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 for a biopharmaceutical manufacturing process!

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 CMO*
- ***Improve product quality***
  - *Addition of a new chromatographic polishing step*
  - *Tightening of product release specifications*
- ***Increase manufacturing capacity***
  - *Higher productivity cell line*
  - *Manufacturing site change for scale-up or scale-out*

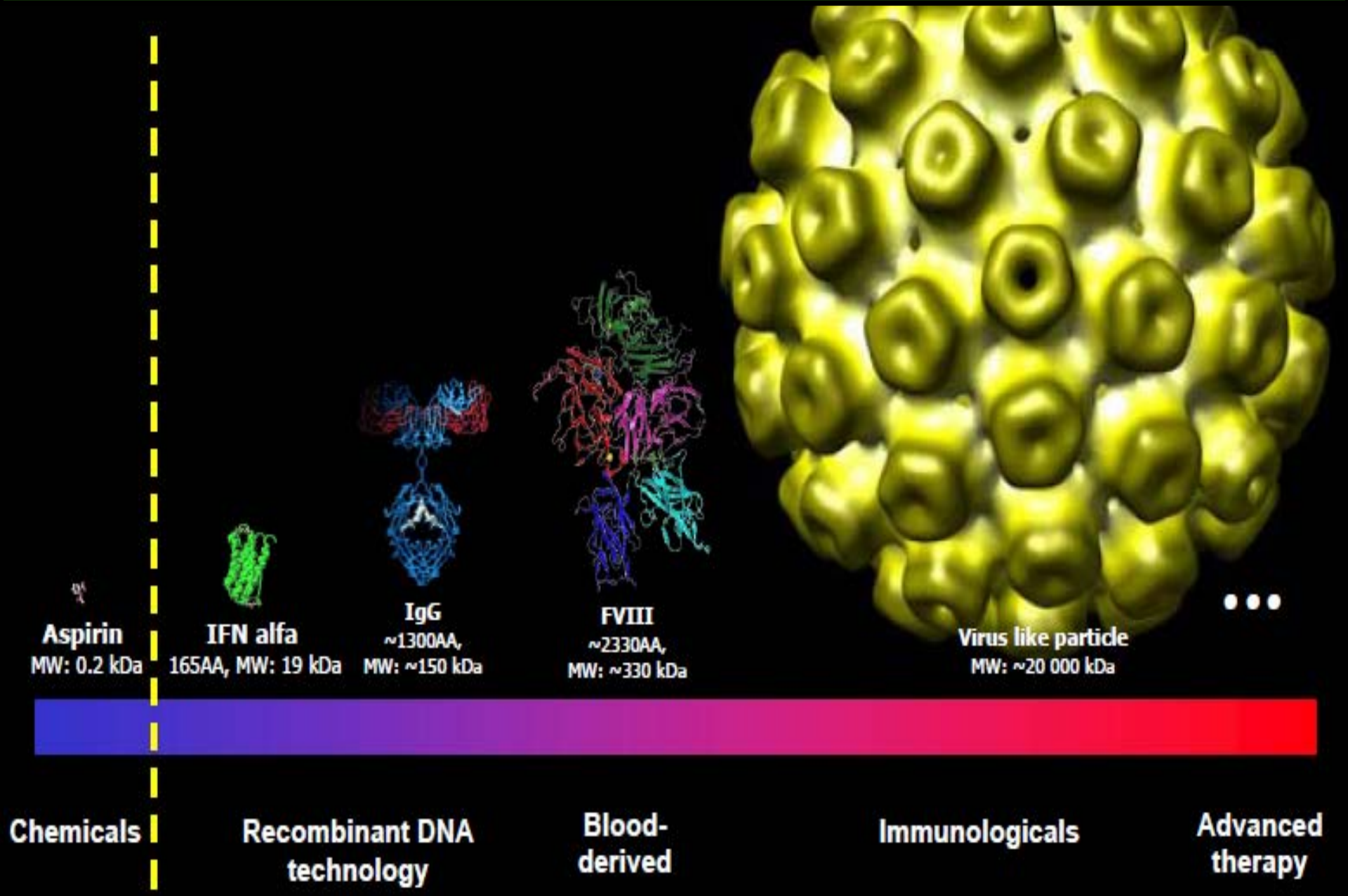
Effectively managing the process change – 2 parts

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 (biopharmaceutical)***

→ *increasing molecular complexity and decreasing analytical analysis* →

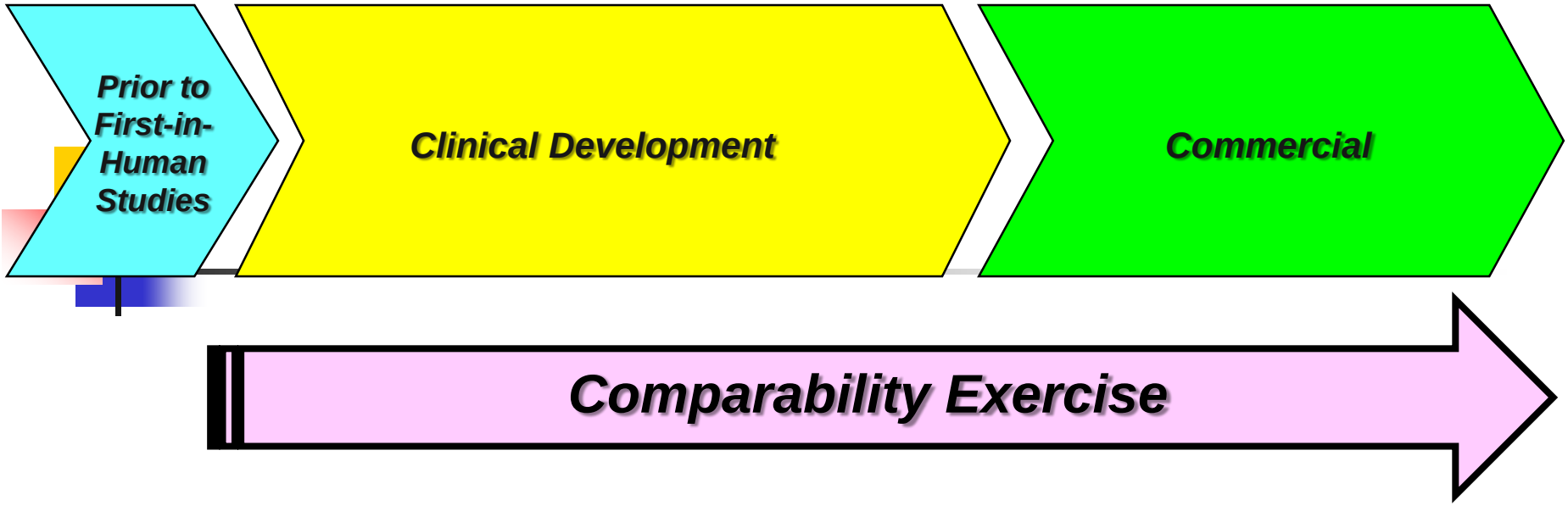
equivalent *'highly similar'*



"Highly Similar"

the standard for all biopharmaceutical process changes (innovator and biosimilar)

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



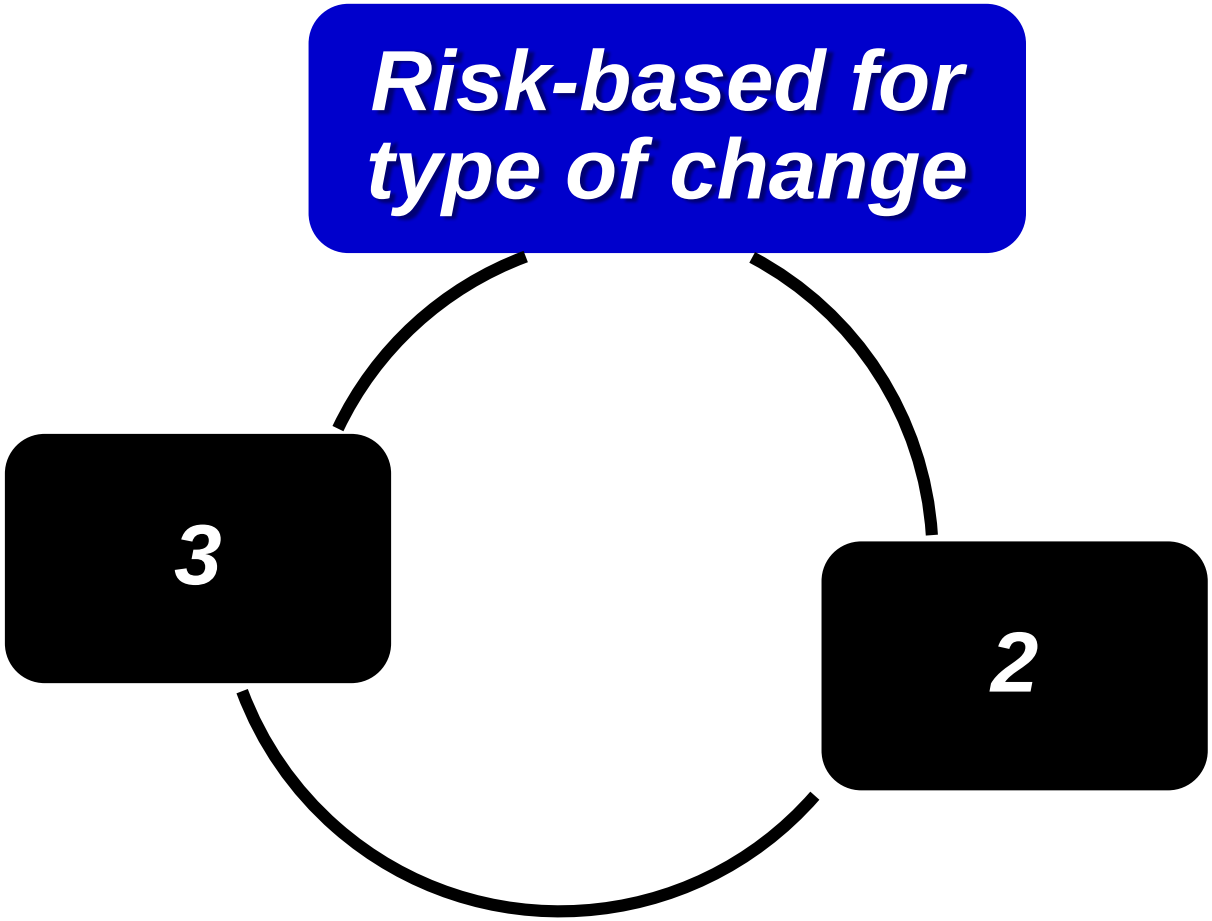
"The goal of the comparability exercise is to ascertain that pre- and post-change drug product is comparable in terms of quality, safety, and efficacy."

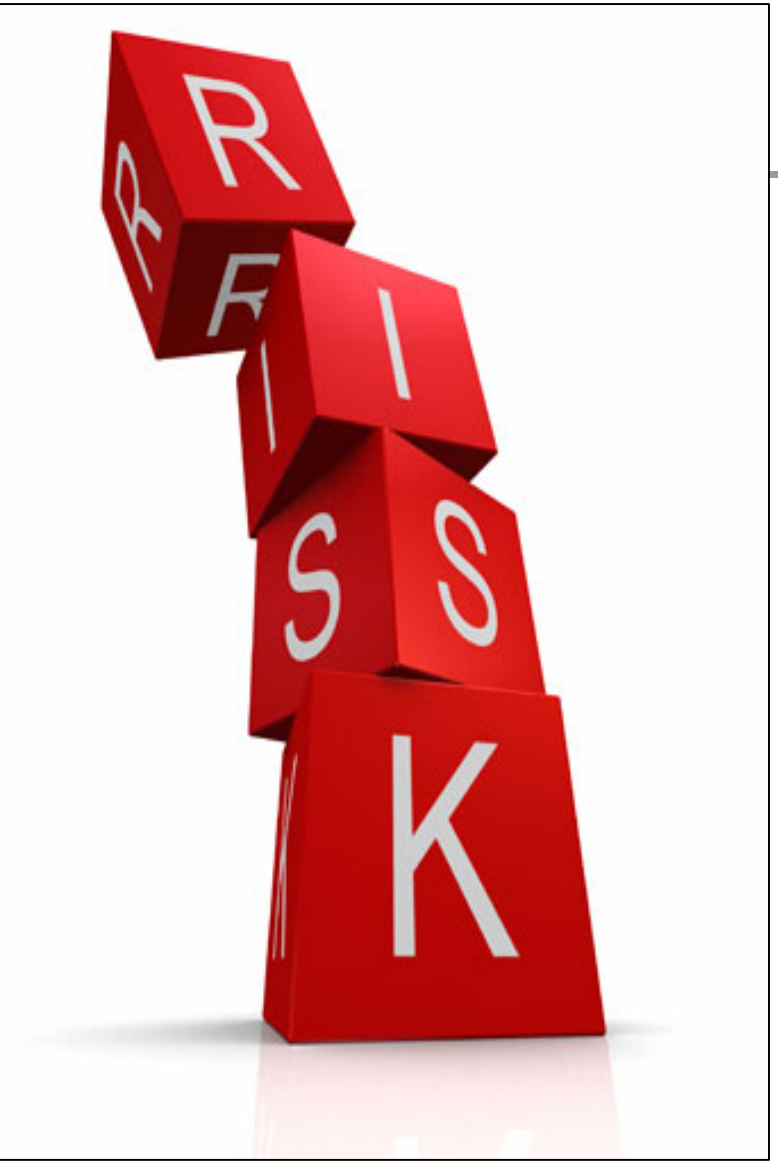
ICH
harmonisation for better health

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

Q5E

3 essential elements of an effective comparability exercise!

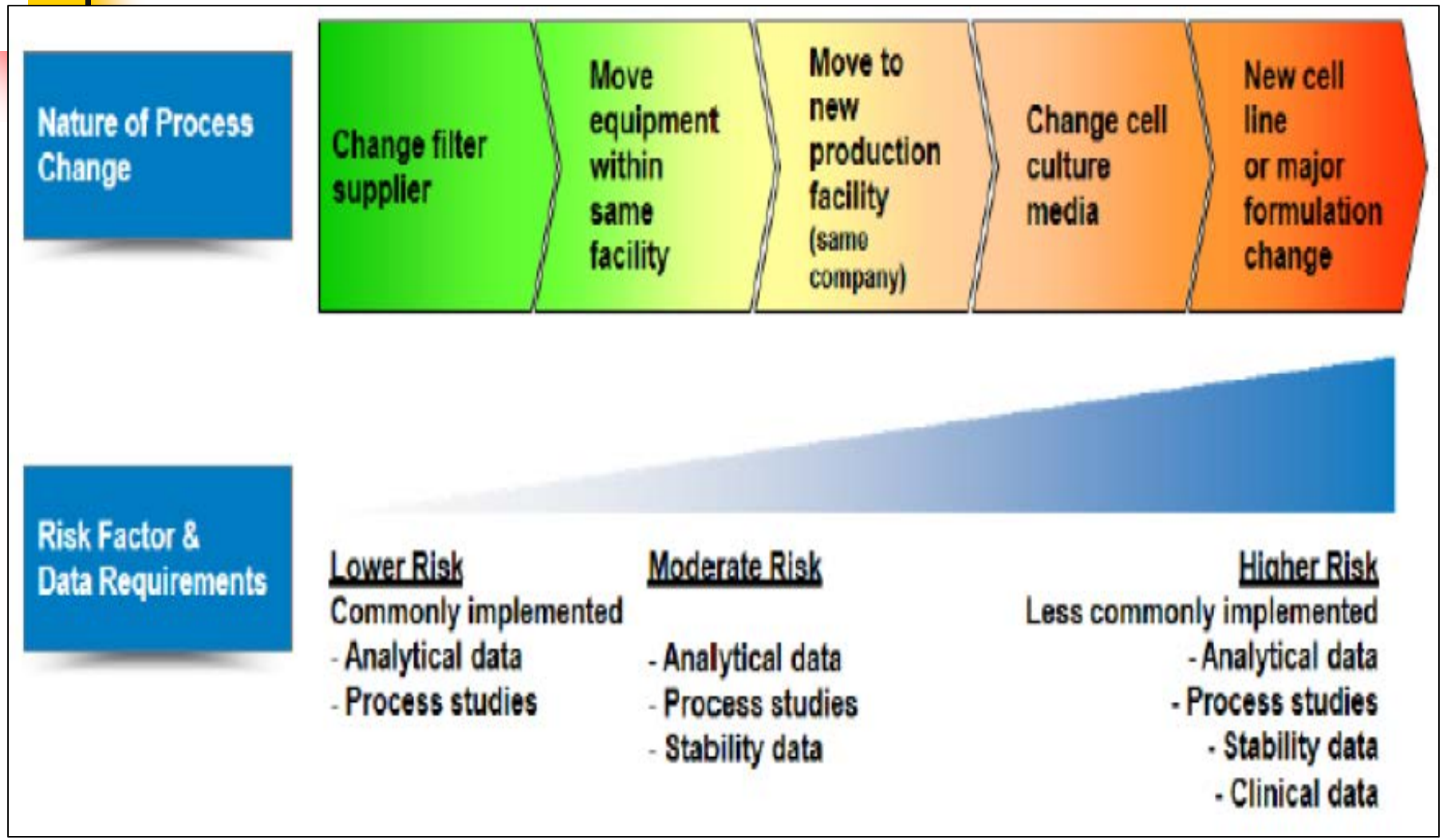




Risk-Based Analysis for Type of Change

1) ***Assess the potential impact of the process change on the quality of the product (e.g., potency, purity, identity)***
   - ***Some process changes are more major – requiring more evidence of comparability***
   - ***Some process changes are more minor – requiring less evidence of comparability***
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



AMGEN

Regulatory recommendations – during clinical development

Risk Level	Examples of Biopharmaceutical 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 Annual Report) **Non-substantial**	– Anything that is not significant or non-substantial

Assessing level of comparability risk 'after market approval

Regulatory authority guidance for manufacturing process changes

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)**

Same 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	

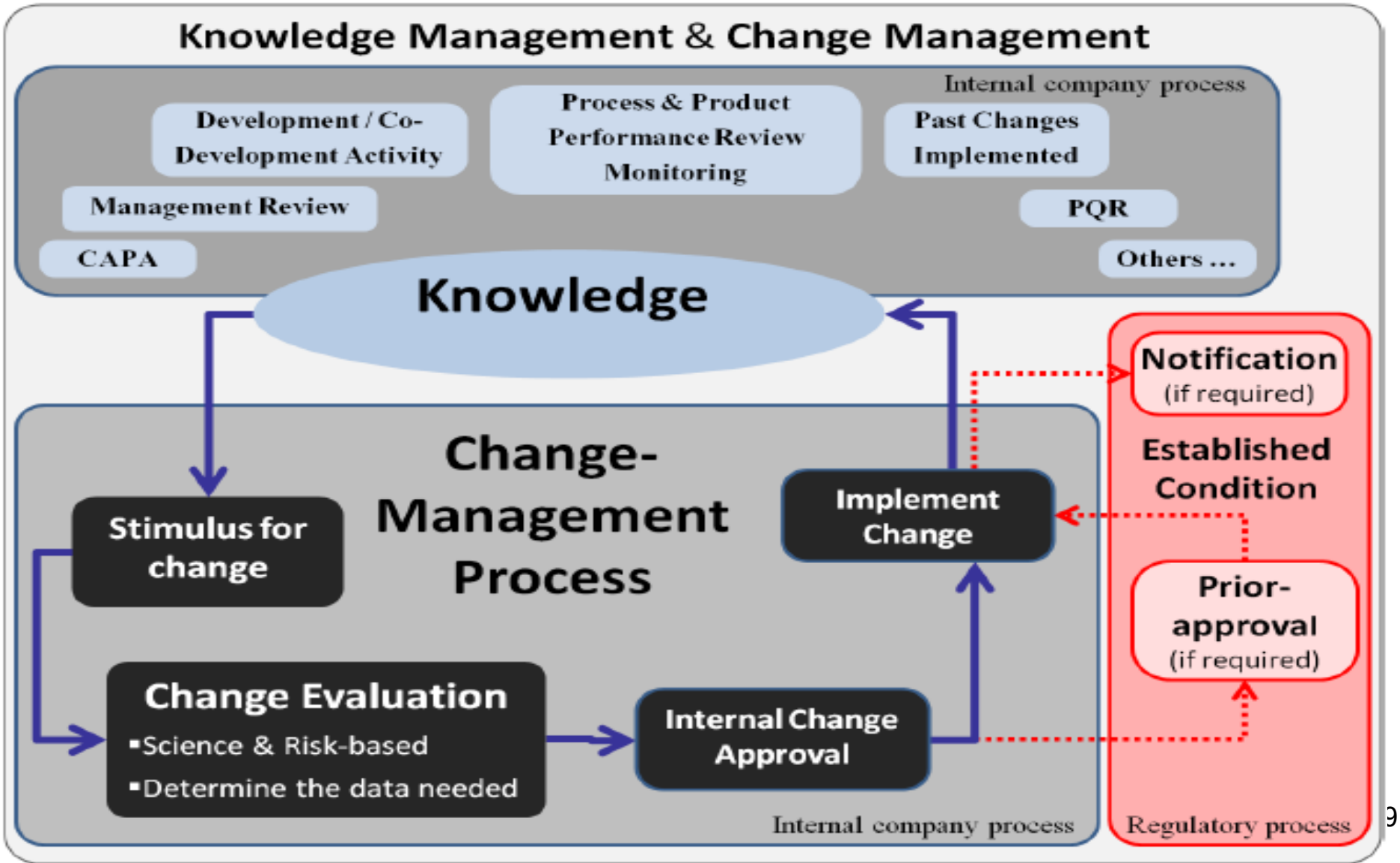
Consistent with FDA PAS for biologics

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



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

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

Warning Letter
January 2017

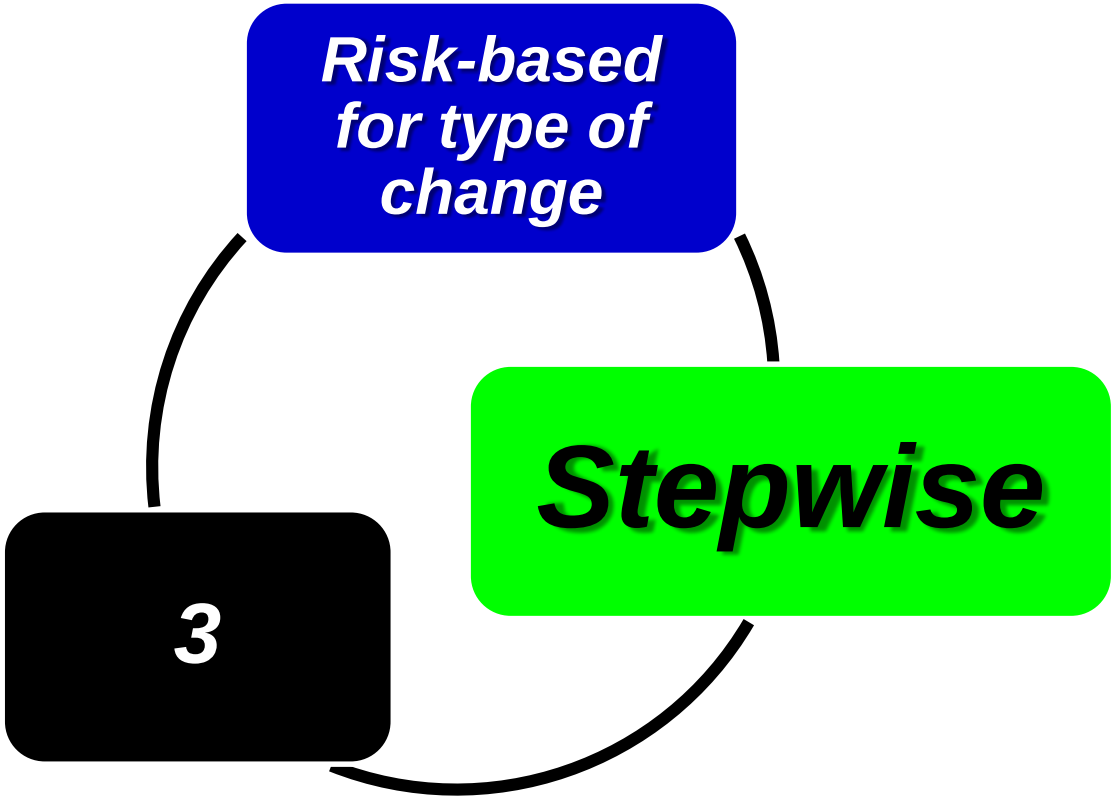
Erwinaze
(Asparaginase)

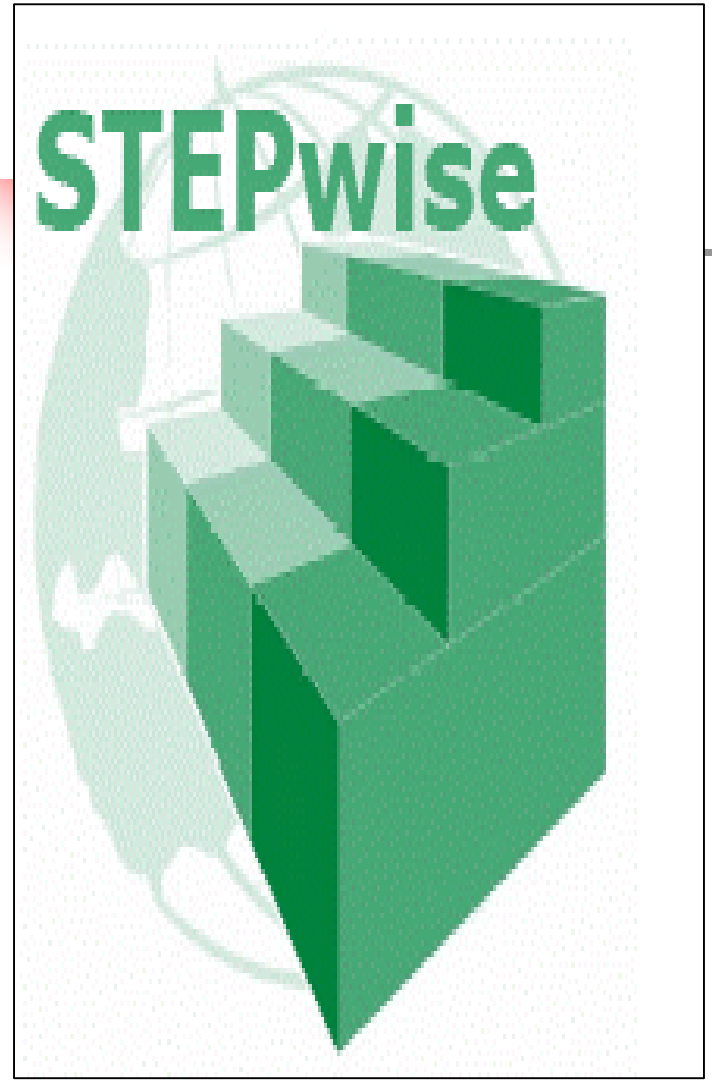
1. Failure to establish and follow change controls to evaluate all changes that could affect the production and control of intermediates or API.

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 Approach

- ***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!

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)***

The extent of 'relevant, comprehensive' product characterization today is illustrated in biosimilarity testing – Enbrel (recombinant Fc fusion protein)

Sandoz EPAR 2017

Molecular parameter	Attribute	Methods for control and characterization	Key findings
Primary structure	Amino acid sequence	Reducing peptide mapping (MS)	Identical primary sequence[1)]
		Amino acid analysis	Ratios amino acids comparable[2)]
	Degradation product N-terminal heterogeneity	LC-MS	Erelzi has lower amounts of diketopiperazine except for one aged batch
	Disulfide bridging	Non-reducing peptide mapping	Identical disulfide bridging pattern
	Free cysteines	Ellman's assay, non-reducing peptide mapping	Slightly lower levels of free cysteins for Erelzi
Higher order structure	Secondary and tertiary structure	CD spectroscopy (NUV, FUV)	Comparable higher order structure
		DSC	Tm1 and Tm2 consistent to EU-authorized batches
		H/D exchange	Comparable higher order structure[3)]
		FT-IR	FT-IR profiles comparable between all batches
		1D-NMR	Overlay of spectra comparable[3)]
		X-ray crystallography	Identical higher order structure

Biosimilars have to be highly similar not equivalent

Molecular parameter	Attribute	Methods for control and characterization	Key findings
Molecular Mass/Size	Molecular mass	MALDI-ToF; SEC-MALLS	Intact mass comparable
Charge	Charge/Size	2D-DIGE	Qualitative pattern comparable to EU-authorized batches. For minor variants quantitative differences detectable
Content	Content	UV/Vis spectroscopy	Equivalent content
Glycosylation	O-Glycans	MALDI-ToF of released O-glycans (after sialidase digestion)	Identical qualitative O-glycan pattern
	Glycosylation site occupancy and site specific (e.g. Fc part) N-glycan analysis	Peptide mapping coupled to ESI-MS NP-HPLC	Qualitatively, Erelzi N-glycan pattern comparable except for additional two minor abundant N-glycans qG3/tG4 and bG1-N-F. Quantitatively, lower levels of non-fucosylated N-glycans detectable for Erelzi
	Glycation	Boronate affinity chromatography	Lower levels of glycated variants detectable for Erelzi
	Sialic Acids incl. NGNA (N-glycolylneuraminic acid)	Overall sialylation by AEX WAX of 2-AB labelled N-glycans RP-HPLC of DMB labelled sialic acids released from N- and O-glycans	Overall amounts of sialic acids comparable (e.g. by DMB labelling)

Molecular parameter	Attribute	Methods for control and characterization	Key findings
AA-sequence	Variability of N-terminus (– Leu, – Leu-Pro)	Reducing Peptide Mapping	Comparable N-terminal pattern; lower amounts of L1(3-34) (=N-terminus – Leu-Pro) for Erelzi
	Variability of C-terminus: – Lys, truncation to proline amide	Reducing Peptide Mapping	Comparable C-terminal pattern; lower amounts of lysine variants for Erelzi
Size	Aggregation	SEC/FFF-MALLS, AUC	Smaller amounts of oligomers for Erelzi
	Fragmentation	CE-SDS, SEC, SDS-PAGE	Slightly higher purity and lower amounts of high molecular weight variants for Erelzi
Charge	Charged variant profile	CZE, cIEF	Lower amounts of basic variants and higher amounts of acidic variants in Erelzi
Hydrophobic	Hydrophobic variants	RPC	Lower amounts of post-peak variants in Erelzi
Amino acid modifications	Oxidation	RP-HPLC, Peptide Mapping	Comparable amounts of oxidized variants
	Deamidation	Reducing Peptide Mapping	Comparable amounts of deamidated variants

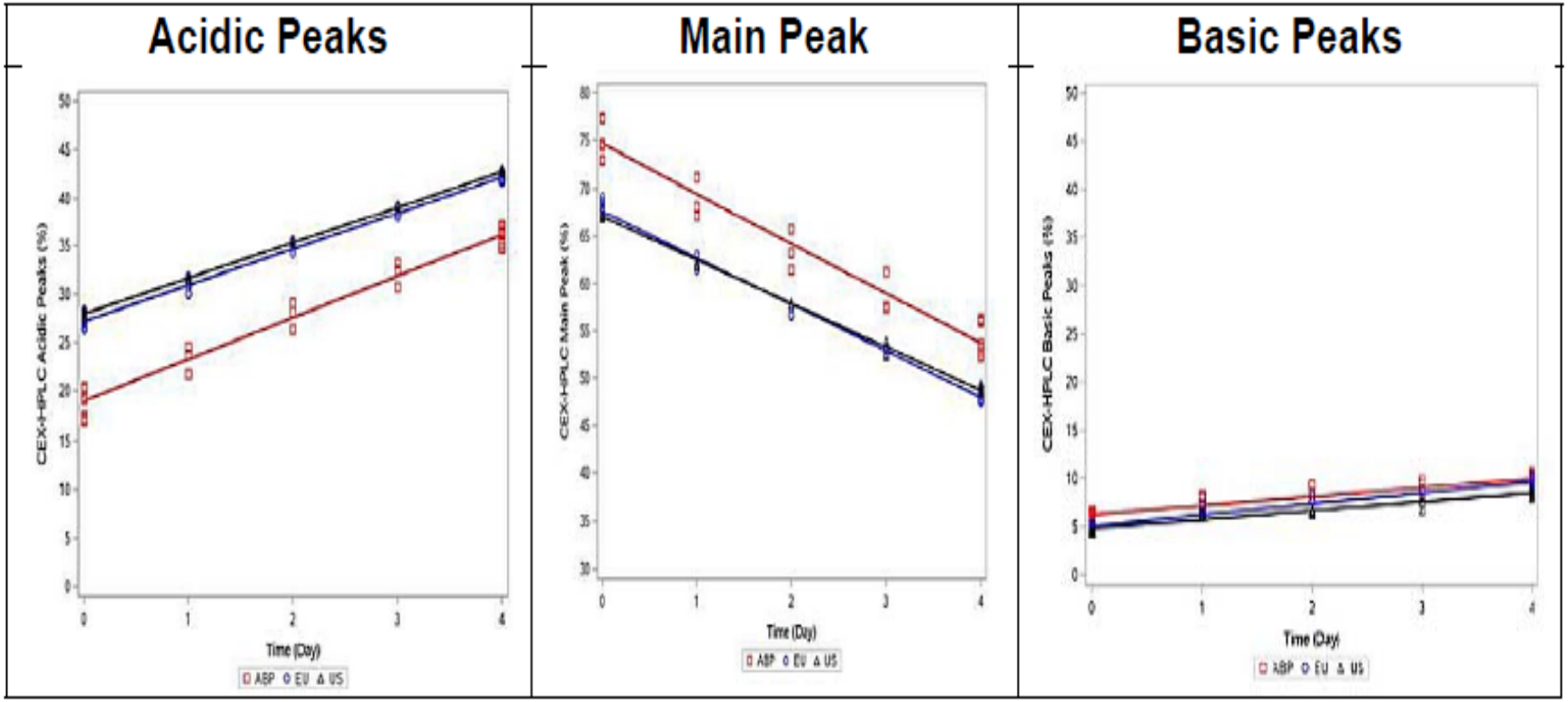
	Test	Method / cell line	Key findings
Binding assays	TNF-α binding assay	Surface plasmon resonance assay	Comparable potency
	FcγRIIIa (F158 and V158) binding assay	Surface plasmon resonance assay	Comparable K_D
	FcγRIIIb binding assay	Surface plasmon resonance assay	Comparable K_D
	FcγRIIa binding assay	Surface plasmon resonance assay	Comparable K_D
	FcγRIIb binding assay	Surface plasmon resonance assay	Comparable K_D
	FcγRIa binding assay	Surface plasmon resonance assay	Comparable K_D
	FcγRn binding assay	Surface plasmon resonance assay	Comparable K_D
	FcRn binding assay	Surface plasmon resonance assay	Comparable K_D
	C1q binding	C1q binding ELISA	Comparable binding
In-vitro bioassays	TNF-α neutralization reporter gene assay	Luciferase reporter gene assay	Comparable potency
	TNF-β neutralization reporter gene assay	Luciferase reporter gene assay	Comparable potency
	Apoptosis inhibition assay	Cell based apoptosis assay	Comparable inhibition
	ADCC assay	Cell based ADCC assay, ADCC surrogate assay	ADCC activity of Erelzi lower than ADCC activity of Enbrel[1)]
	CDC assay	Cell based CDC assay	Slightly outside the range for CDC activity

Comparison of stability stress studies today illustrated by biosimilarity testing – Avastin monoclonal antibody

Avastin (monoclonal antibody) – 50°C; 4 days

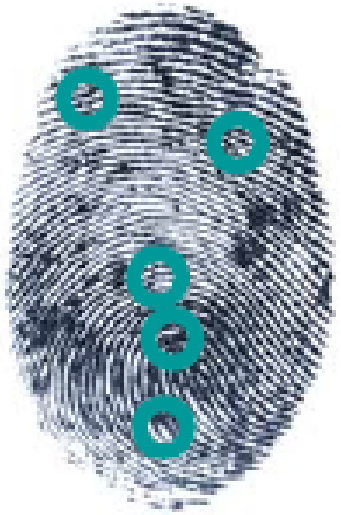
2017 FDA Advisory Committee Amgen

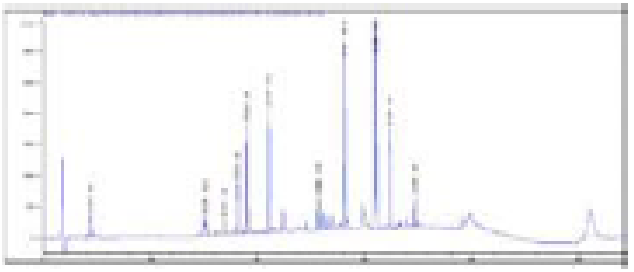
Figure 11 - CEX-HPLC acidic, main, and basic peak degradation rates for ABP215, US-licensed Avastin, and EU-approved bevacizumab at 50°C



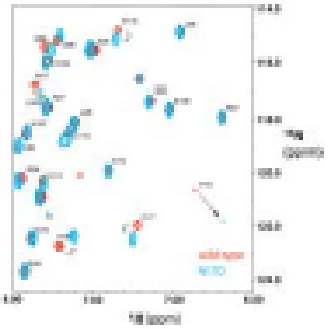
Source: Figures excerpted from the Applicant's 351(k) BLA submission

Fingerprinting

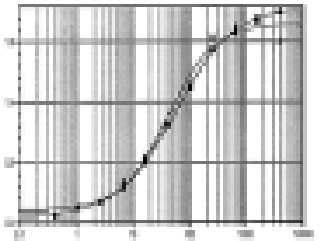




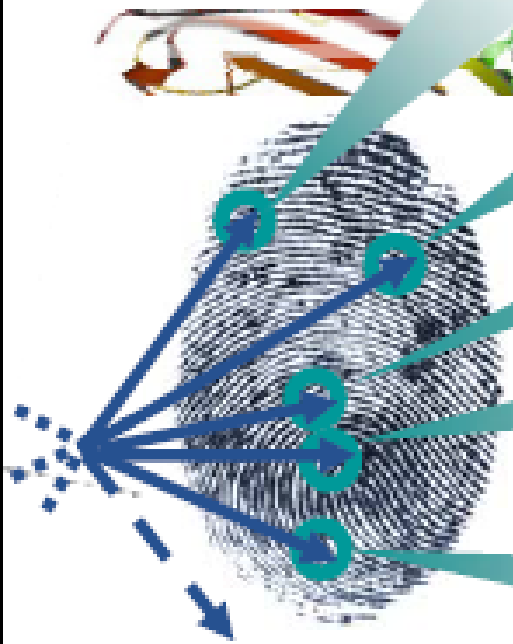
Sequence & Modifications

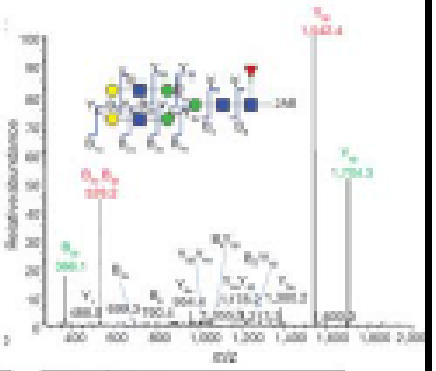


Higher Order Structure

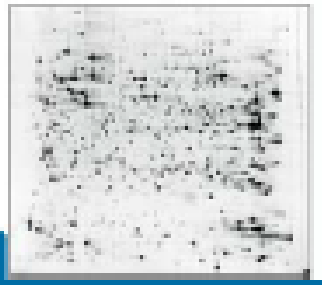


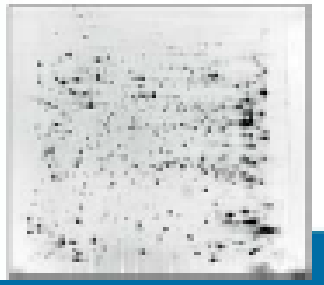
Bioactivity





Glycoforms





Impurity Profile

Regulatory authorities question the step 1 quality comparability results presented in submissions!

4 case examples – different outcomes

- ***Recombinant protein – rejected, not comparable***
  - *Process changes: lyo → liquid, formulation composition*
  - *Quality comparability not done head-to-head, and weakness of analytical methods used*
- ***Recombinant protein – comparable, but only after more testing***
  - *Process change: manufacturing site change*
  - *Stress stability testing 'appeared' different*
- ***Genetically engineered virus – comparable***
  - *Process change: plasmid vector construct for transient virus production*
- ***Genetically engineered cell – not comparable, but better***
  - *Process change: manufacturing site change*

Rejected, not comparable: IFN-β1 recombinant protein

Since that time, some process changes have been introduced to further refine production and purification of IFN beta-1a derived from the BIC 8622 cell line. One of the major changes was the change from the human serum albumin (HSA)-containing, lyophilised dosage form to the HSA-free liquid formulation.

The Company has conducted comparability studies both between developmental manufacturing processes and between batches produced at pilot and commercial scale using the current manufacturing process. Comparability between the developmental lyophilised formulation and the current liquid formulation cannot be regarded as demonstrated because of the limitations of the analytical methods at the time of their manufacture and a lack of direct comparison of different material in the same test .For pilot and commercial scale batches of the current manufacturing process, the Company has compared results of in-process controls, characterisation data, batch release data and stability data. Generally, comparability between material from pilot and commercial scale production is regarded as proven.

BioPartners

not recommend the granting of the marketing authorisation

Biferonex

July 2009
EMEA/334517/2009

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: change in plasmid vector for transient production of genetically engineered virus

A number of changes and improvements were made to the manufacturing process throughout clinical development. Between Phase I/II and the Phase III study there was a more substantial change in the manufacturing process. The vector used for transduction was changed from #35 to #48, with a different sequence and manufactured in a different cell line with a different vector manufacturing process.

To demonstrate comparability between the commercial process and previous versions of the processes, the Applicant submitted data on validation (active substance and finished product), stability (vector, active substance and finished product), and comparability (vector, active substance and finished product). These validation data were considered adequate to confirm comparability for vector in a head-to-head comparison. The comparability of viral vector commercial manufacturing process with previous versions of the process was considered to be demonstrated.

Zalmoxis replication-defective retroviral vector

23 June 2016
EMA/CHMP/589978/2016

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.

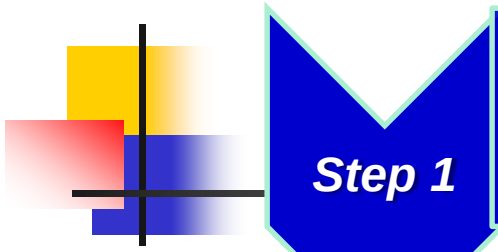
A site-to-site comparability study was conducted at the Novartis and University of Pennsylvania facilities, and demonstrated that CD19 CAR-positive T cells manufactured by both facilities met all lot release specifications. However, the characterization of cell growth and transduction efficiency showed 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

Comparability Exercise – Stepwise!



Step 1

- **Quality Comparability (Analytical Studies)**

continue if residual uncertainty remains

Optional for innovator biopharmaceuticals

Mandatory for biosimilars

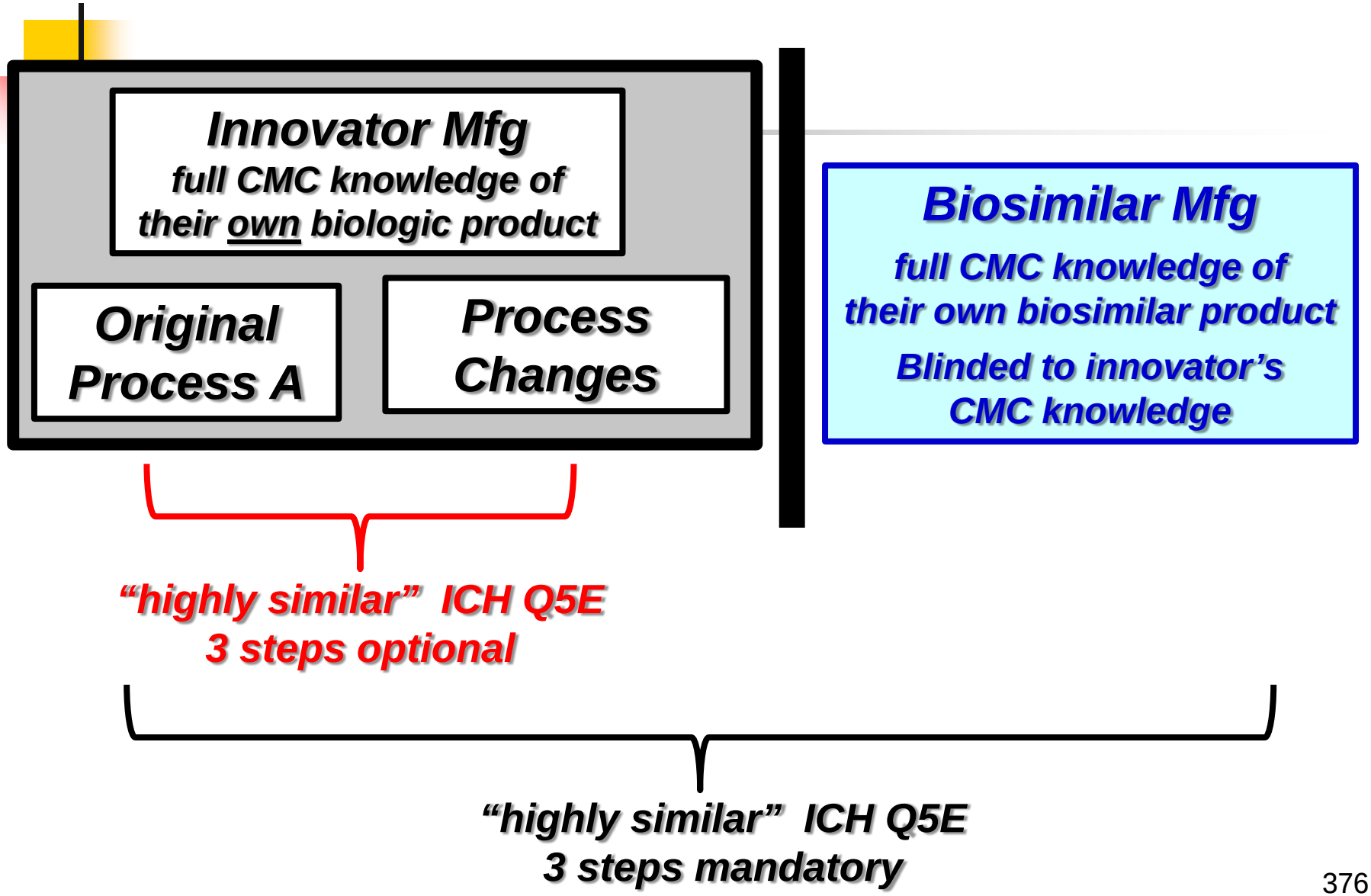
Step 2

- **Nonclinical Comparability (Animal Studies)**

Step 3

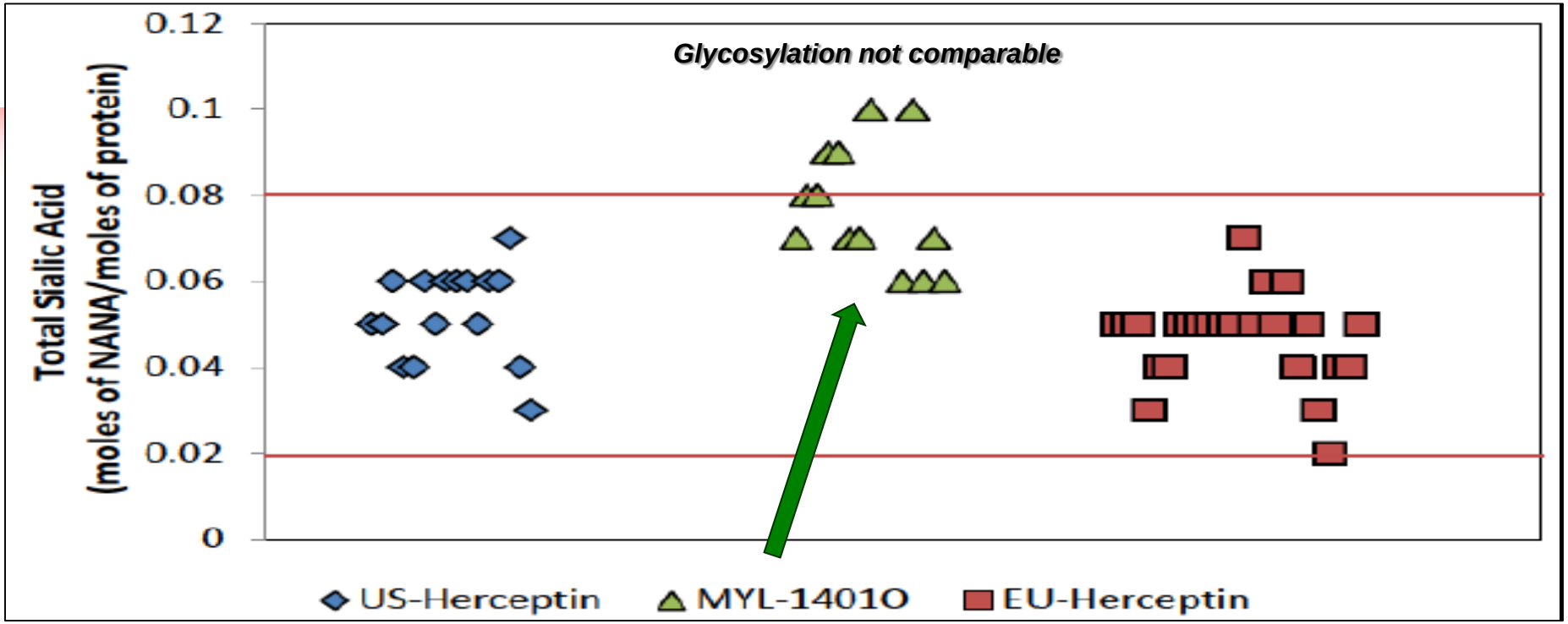
- **Clinical Comparability (Human Studies)**

Residual uncertainty drives need for Steps 2 and/or 3



Residual uncertainty in a biosimilar: Ogivri

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

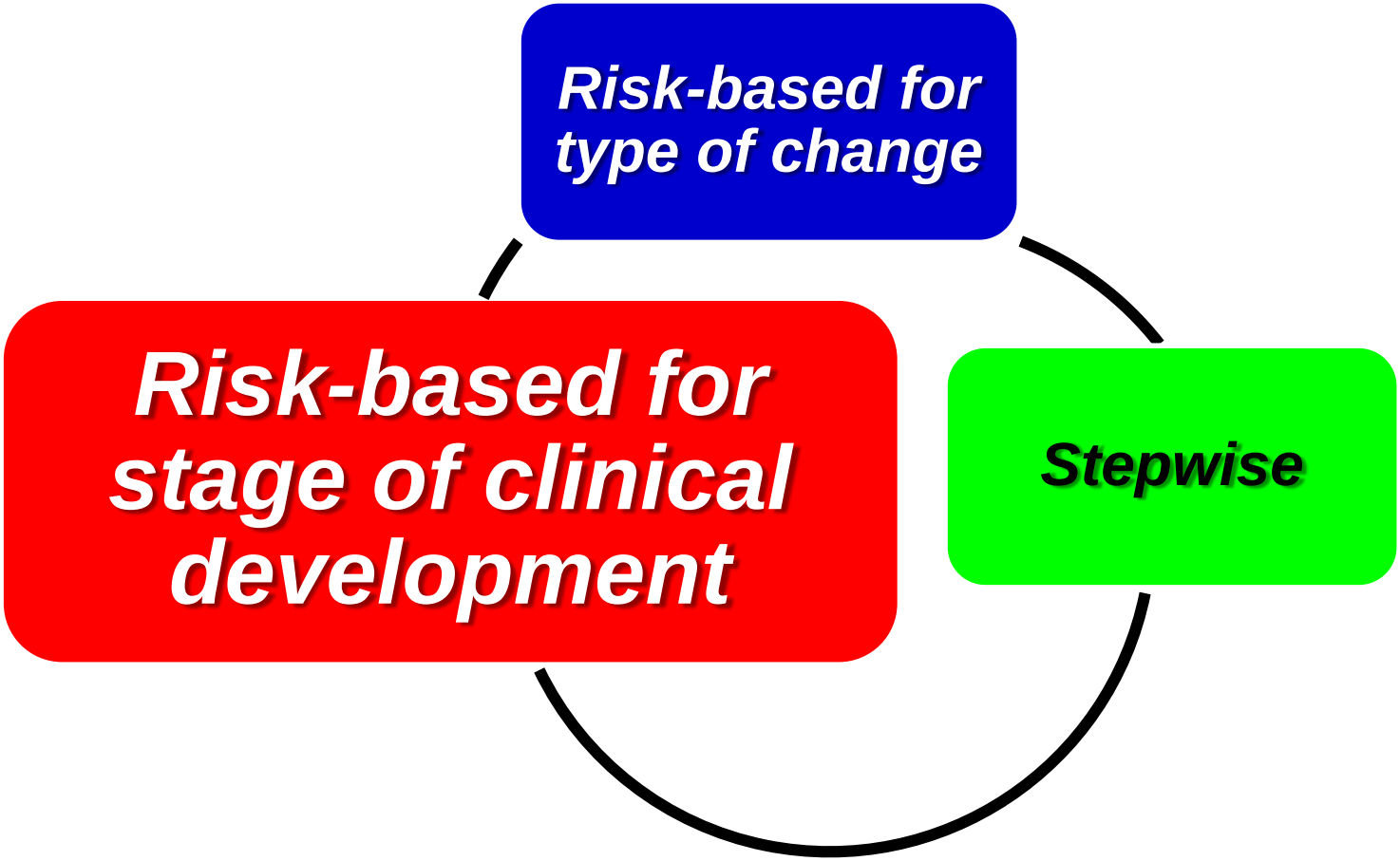


Residual uncertainly addressed by human PK (Step 3)

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

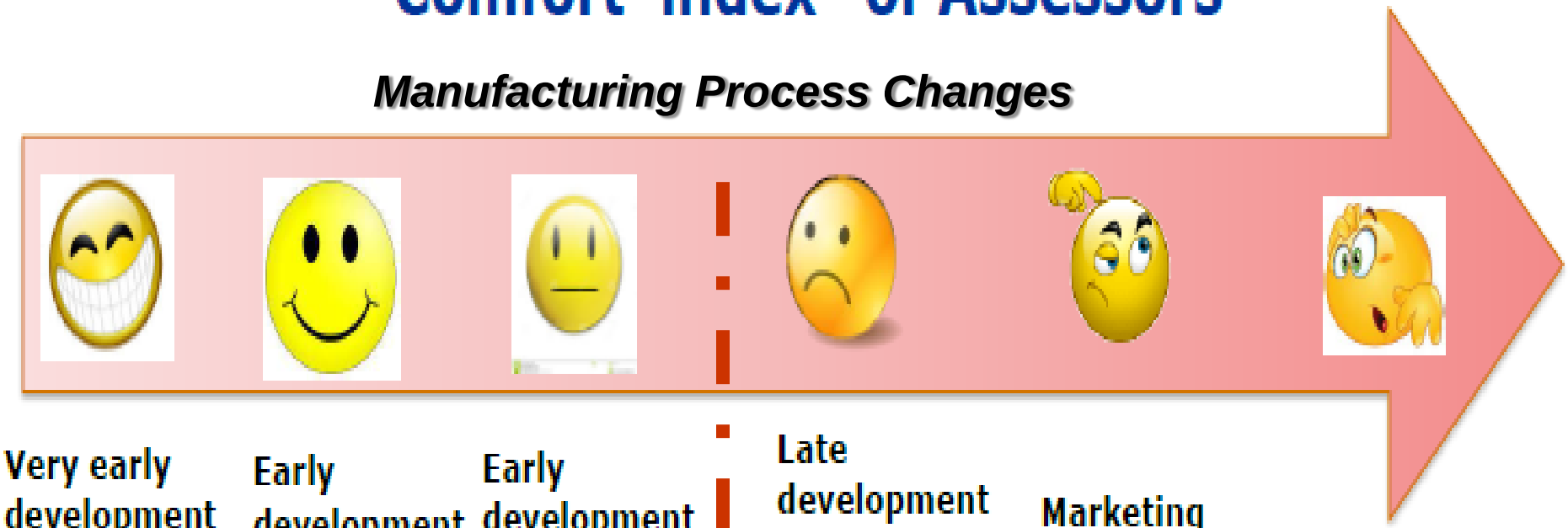
2017 FDA Advisory Committee Meeting

3 essential elements of an effective comparability exercise!



"Comfort index" of Assessors

Manufacturing Process Changes



Very early development before non- and clinical studies

Early development non- clinical studies conducted

Early development phase I/II clinical studies conducted

Late development phase III pivotal clinical studies conducted

Marketing Authorisation

Post Approval

comparability testing to be 'adequate'

comparability testing to be 'comprehensive and thorough'

regulatory concern increases if efficacy data could be impacted

Phase-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 issues with a phase-appropriate approach mentioned earlier due to expedited (seamless) clinical studies, biosimilars, and gene therapies

Biopharmaceutical 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.

Phase-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.'

2 case examples of manufacturing process changes at late clinical phase

- ***Monoclonal antibody produced by CHO cells***
  - ***Process changes: DS & DP manufacturing site(s), new dosage form (prefilled syringe)***
  - ***Comparability outcome: SUCCESSFUL***
- ***Recombinant protein produced by CHO cells***
  - ***Process change: DS manufacturing scale***
  - ***Comparability outcome: VERY INTERESTING***

Amgen – monoclonal antibody from CHO

Prolia (denosumab)

Goal: convince both FDA and EMA of biologic comparability between 2 different DS and DP manufacturing sites and between 2 different dosage forms

Early Clinical	Phase 3 Clinical	Proposed Commercial
ATO DS ATO DP vial	(product comparability needed to support changes)	ACO DS + BID DS BIP DP PFS ACO DS APR DP vial + PFS

ATO – Amgen California

ACO – Amgen Colorado APR – Amgen Puerto Rico

BIP – Boehringer Ingelheim Germany

Product comparability between the two DS manufacturing sites

(Amgen site and Boehringer Ingelheim site)

Step 1

- ***Quality Comparability***
  (Analytical & Functional Studies)

During scale-up of the process and transfer, minor changes to the process related to up-scaling and facility/equipment related have been made. As regards the process as performed at the two authorised manufacturing sites, comparability was demonstrated by comparison of IPC data, batch data on drug substance, additional characterisation data and data of forced degradation.

Step 2

- ***Nonclinical Comparability***
  (Animal Studies)

comparative non-clinical PK/PD study in cynomolgus monkeys.

Product comparability between the two DP dosage forms

(glass vial and pre-filled syringe)

Step 1

- ***Quality Comparability***
  (Analytical & Functional Studies)

Comparability studies to address a change of manufacturing site and the difference in composition between the vial and the pre-filled syringe were performed. Analytical comparability between the two presentations, lot release, additional product characterization, forced degradation, and accelerated stability studies were performed. In the extended characterisation, the two presentations have been thoroughly compared side-by side using a wide range of biochemical and biophysical methods along with a comparison of the potency. The comparability program is considered sufficient, and, based on

Step 3

- ***Clinical Comparability***
  (Human Studies)

Furthermore, a bioequivalence study and an immunogenicity study

Goal was achieved!

EUROPEAN MEDICINES AGENCY

MAA Approval

London, 18 March 2010
Ref.: EMA/21672/2010

ACO (DS) → BIP (DP PFS)

BIP (DS) →

Food and Drug Administration
Silver Spring MD 20993

BLA APPROVAL
June 1, 2010

ACO (DS) → APR (DP vial + DP PFS)

Genzyme – recombinant protein from CHO

Myozyme

Goal: convince both FDA and EMA of biologic comparability between 2 different drug substance manufacturing scales

Early Clinical	Phase 3 Clinical	Proposed Commercial
160L DS scale	2000L DS scale (late introduction)	160L + 2000L DS scales

(product comparability needed to support scale-up)

Both DS manufacturing scales needed to meet anticipated worldwide supply needs! (~36 kg/year)

Genzyme CMC strategy for the 2000L DS scale up

Targeted scale-up – minimize changes to the process

During scale-up of the process from the 160 L to 2000 L scale, efforts were made to minimize the number of process changes implemented during scale up, due to the potential for such changes to alter the biochemical attributes of the macromolecule. Changes were made to the seed train (bioreactor inoculum preparation) and bioreactor operations to improve process productivity and to facilitate bioreactor operations at the larger scale. The purification train was also scaled up in accordance with the capacity required for the increased conditioned medium feedstream at each scale. Purification process changes were minimized, and chromatography scale-ups were linear, such that column heights, linear flow rates, column volumes of buffer applied and column loading remained constant. All changes were implemented only after process development data indicated that they would have the desirable outcomes with no adverse impact on product quality.

The challenge: the late introduction during Phase 3 of the 2000L scale!

Product comparability between the <u>two DS scales</u>

(160L and 2000L)

Step 1

- ***Quality Comparability***
  (Analytical & Functional Studies)

- ***<u>Upon review of BLA</u>: FDA raised significant concerns about the difference in phosphorylated and sialylated glycan pattern between the 160L and 2000L product***
- ***<u>Upon review of MAA</u>: EMA raised significant concerns about the higher process-related impurity levels (especially the host cell proteins) in the 160L product compared to the 2000L product***

Desired goal was not exactly achieved!

EUROPEAN MEDICINES AGENCY

MAA Approved – March 2006

160L scale – rejected
2000L scale - approved

Food and Drug Administration
Silver Spring MD 20993

BLA Approved – April 2006

160L scale – approved
2000L scale – rejected

(Furthermore, all references to the 2000L scale had to be removed from Module 3 and the BLA resubmitted)

Also of note, when the 2000L scale material (actually 4000L) was finally approved by the FDA in 2010, because of the glycan differences, it was considered a separate product from the 160L material – Lumizyme BLA

WARNING

Do not make manufacturing process changes while your market application dossier is under review!

Case Example

Savient Pharm – recombinant protein enzyme

Krystexxa (PEGloticase)

Submitted in BLA	***While BLA was under FDA review***
Phase 3 process	***'minor' process change***

pegylation of drug product was changed from 9 PEGs per protein molecule to 10 PEGs

After a 10-month review, FDA issues a Complete Response Letter (CRL) July 2009

"The major issue resulting in a recommendation to not approve the original BLA application centered on the fact that the sponsor made a major change to the manufacturing process after the Phase 3 clinical trial.

This change resulted in a to-be-marketed product that was not physico-chemically comparable to the product used in the Phase III clinical trial."

FDA gave Savient Pharm a choice

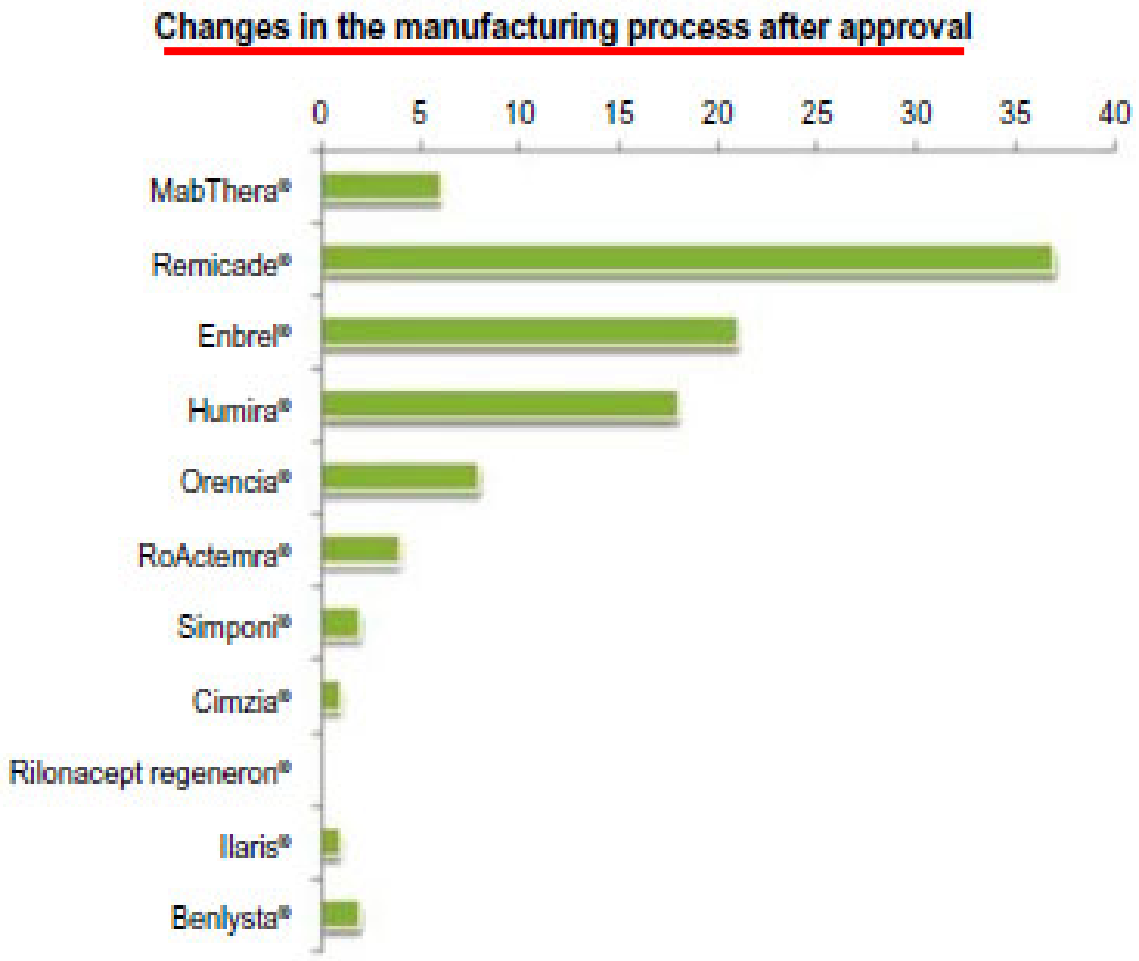
"Additional clinical studies are necessary to support the use of pegloticase manufactured with the commercial process or, alternately, you may validate the Phase 3 process for commercialization."

Which option would you choose?

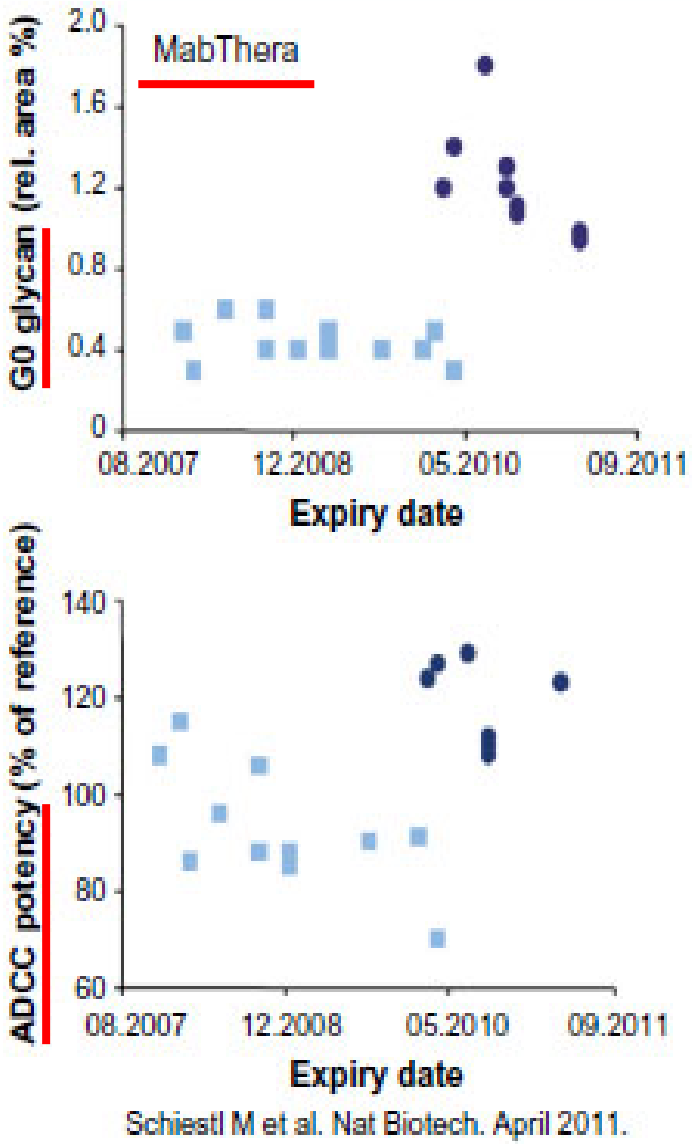
Market approval September 2010 (16 month delay)
First commercial campaign (2011) – batches rejected for failing to meet specs

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.

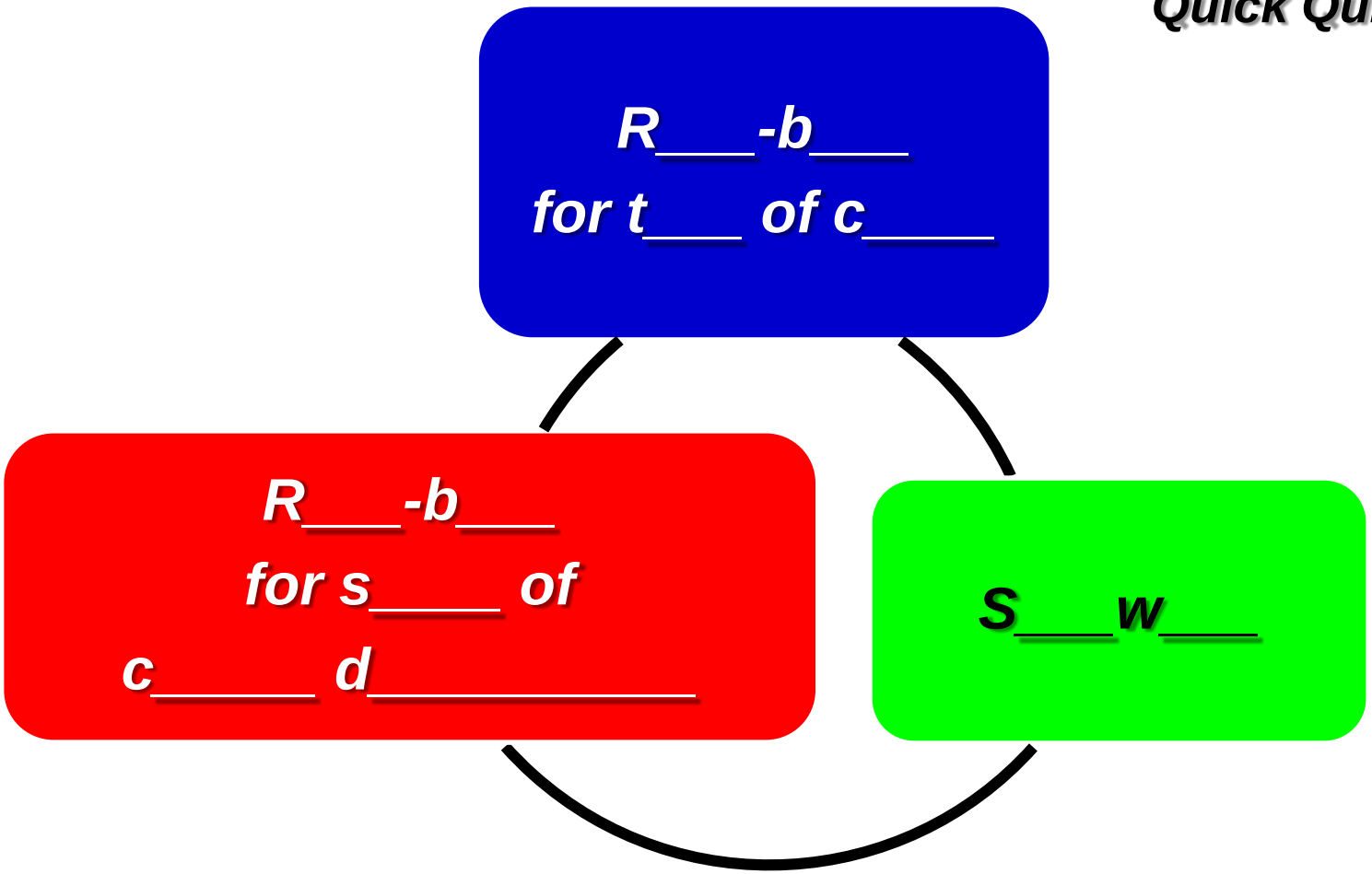


Schiestl M et al. Nat Biotech. April 2011.

ADCC: Antibody-dependent cell-mediated cytotoxicity.

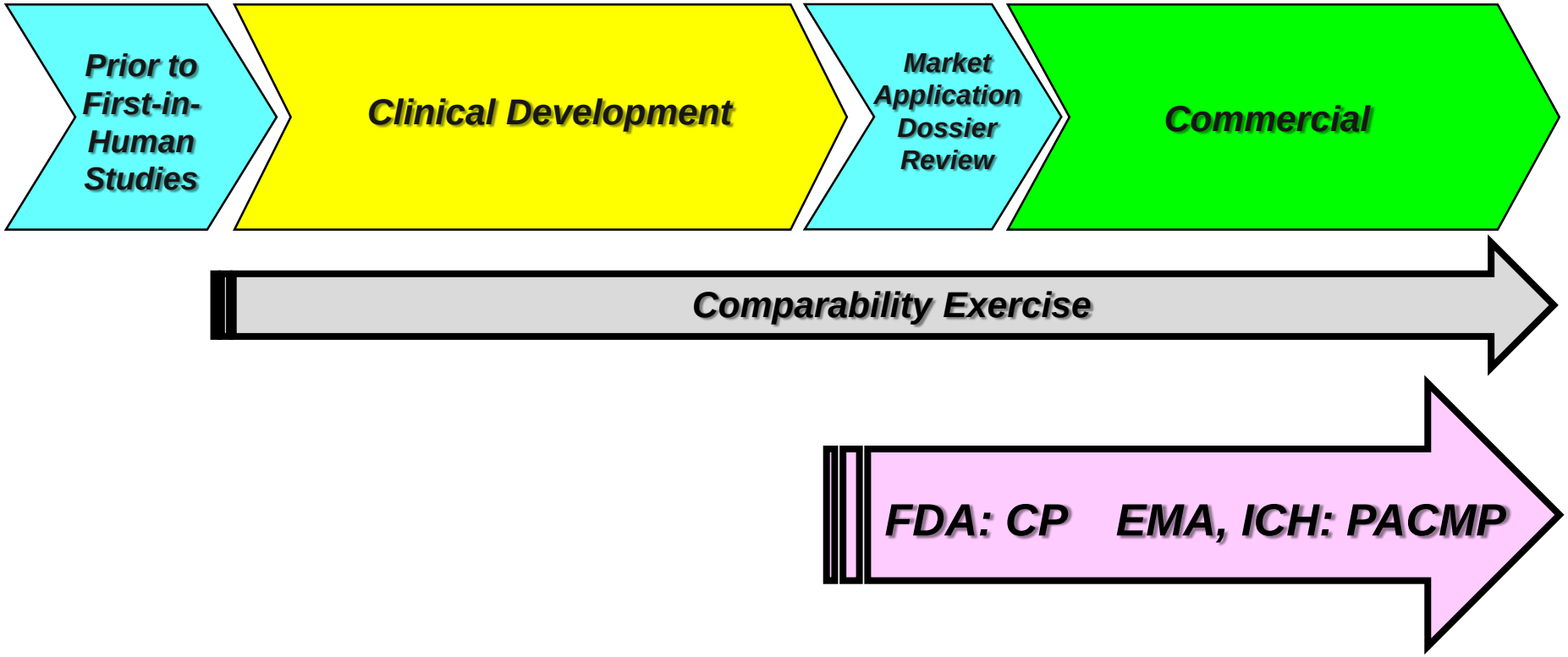
3 essential elements of an effective comparability exercise!

Quick Quiz



Managing Future Process Changes

Regulatory Authority Contracts



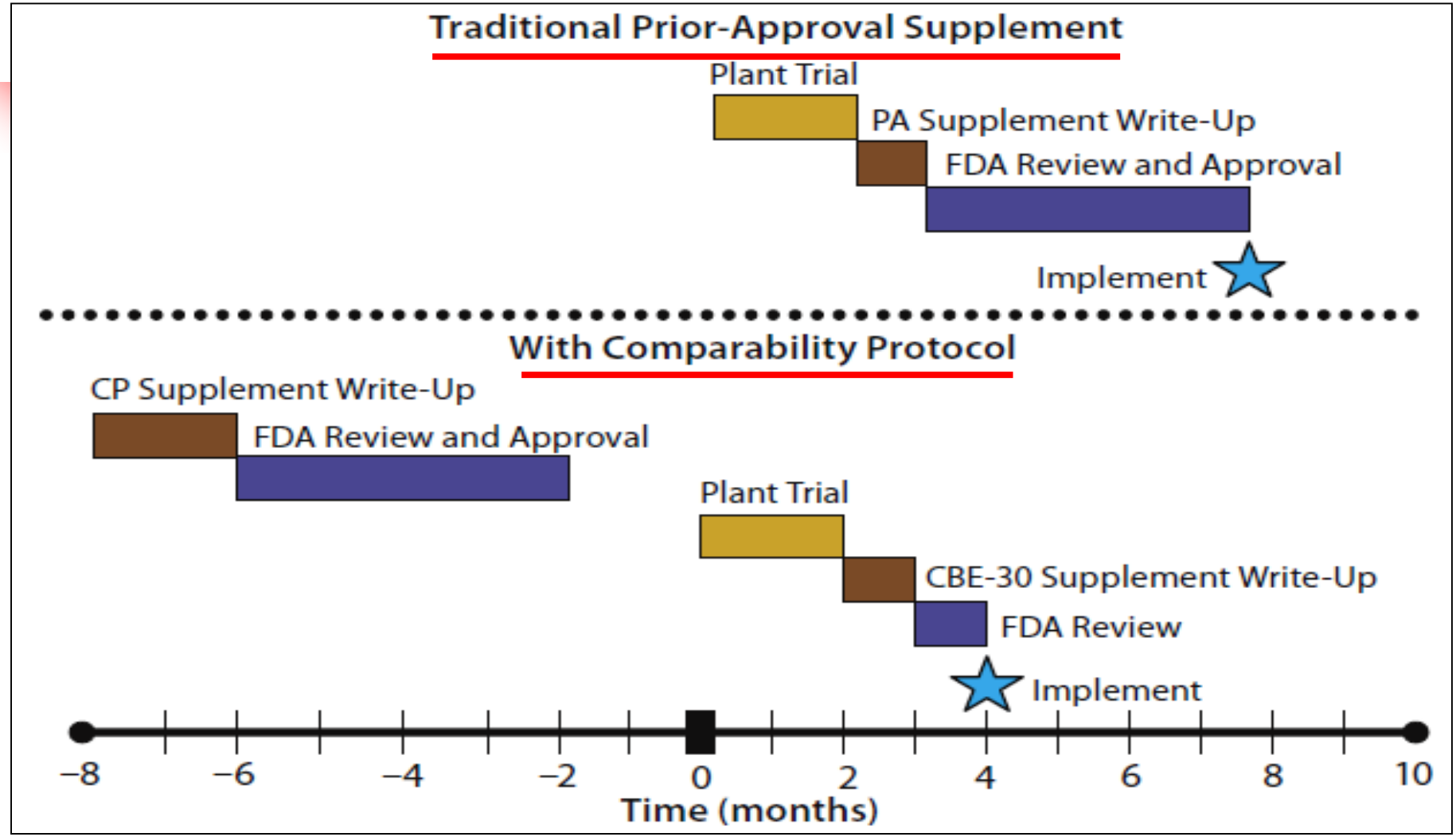
Comparability Protocols (CPs)
Post-Approval Change Management Protocols (PACMPs)

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!

Contracts are not easy to obtain!

regulatory agency major concerns with submissions

- ***a lack of data to support the acceptance criteria***
- ***acceptance criteria for comparability that are the same as the release criteria***
- ***very few 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***

IPQ SEPTEMBER 2016

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***
- ***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 contact expectations

Qualification for a New Working Cell Bank

Establish and qualify a Working Cell Bank (WCB) to be used for production of dinutuximab. Qualification of the WCB will include safety testing, an evaluation of the growth of WCB cultures relative to the growth of Master Cell Bank (MCB) cultures, testing of end of production cells generated from the commercial scale process, and a comparability assessment that includes the first three lots manufactured from the WCB using the commercial process. One lot manufactured using the commercial process will be placed on a stability protocol and the data will be submitted in the subsequent BLA annual reports. The WCB qualification report will be submitted in a prior approval supplement.

Unituxin (dinutuximab) United Therapeutics Corporation **BLA APPROVAL** 03/10/2015

Guidance on 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

Contracts used to extend 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!

Contracts used 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.

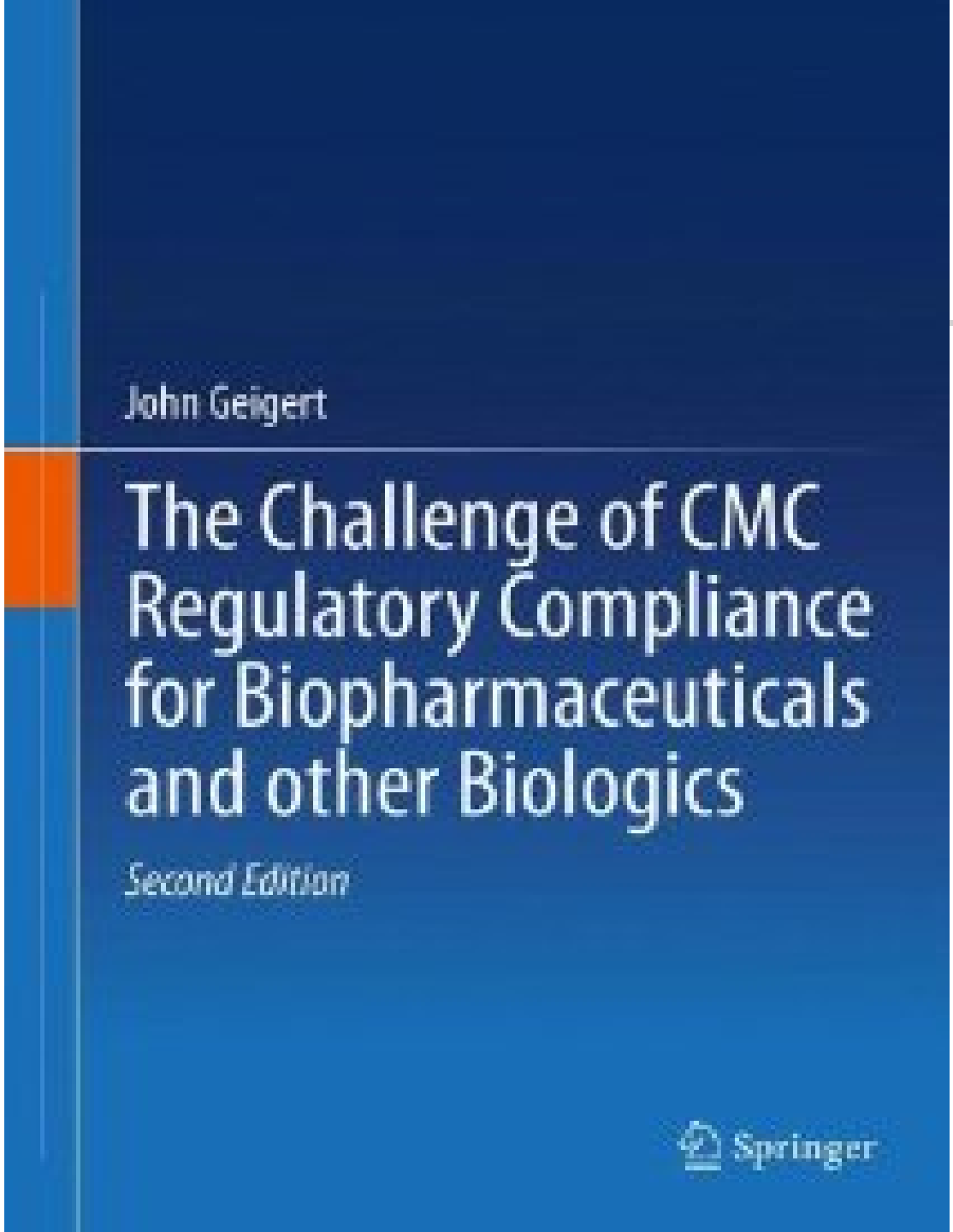
Hard to get a contract to add a new drug substance manufacturing site

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!