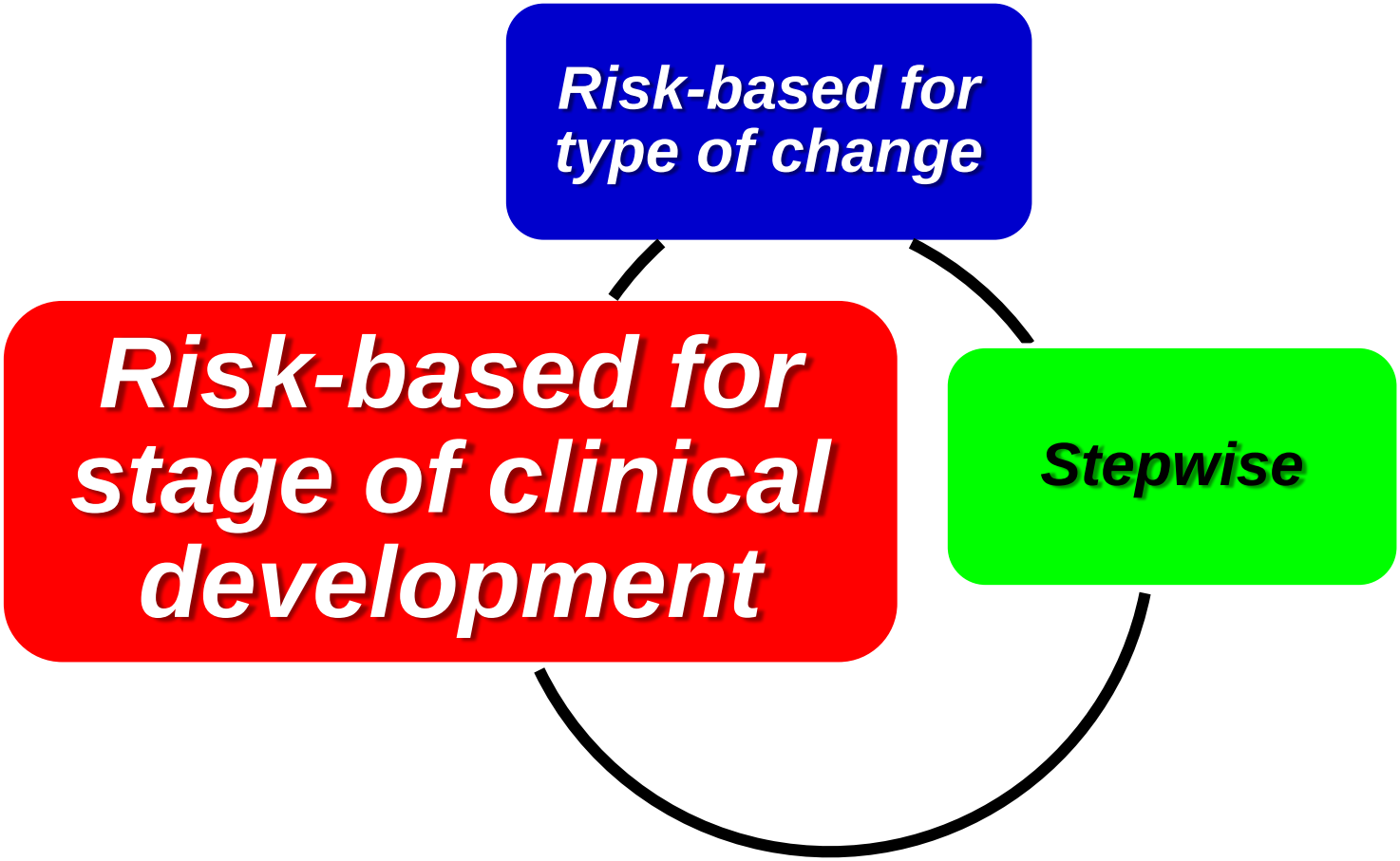


Residual uncertainly addressed by human PK (Step 3)

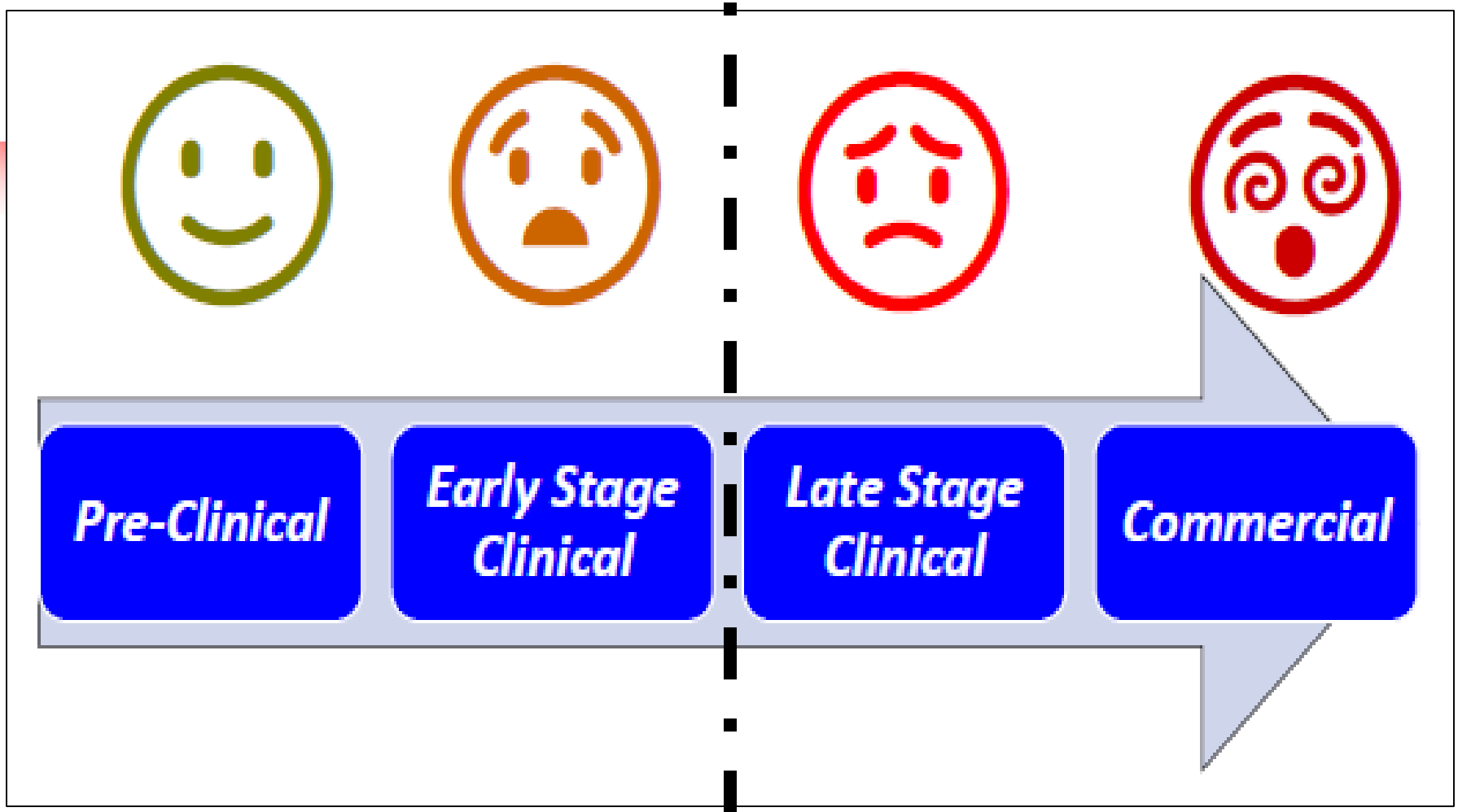
mol/mol). MYL-1401O lots with minor differences in glycosylation with respect to the US-Herceptin lots were included among those used in clinical studies. Residual uncertainty about biosimilarity that resulted from the differences in high mannose and sialylated glycans is adequately addressed by data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

2017 FDA Advisory Committee Meeting

3 essential elements of an effective comparability exercise!



regulatory concern increases if efficacy data could be impacted



comparability testing to be 'adequate'

comparability testing to be 'comprehensive and thorough'

Stage-Appropriate Comparability

Early clinical phase (Phases 1/2)

Q5E

'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.'

Note all the challenges with a phase-appropriate approach mentioned earlier due to expedited (seamless) clinical studies, biosimilars, and gene therapies

Biologic companies aggressively make changes during the early clinical stages

Case example

Vimizim **elosulfase alfa** BioMarin

20 February 2014
EMA/357933/2014

Manufacturing process development

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

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

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

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

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

Stage-Appropriate Comparability

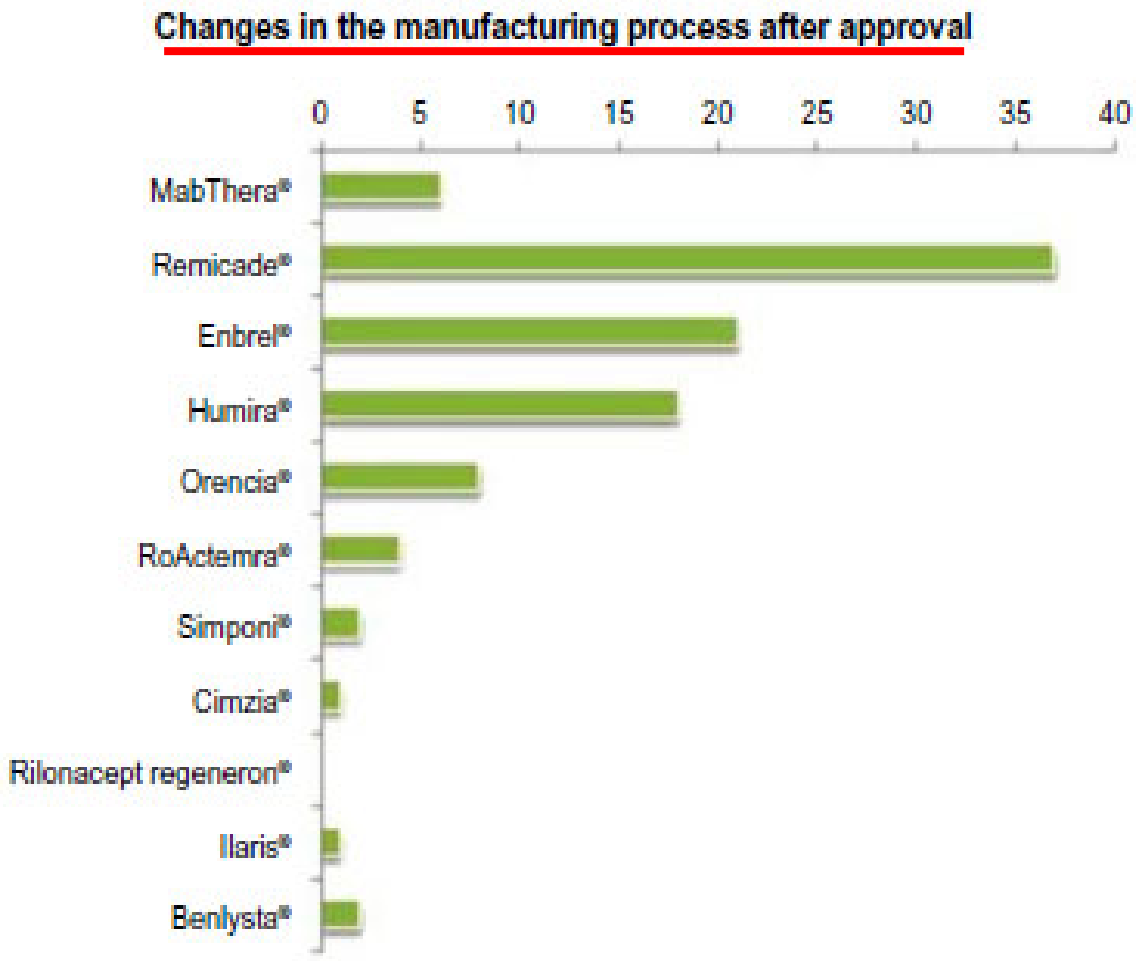
Late clinical phase (Phase 3 and Commercial)

Q5E

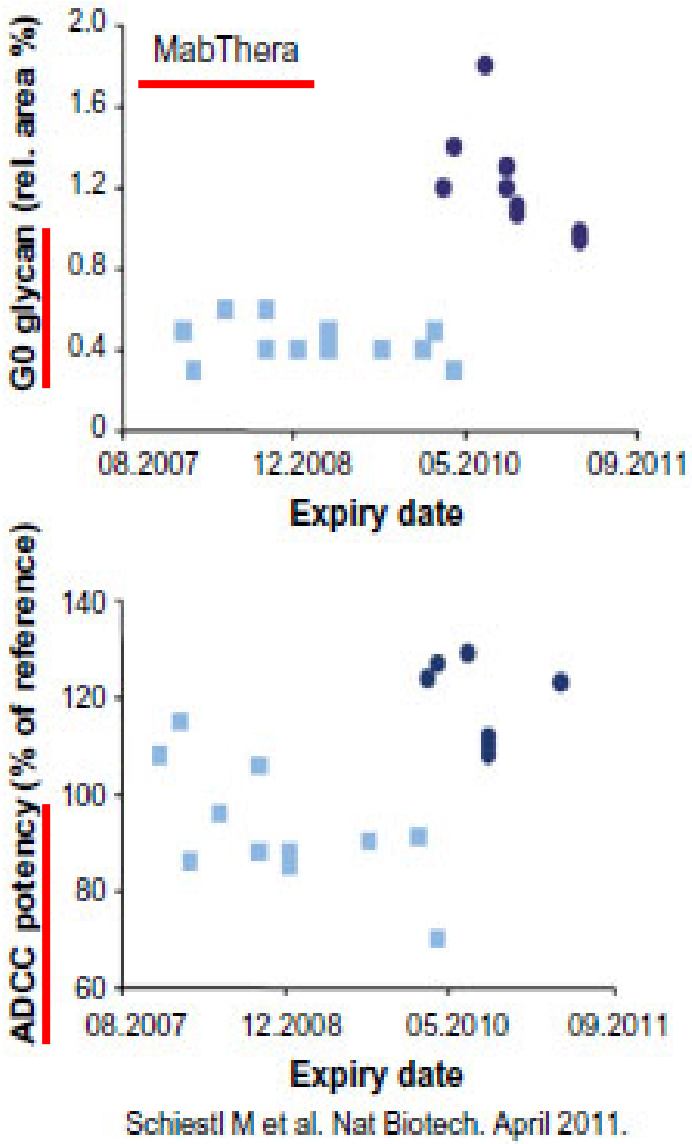
'Where process changes are introduced in late stages of development and no additional clinical studies are planned to support the marketing authorisation, the comparability exercise should be as comprehensive and thorough as one conducted for an approved product.'

Process changes continue even after going commercial!

(sharing information on innovators by biosimilar manufacturers)



Schneider C. Ann Rheum Dis. March 2013 Vol 72 No 3.



Schiestl M et al. Nat Biotech. April 2011.

ADCC: Antibody-dependent cell-mediated cytotoxicity.

Regulatory authorities question product comparability reports presented in market application dossiers!

5 *case examples – different outcomes*

- ***Recombinant protein – comparable, but only after more testing***
  - *Process change late stage: manufacturing site change*
  - *FDA concern: stress stability testing 'appeared' different*
- ***Recombinant protein – comparable, but only after more testing***
  - *Incomplete support for product comparability after process changes*
  - *EMA concern: poor presentation of data; incomplete data submitted*
- ***Monoclonal antibody – comparable, but only after more testing***
  - *Incomplete support for product comparability*
  - *EMA concern: more than release spec comparison*
- ***Recombinant protein – moved too fast on making changes***
  - *Process change at market approval stage: not enough data*
  - *FDA concern: wanted step 3 data first*
- ***Genetically engineered cells – not comparable, but better***
  - *Process change late stage: manufacturing site change*
  - *FDA concern: new site produces better quality product*

Comparable, but only after more testing: recombinant protein enzyme

The Agency stated that Statistics would need to be involved to go over data provided in slides. The sponsor was informed that in general when a linear regression is done, the mean data points are not looked at but rather the individual slopes. The Agency stated that even though there may not be a statistically significant difference among the sites, they look different. The sponsor agreed to the difference but stated that at this time, the amount of data is small. The Agency responded that saying there was not enough evidence to prove the sites were not significantly different is not the same as saying there is no difference. The Agency further stated that another way of showing the sites are comparable will be needed.

The sponsor stated that from a bulk stability perspective, there doesn't appear to be a difference. The Agency was not sure of this analysis. When looking at forced degradation studies, conducted at 50°C, a difference in degradation slope was shown, suggesting a difference between lots of DS manufactured at the clinical and at the commercial sites. The sponsor responded that data was

MEMORANDUM OF MEETING MINUTES

Biomarin **Vimizim (elosulfase alfa)**

MEETING DATE: September 27, 2013

Comparable, but only after more testing: recombinant protein nerve growth factor

Not the best start of a review

'From the quality point of view the CHMP considered the quality dossier at submission, to be poorly presented and incomplete with respect to critical data to support a sufficient knowledge of active substance and an appropriate control strategy for both manufacturing process and active substance'.

Linked to this major objection was also a concern related to insufficient demonstration of comparability between commercial batches and batches used during clinical trials. The batches used during clinical trials were mostly manufactured according to historical processes although a single Phase II clinical trial was carried out with a batch manufactured according to the commercial process. A more thorough characterisation study was requested to support the claim that batches manufactured according to previous manufacturing process are representative of batches manufactured according to the proposed commercial process. Specifically, further information was sought on the purity profile, functional characterisation, post translational modification and secondary/tertiary structure of the active substance. Furthermore, process performance data and active substance stability profile were requested to be addressed as part of the comparability exercise… During the procedure the Applicant provided the information requested.

OXERVATE cenegermin ***EPAR***

18 May 2017
EMA/351805/2017

Comparable, but only after more comparability testing: monoclonal antibody

During the upstream scale-up, the major change to the downstream process was increased number of cycles for the chromatography steps.

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

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

TAKHZYRO lanadelumab ***EPAR*** 18 October 2018 EMA/794314/2018

Recommendation not to proceed with change: recombinant protein Factor Xa

BLA was filed in 2015; and a Complete Response Letter (CRL) issued in August 2016 [19]. Of the 18 major issues described in the 20-page CRL, 12 major issues were for CMC. One of these CMC major issues was the lack of comparability between the biopharmaceutical used in the pivotal clinical trials (referred to as Gen 1) and the biopharmaceutical to be approved for the market (referred to as Gen 2) Among the process changes in the Gen 2 process was the major scaleup of the drug substance manufacturing process to 10,000L. In November 2016, a Type A meeting was held with the FDA to discuss resolving the CMC issues in the CRL, especially the lack of comparability between the two processes.

FDA explained that GEN 2 introduces many major manufacturing changes that may have significant impact on the identity, strength, quality, purity or potency of the product as they may relate to its safety and efficacy. There are still much we do not know about the molecule and its manufacturing process as evidenced by the extensive list of deficiencies identified in the CR Letter… With the GEN 2 process, the FDA has specific concerns about product safety (immunogenicity and thrombogenicity) and efficacy (anti-TFPI activity versus anti-FXa activity reversal effects). That is why analytical characterization by itself is not sufficient to support the use of the GEN 2 material in the clinics.

Andexxa

GEN 1 – FDA market approved May 2018
GEN 2 – FDA market approved Dec 2018

Not comparable, but better: change in manufacturing site for production of genetically engineered cells

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

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

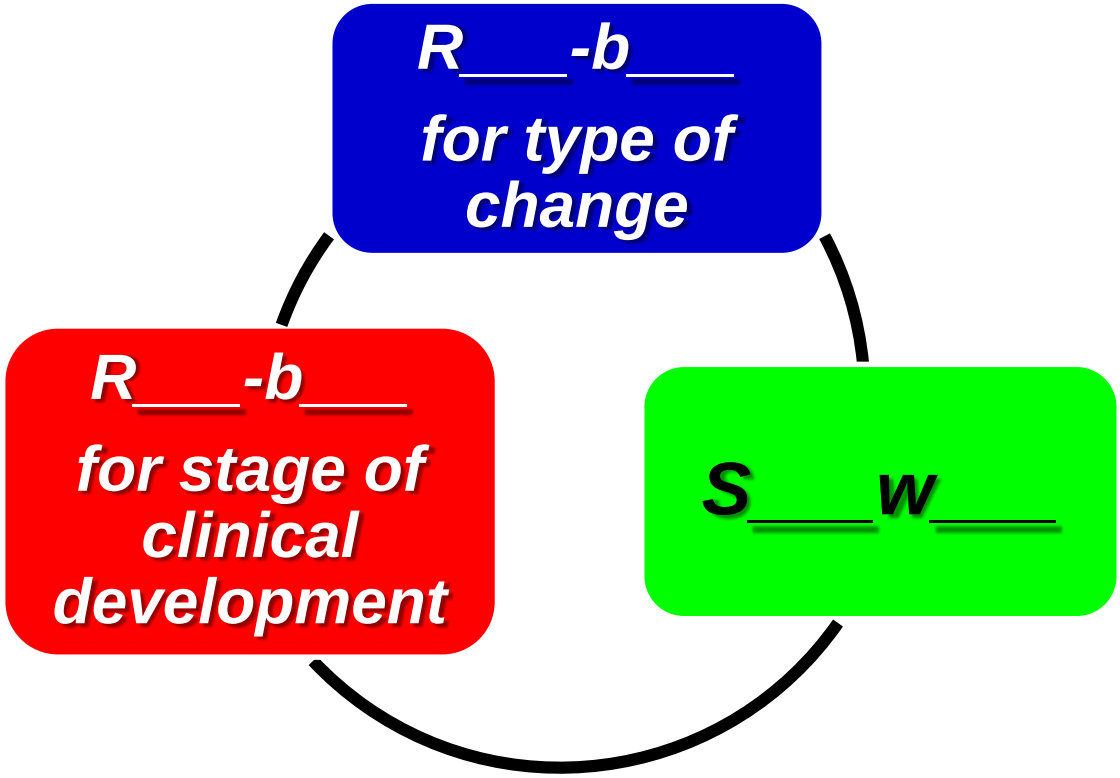
Significantly, the modified manufacturing process at the Novartis Manufacturing Facility at Morris Plains is able to produce a more pure intermediate T cell population before the transduction steps. This important change is expected to improve the vector transduction efficiency and cell growth. Furthermore,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

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

Kymriah

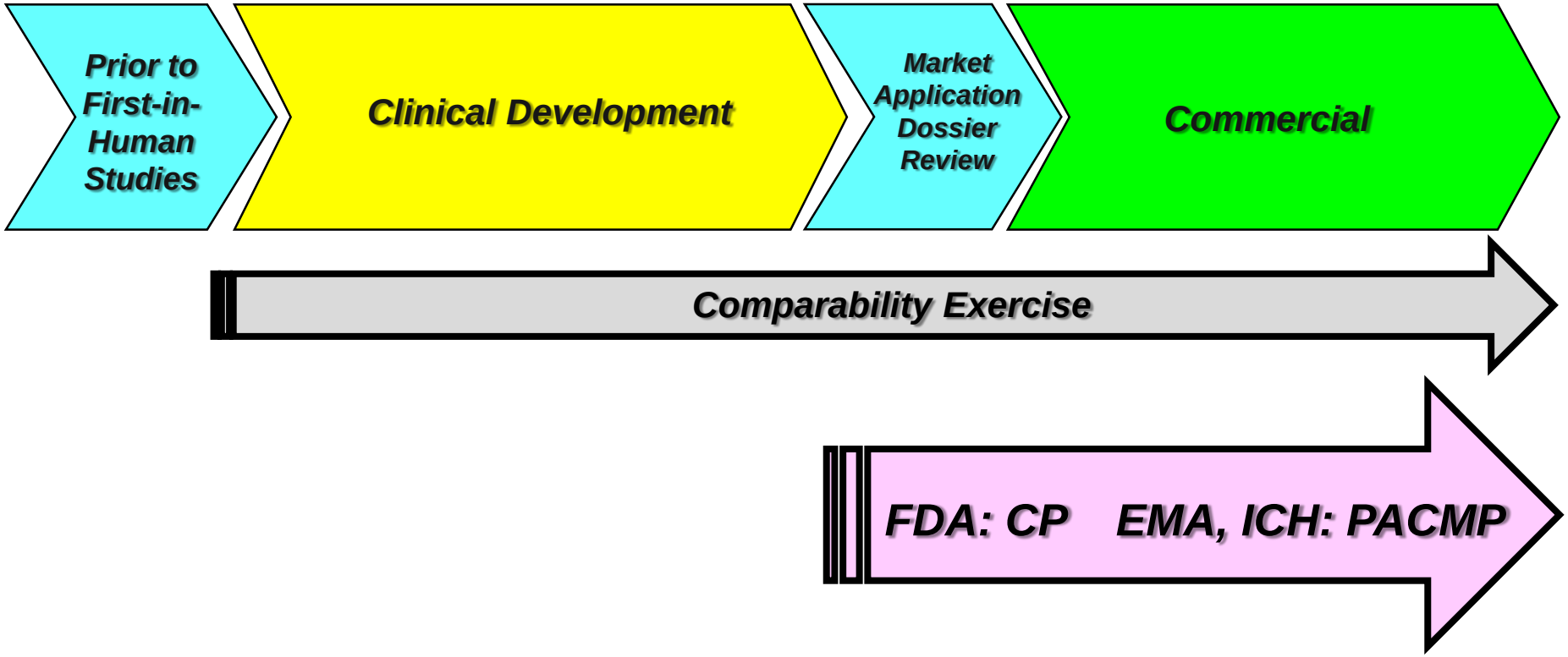
3 essential elements of an effective comparability exercise!

Quick Quiz



Managing Future Process Changes

Regulatory Authority Contracts



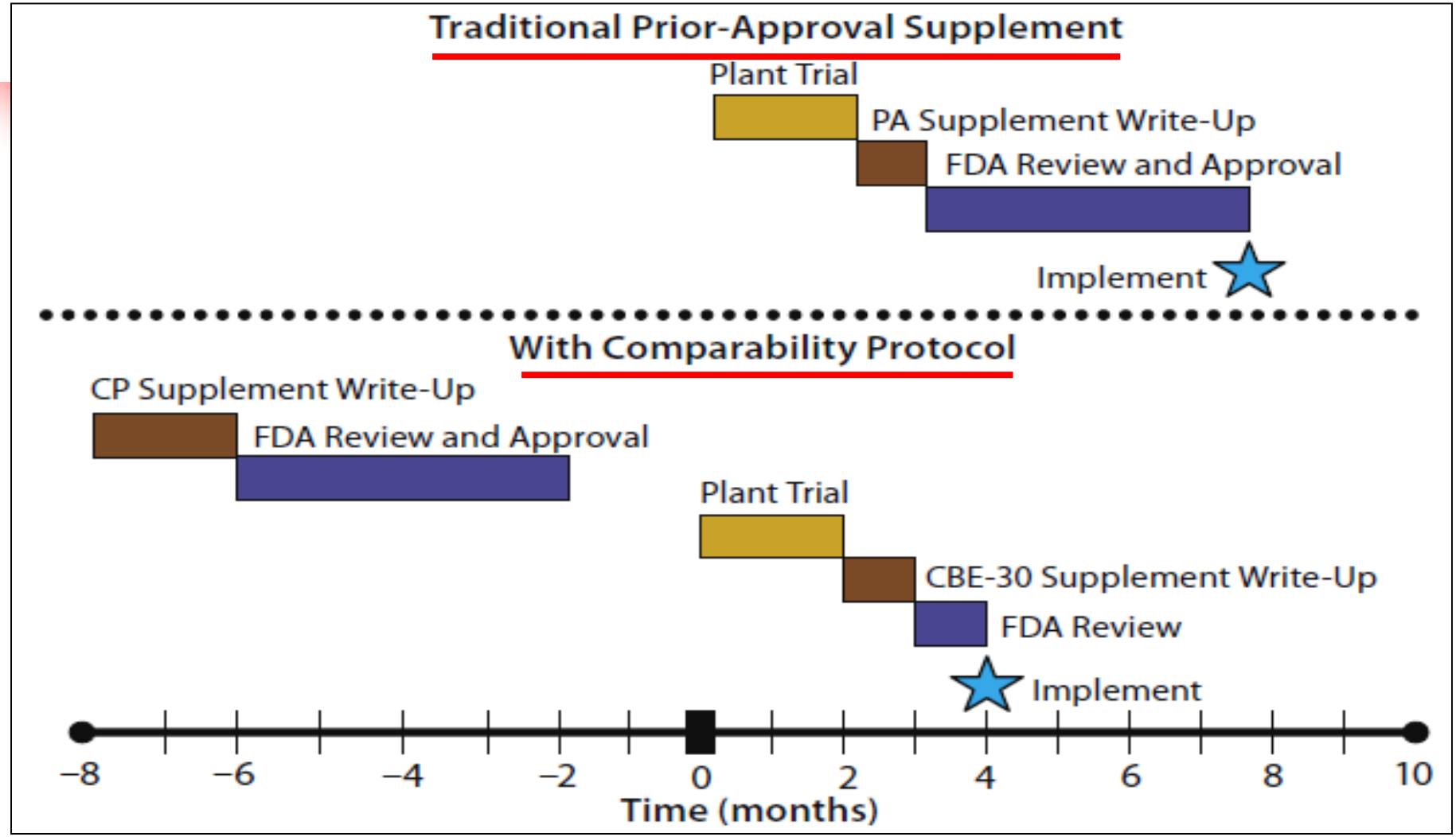
Comparability Protocols (CPs)
Post-Approval Change Management Protocols (PACMPs)

Regulatory Authority 'Contracts'

- ***Prospective*** ***(for future process changes)***
- ***Comprehensive*** ***(must contain sufficient detail)***
  - ***exactly where the process change is occurring***
  - ***what will be done to control the change***
  - ***how will the change be carried out***
- ***Acceptance Criteria*** ***(must be pre-defined)***
  - ***what testing will be carried out***
  - ***relevant and clearly defined acceptance criteria***
  - ***reporting outcome to regulatory authority***

"Potential" Benefit of a Contract

Time to implementation (reduced review time) after study submission!



Caution: if the manufacturer does not follow the 'contract' or if pre-defined acceptance criteria are not met → defaults to PAS!

Comparability contracts are not easy to obtain!

regulatory agency major concerns with submissions

- ***lack of data to support the proposed acceptance criteria***
- ***acceptance criteria for comparability set the same as the release criteria***
- ***Incomplete descriptions of the mechanism for evaluating stability with respect to comparability***
- ***requests for downgrade of submissions that are just not going to be able to be downgraded, because there are requirements in addition to comparability, such as GMP inspections***

Comparability contracts that should be considered most likely future changes

- ***Changing over to a new Working Cell Bank***
- ***Changing over to a new Reference Material***
- ***Extending the approved product shelf life from ongoing stability studies of the PPQ batches***
- ***Drug product manufacturing site change***
- ***Any other manufacturing process change that might happen – e.g., reprocessing due to an integrity test failure after a sterile filtration of the formulated bulk drug prior to filling***

Guidance on comparability contract expectations

Qualification for a New Reference Standard

Q9: You are proposing a qualification protocol for your drug product reference standard that includes assays used for release testing and additional characterization assays. In general, the acceptance criteria you have established for the analytical results of the qualification program are based on a calculation of the mean ± 3SD and would allow for product characteristics in the new reference standard that are out of trend with the desired or expected product characteristics. In our view, the reference standard chosen should be suitable for its intended purpose and provide assurance that the critical quality characteristics of the product do not drift over time. This is particularly important when

EUSA Pharma: We accept the observation, and will withdraw the reference standard qualification protocol from the BLA and will submit a revision as a post-approval supplement, taking into account the Agency's comments by November 2011.

Draft Responses / Comments - BLA 125359 EUSA Pharma and "Erwinaze" Meeting of August 5, 2011 to Discuss CMC Deficiencies

Guidance on comparability contract expectations

Extending the approved shelf life

DUPIXENT (dupilumab) Regeneron Pharmaceuticals, 03/28/2017

We have approved the stability protocol in your license application for the purpose of extending the expiration dating period of your drug product under 21 CFR 601.12.

Imfinzi® (durvalumab) AstraZeneca UK 05/01/2017

We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance **and** drug product under 21 CFR 601.12.

Typically these are the post-approval stability protocols listed in the commitment of Module 3.2.S.7.2 and 3.2.P.8.2

Ocrevus (ocrelizumab) Genentech, Inc. 03/28/2017

Statement not included in the FDA market approval letter!

Manageable to get a comparability contract to add a new drug product manufacturing site

Repatha
evolocumab

Amgen Europe B.V.

21 May 2015
EMA/CHMP/222019/2015

Post Approval Change Management Protocol

The applicant submitted a Post Approval Change Management Protocol (PACMP) for the addition, an alternative manufacturing facility for the formulation and aseptic filling of evolocumab 140 mg/mL prefilled syringes (PFS).

The changes in the manufacturing process were considered to be primarily of GMP concern which would be evaluated at the relevant GMP inspection for the use AML-14. The presented investigational quality results did not reveal any significant impact on quality attributes. Overall the strategy described in the comparability protocol seems suitable. The approach taken by the applicant in determining the equivalence limits is considered acceptable and would be appropriate for the PACMP as well. The proposed post approval change management protocol is considered suitable to support a finished product manufacturing site addition.

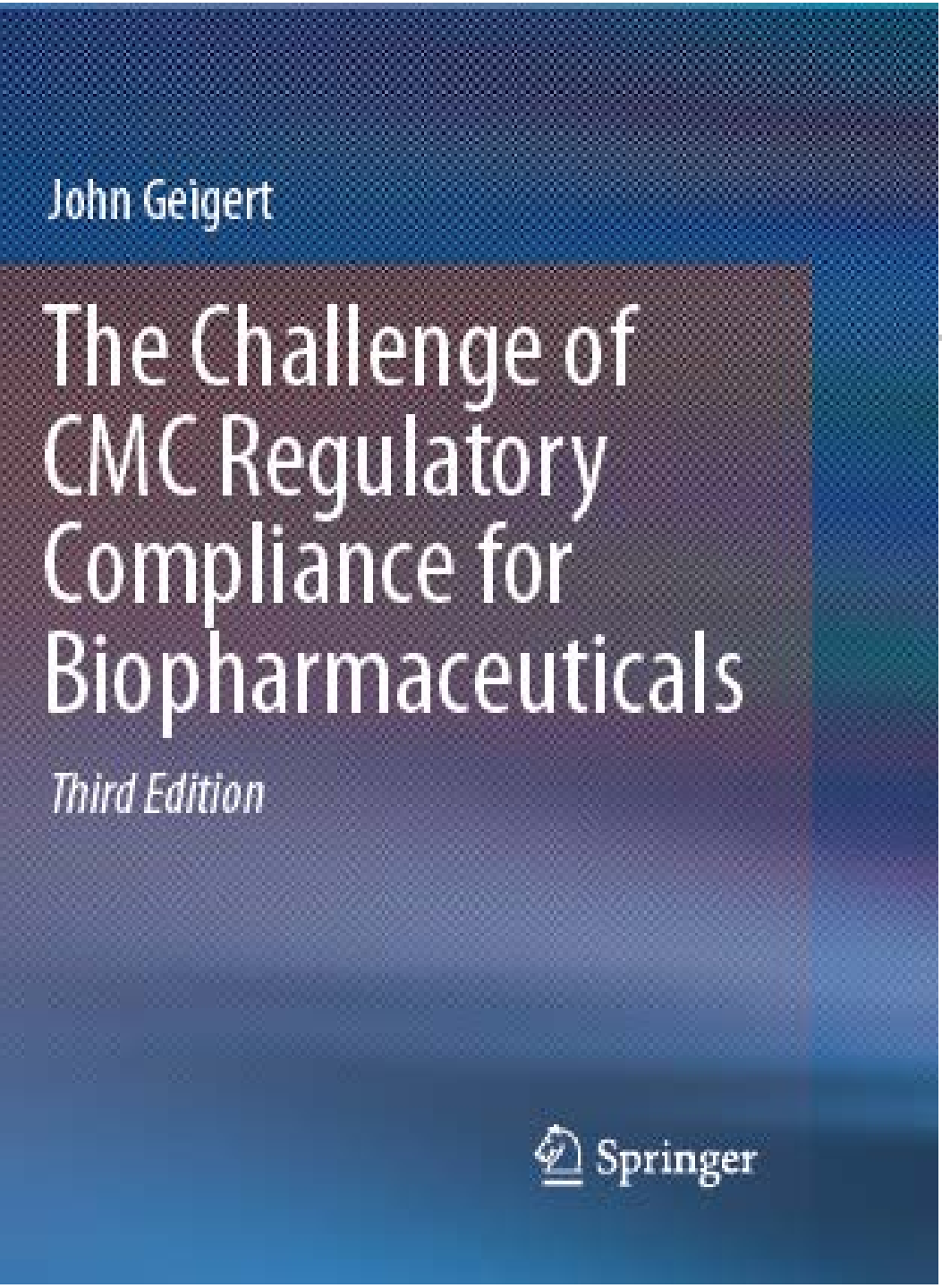
Challenging, but doable, to get a comparability contract to add a new drug substance manufacturing site

Question 6a: Does the Agency agree that an appropriately designed comparability protocol, submitted with the BLA, may upon favorable review be considered the basis for acceptability of the new drug substance manufacturing site?

FDA Response to Question 6a and 6b: Although an appropriately designed protocol may provide a foundation for the acceptability of the new drug substance manufacturing site, the described protocol is not likely to be sufficient to form the basis for downgrading the reporting category of the anticipated new drug substance manufacturing site. The depth of the detail to be provided in the proposed comparability protocol is not clear. A protocol to support a reduced reporting category for a drug substance site change would require, for example, a significant level of detail regarding the changes to the manufacturing process, the risk evaluation performed to assess the potential for effects of these changes on product quality, and the planned validation strategy, in addition to the details of the analytical comparability approach. An inspection "directly for blinatumomab" would be performed in the context of the review of a PAS. It is unlikely that a successful GMP inspection for a comparable commercial product would be sufficient to result in a reduced reporting category for a drug substance site transfer. Issues related to the anticipated drug substance site transfer and inspections are compounded due to the intended use of a contract manufacturing site.

Meeting Category:	CMC pre-BLA	**Product Name:**	blinatumomab ***Blincyto***
		Indication:	Treatment of B-cell lymphoma/leukemia
Meeting Date and Time:	April 9, 2014 from 3:00 - 4:30 P.M.	**Sponsor/Applicant Name:**	Amgen, Inc.

All to easy to make a mistake (be excessively optimistic and too subjective) in interpreting product comparability – get a second honest opinion!



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Thank you!