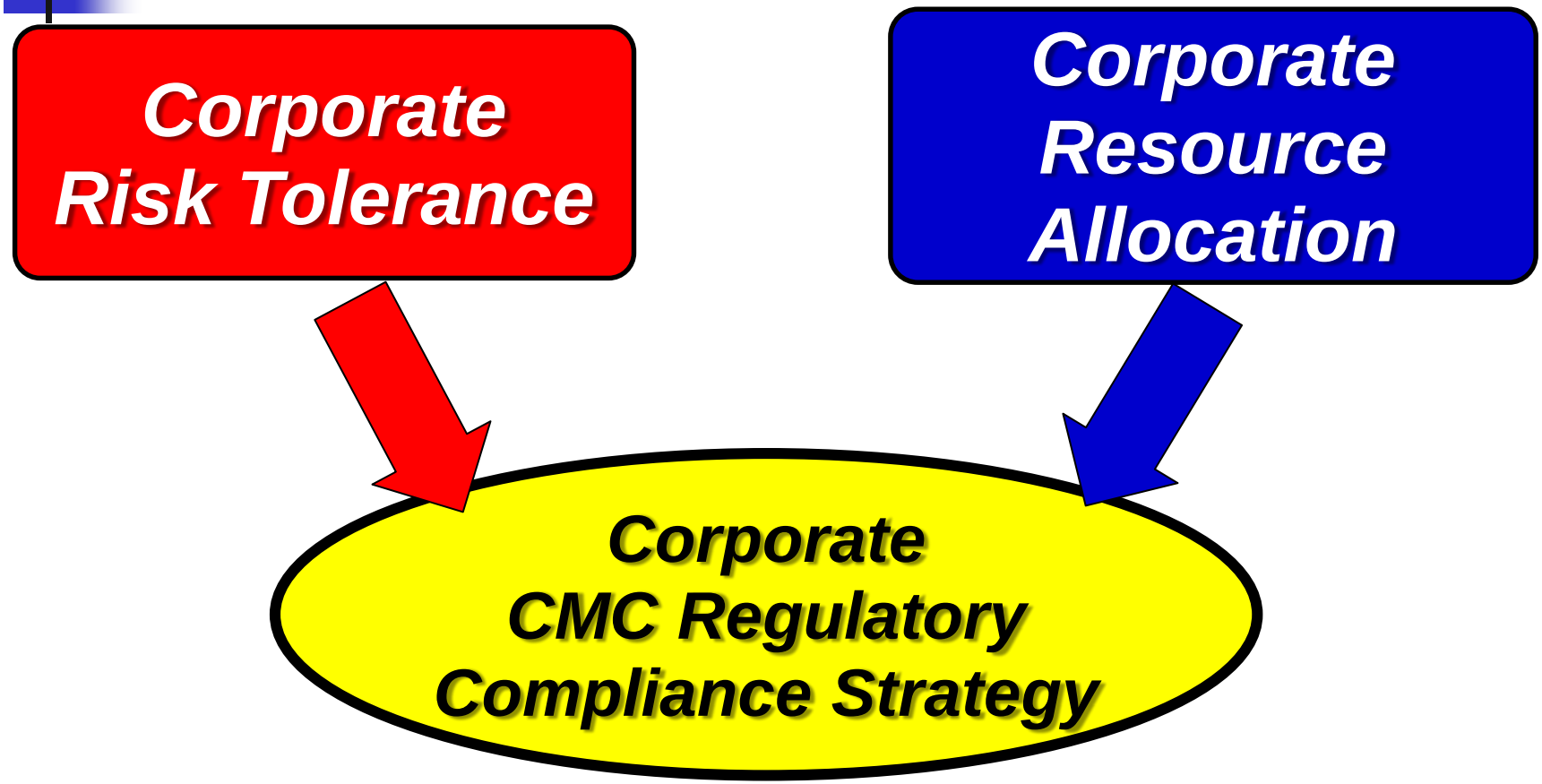
CMC Regulatory Compliance Strategy For Biopharmaceuticals

Course Outline

2. How to Develop an Effective Corporate Risk-Managed CMC Regulatory Strategy For Biopharmaceuticals

- ✓ *2 major forces that shape the CMC regulatory strategy*
- ✓ *5 key design elements of an effective CMC strategy*

2 Major Forces That Shape the Corporate CMC Regulatory Compliance Strategy



Risk Tolerance

Personal Risk-Tolerance: You

Event	Severity	Statistical Probability	Perceived Probability
Should I fly in an airplane?			

Acceptable Risk?

Corporate Risk-Tolerance: QA/ QC/ Mfg/ Dev/ Reg Affairs

Event	Severity	Statistical Probability	Perceived Probability
Should I drop bioburden testing through purification steps and only test at the DS?			

Acceptable Risk?

Detectable microbiological contaminants
- cultivable micro-organisms
- endotoxines

Non detectable contaminants
- non cultivable viable micro-organisms
- biofilm
- endotoxins fragments
- peptidoglycans
- DNA
- etc … can pass the dialysate membrane and induce inflammation

Peptidases can break down the protein during its shelf life

Differences Between Exotoxins and Endotoxins

(a) Exotoxins are proteins produced inside pathogenic bacteria, most commonly gram-positive bacteria, as part of their growth and metabolism. The exotoxins are then secreted or released into the surrounding medium following lysis.

(b) Endotoxins are the lipid portions of lipopolysaccharides (LPSs) that are part of the outer membrane of the cell wall of gram-negative bacteria (lipid A; see Figure 4.13c). The endotoxins are liberated when the bacteria die and the cell wall breaks apart.

A high risk tolerance may sometimes lead to not getting all of the facts!

Case Example: taking too much risk! (Genzyme: can't happen to us)

In a 2006 report, a clear warning was given to those in the biotech industry whose production systems required FBS:
'The laboratory-based study reported here provides evidence of widespread Vesivirus infections in cattle across a large area of the United States. The clinical, zoonotic, and other implications of this finding in a major food animal species warrant further investigation'."

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

(A PCR test was available to give a rapid detection of Vesivirus but it was considered too costly by Genzyme – ~$2000 per sample)

In 2008, Genzyme encountered loss of cell productivity in both their 4000L bioreactor at their Belgium site, and their 2000L bioreactor at their US site – but manufacturing saw this occurring and did not break bioreactor integrity – instead killed the cells and contamination inside the bioreactor

June 2009, the nightmare hits!
Genzyme confirms Vesivirus in their bioreactors,
but only after containment was broken, and the virus was spread into purification and throughout the entire facility!

Genzyme Press Release Sept 2009

Estimated impact on Genzyme ~$500 million

For want of a ~$2000 test!

The recovery effort at Allston Landing involved the efforts of hundreds of Genzyme employees as well as many outside experts. In this process:

- The duration of the sanitization effort was almost 2 months and used approximately 2,236 gallons of solution and 1,488 cans of isopropyl alcohol for cleaning and sterilization.
- Outside contractors worked more than 40,000 service hours in this effort in June and July. At the height of the effort, 72 different contractors were at work on-site at Allston Landing for six consecutive days.
- A team of eight security officers were on-site 24/7 to control access to the plant during the decontamination.
- This effort required replacement of many fixtures at Allston Landing. As a result of this effort, the entire U.S. inventory of sanitary ball valves was depleted. The inventory of food grade ceiling tile caulk in the northeastern US was also depleted. The factory that supplied T-tube installation for this effort was required to run three shifts to meet demand.
- Five miles of insulation, one mile of copper tubing and fittings, and 660 feet of sanitary tubing and fittings were sanitized or replaced. Several key vessels were replaced during this period also.
- More than 700 fluorescent light lenses were removed and replaced. In addition, approximately 3,253 valve diaphragms, 36,625 gaskets, 267 HEPA filters, 233 ball valves and 358 rebuild kits were used.

Corporate Resource Allocation

Public Presentation by Robert Garnick, Genentech, 2004 sharing his experiences between proteins and small molecules		
Requirements per API Batch (Number per Batch)	**Small Molecule (Chemical Drug)**	**Protein (Biologic)**
Batch Records	**< 10**	**> 250**
Process Data Entries	**< 4000**	**> 60,000**
Public Presentation by Pat O'Driscoll, Eli Lilly, 2011 sharing his experiences in adding a biologic manufacturing facility at an existing small molecule manufacturing site		
Requirements per API Batch (Number per Batch)	**Small Molecule (Chemical Drug)**	**Monoclonal Antibody (Biologic)**
Consumables (Single-Use)	**3**	**500**
In-Process Samples	**8**	**350**
Manufacturing Days	**6**	**62**

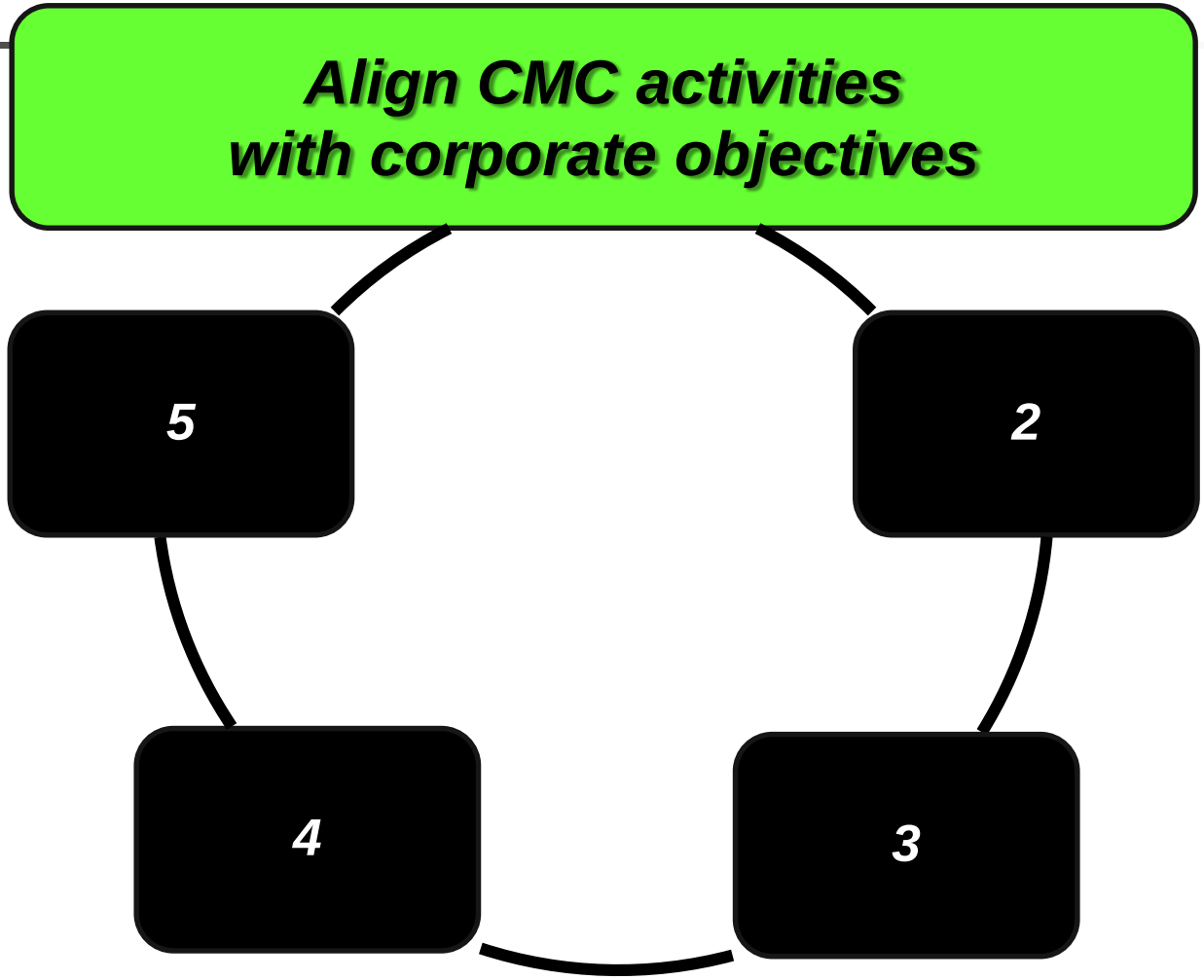
Robert Garnick (September 2004)

Pat O'Driscoll, *Design Through Start-up of a Multi-Product mAb Launch Facility,* (August 2011)]

Note: Gene therapy's manual manufacturing and quality challenges blow resource needs out of the water!

Composing an Effective Corporate CMC Regulatory Compliance Strategy

5 Key Design Elements



1. Align CMC activities with corporate objectives

The big picture of CMC …

C **Chemistry**

product characterization, release and stability testing, …

M **Manufacturing**

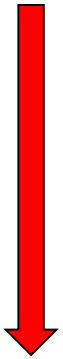
facilities, utilities, raw materials, process, …

C **Controls**

SOPs, batch records, training, auditing, batch release, …

So much to do,
but never enough time or resources to do it all!

Knowing the corporate regulatory objective, defines which CMC activities need to be done when



- ***Completing only the Phase 1 first-in-human studies***
- ***Completing up to the Phase 2 proof of concept studies***
- ***Completing up tp the Phase 3 confirmatory studies***
- ***Becoming a commercial biological company***

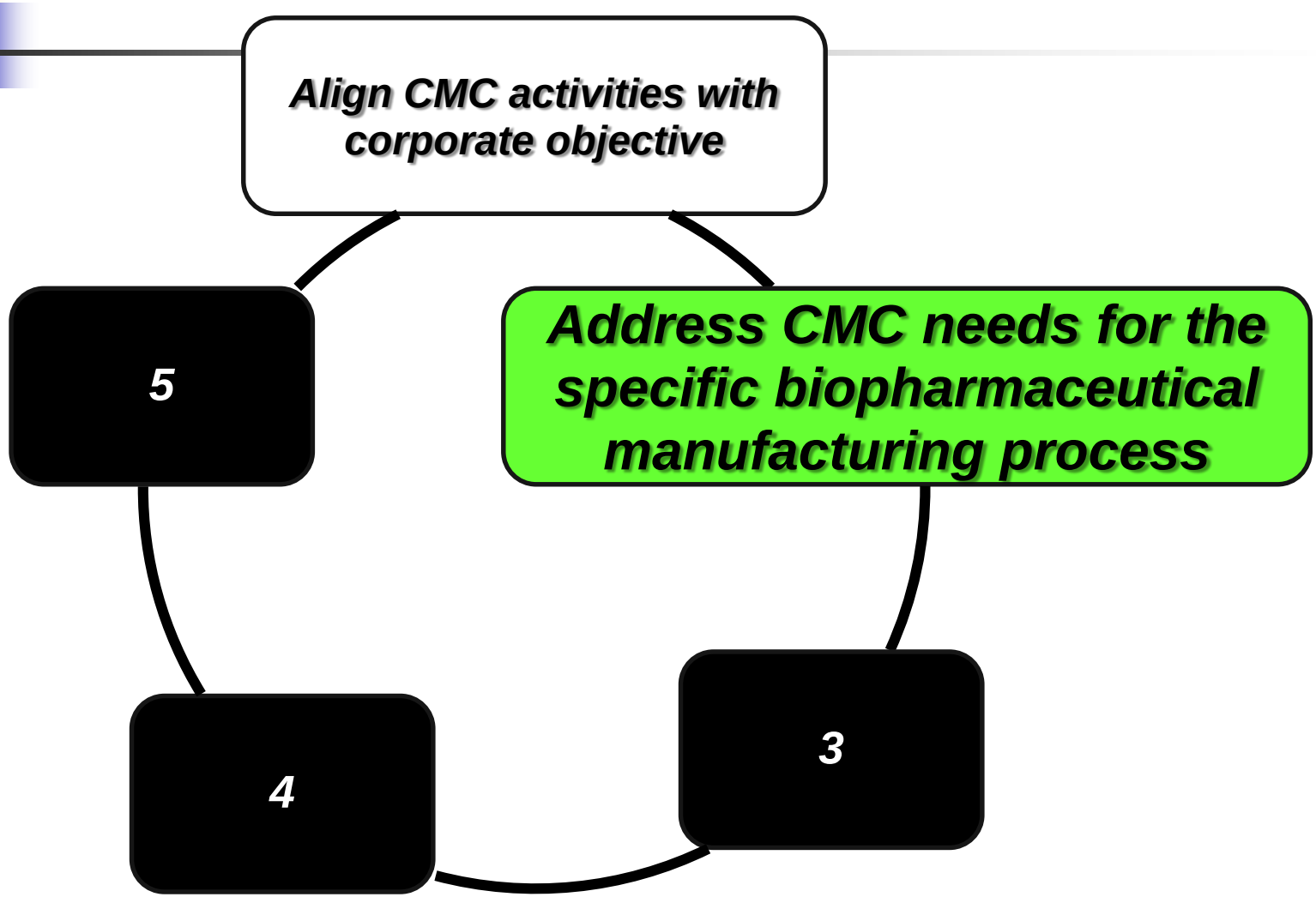
Increasing CMC effort and maturity of control systems

The level of maturity of the CMC control systems is dependent upon the corporate objective

Caution: corporate objectives can always change!

Composing an Effective Corporate CMC Regulatory Compliance Strategy

5 Key Design Elements



From the following two videos, identify three (3) CMC regulatory concern differences between these two manufacturing processes?

Monoclonal antibody manufacturing

Cell-based biologic manufacturing

1) _____

2) _____

3) _____

Video

Video

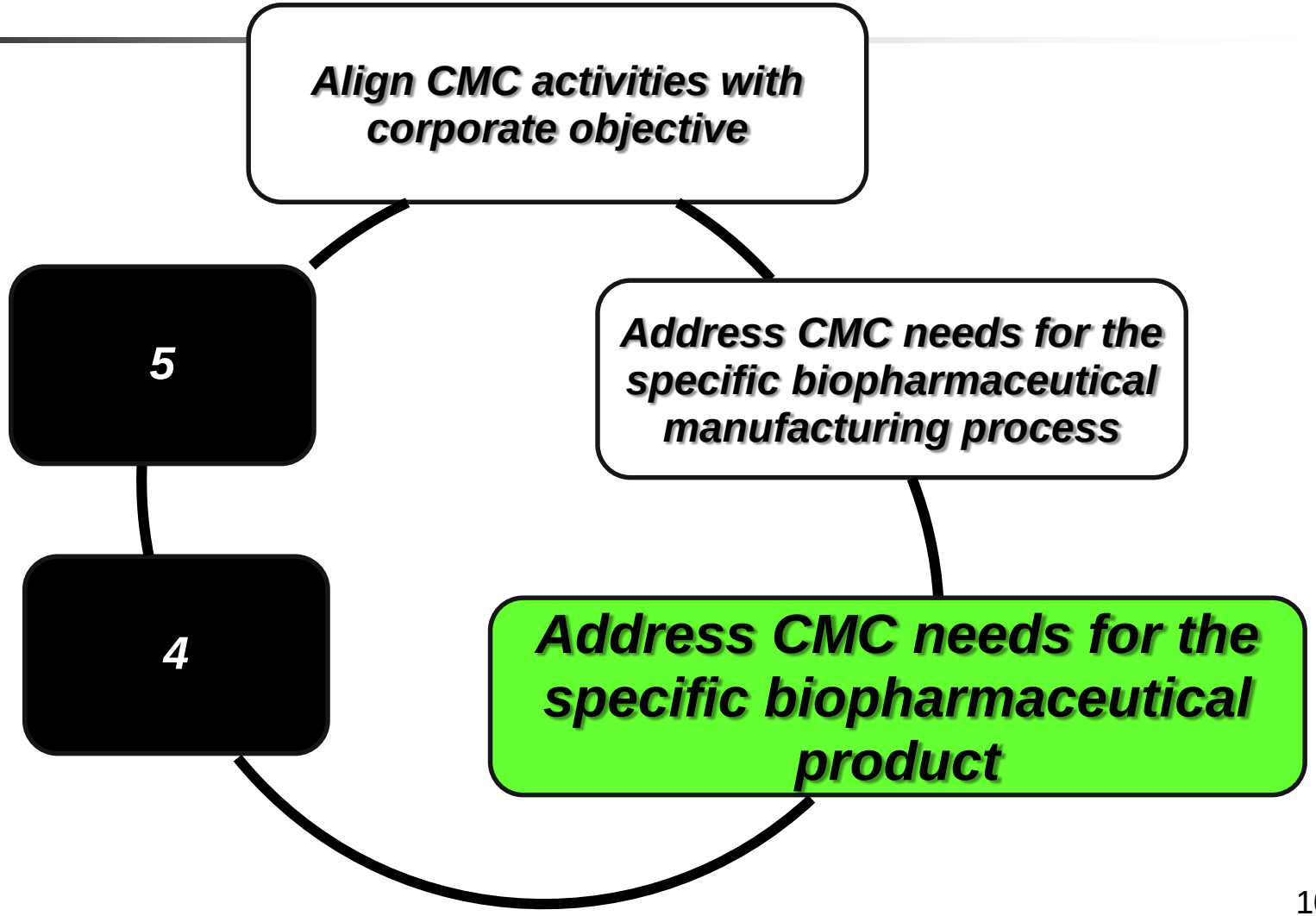
No one-size CMC regulatory strategy fits all manufacturing processes!

No magic formula!

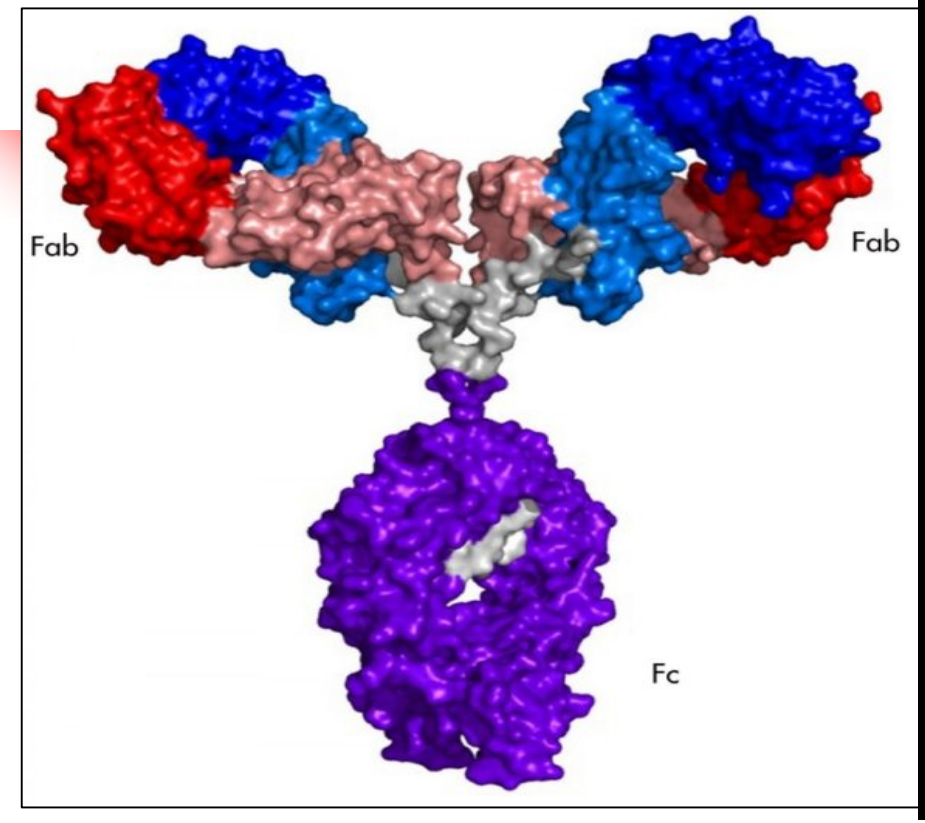
Each biopharmaceutical manufacturing process has specific regulatory compliance concerns that need to be addressed

Composing an Effective Corporate CMC Regulatory Compliance Strategy

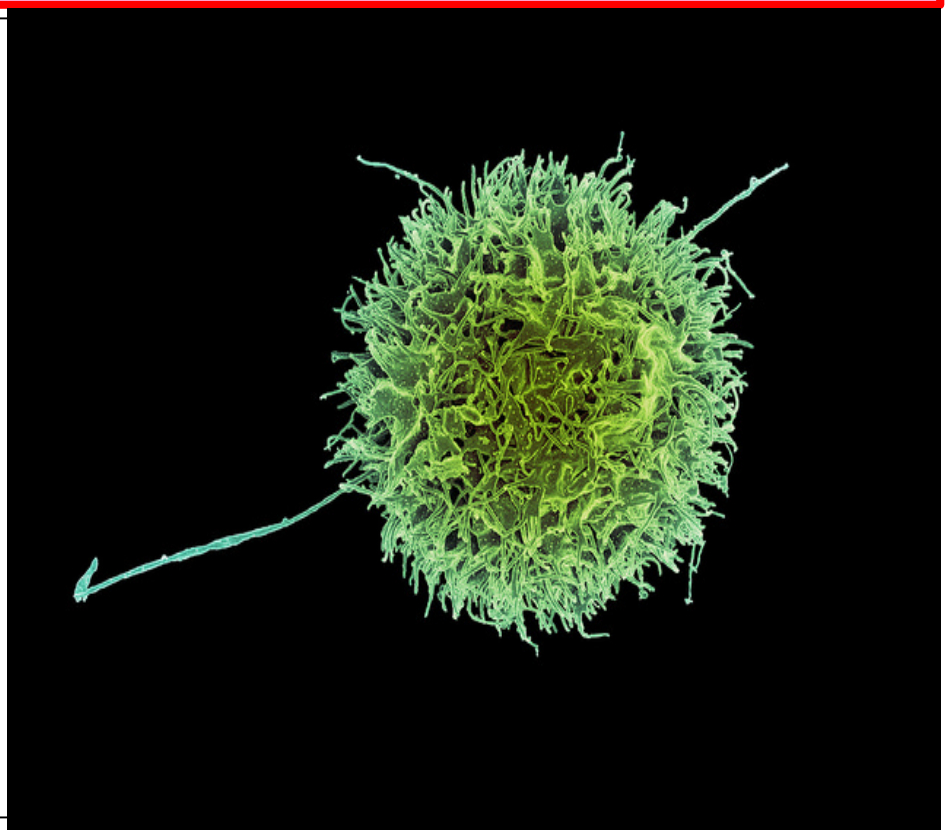
5 Key Design Elements



From the following two videos, how would you approach measurement of therapeutic activity (potency) for each type of biologic product?



Monoclonal antibody



Cell-based biologic

Potency for a MAb_____

Potency for a Cell_____

Video

Video

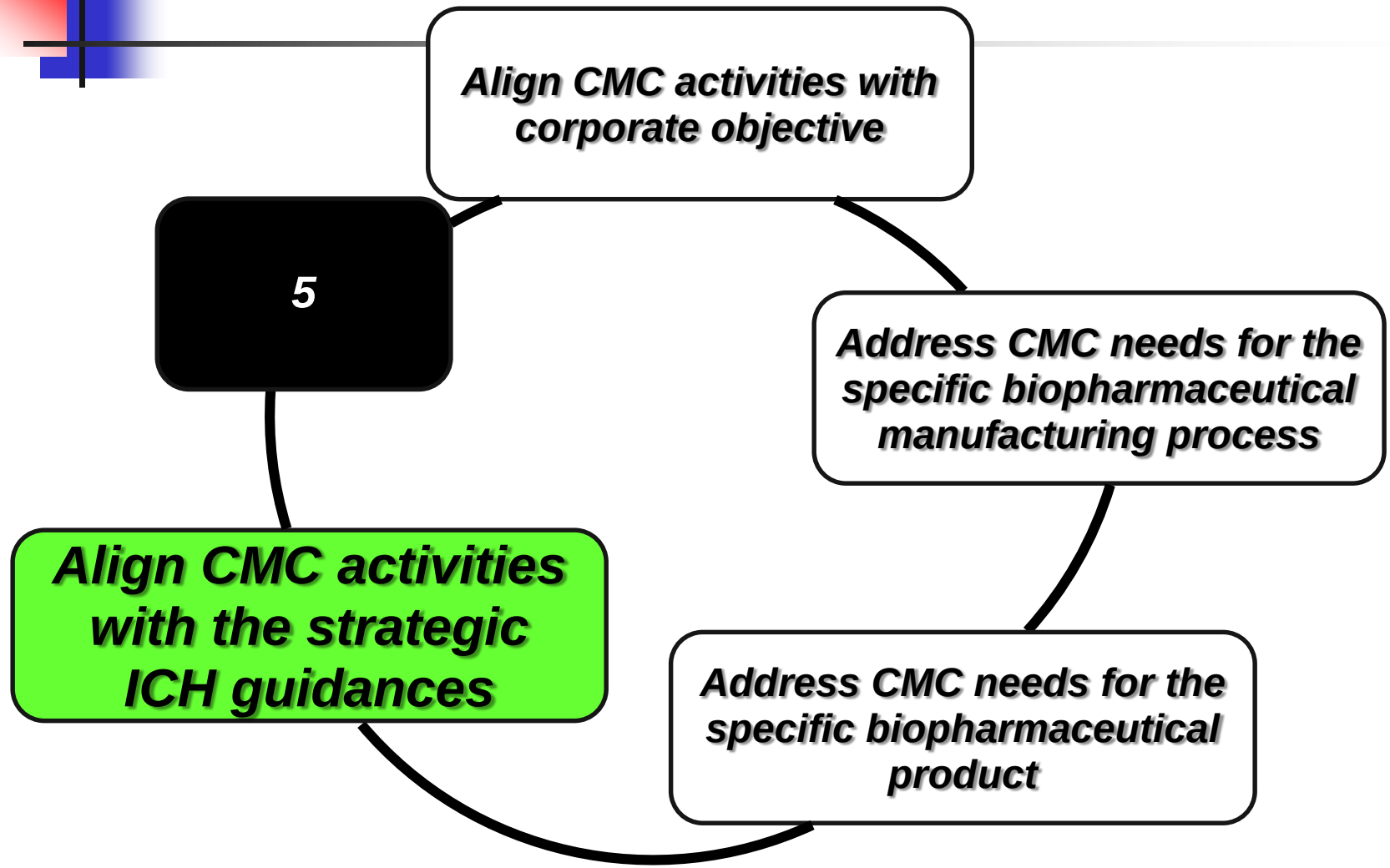
No one-size CMC regulatory strategy fits all biopharmaceutical products!

No magic formula!

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

Composing an Effective Corporate CMC Regulatory Compliance Strategy

5 Key Design Elements



International Council for Harmonisation

The ICH content guidances have been a tremendous help in the CMC regulatory compliance arena for almost 2 decades!

Q CMC

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

- **Q7** **GMP of Active Pharmaceutical Ingredients (APIs)** ***[2000]***
- **M4Q** **Common Technical Document (CTD) Format** ***[2000]***

The ICH strategy guidances are now widely applied in the CMC regulatory compliance arena for biopharmaceuticals!

- ***ICH Q8(R2) Pharmaceutical Development (2005/2008)***
  - ***Quality by Design (QbD)***
  - ***Design Space (DS)***
- ***ICH Q9 Quality Risk Management (2005)***
  - ***Quality Risk Management' (QRM)***
- ***ICH Q10 Pharmaceutical Quality System (2008)***
  - ***Pharmaceutical Quality System (PQS)***
  - ***Knowledge Management (KM)***
  - ***Senior Management Accountability***
- ***ICH Q11 Applied ICH Q8-10 to Chem/Biotech APIs (2012)***
- ***ICH Q12 Post-Approval Product Lifecycle (step 2)***

ICH Q8

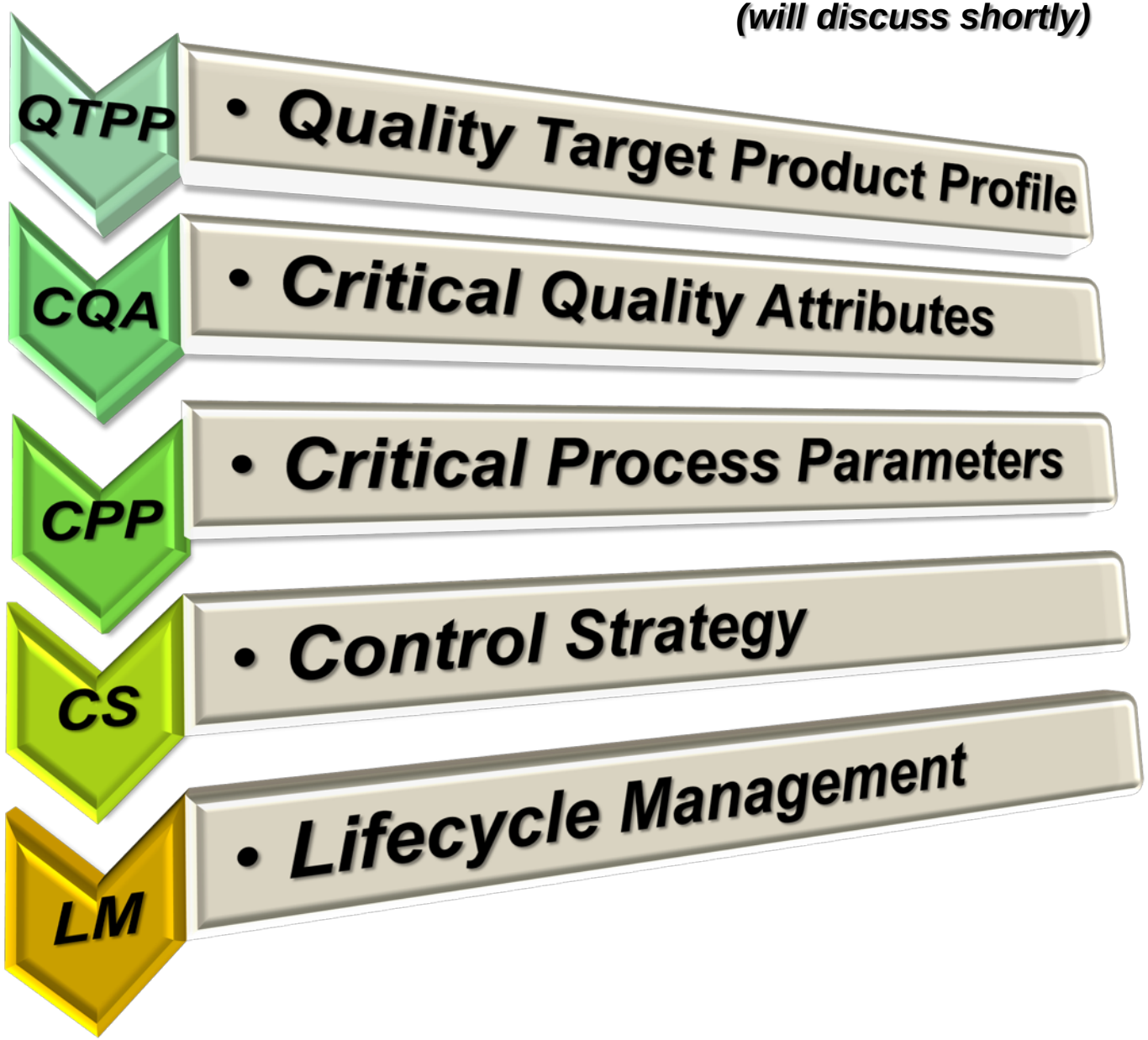
Quality by Design (QbD):

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

- ***How to design a quality product and its manufacturing process to consistently deliver the intended performance of the product***

ICH Q8: QbD – Five Steps to Implementation

(will discuss shortly)

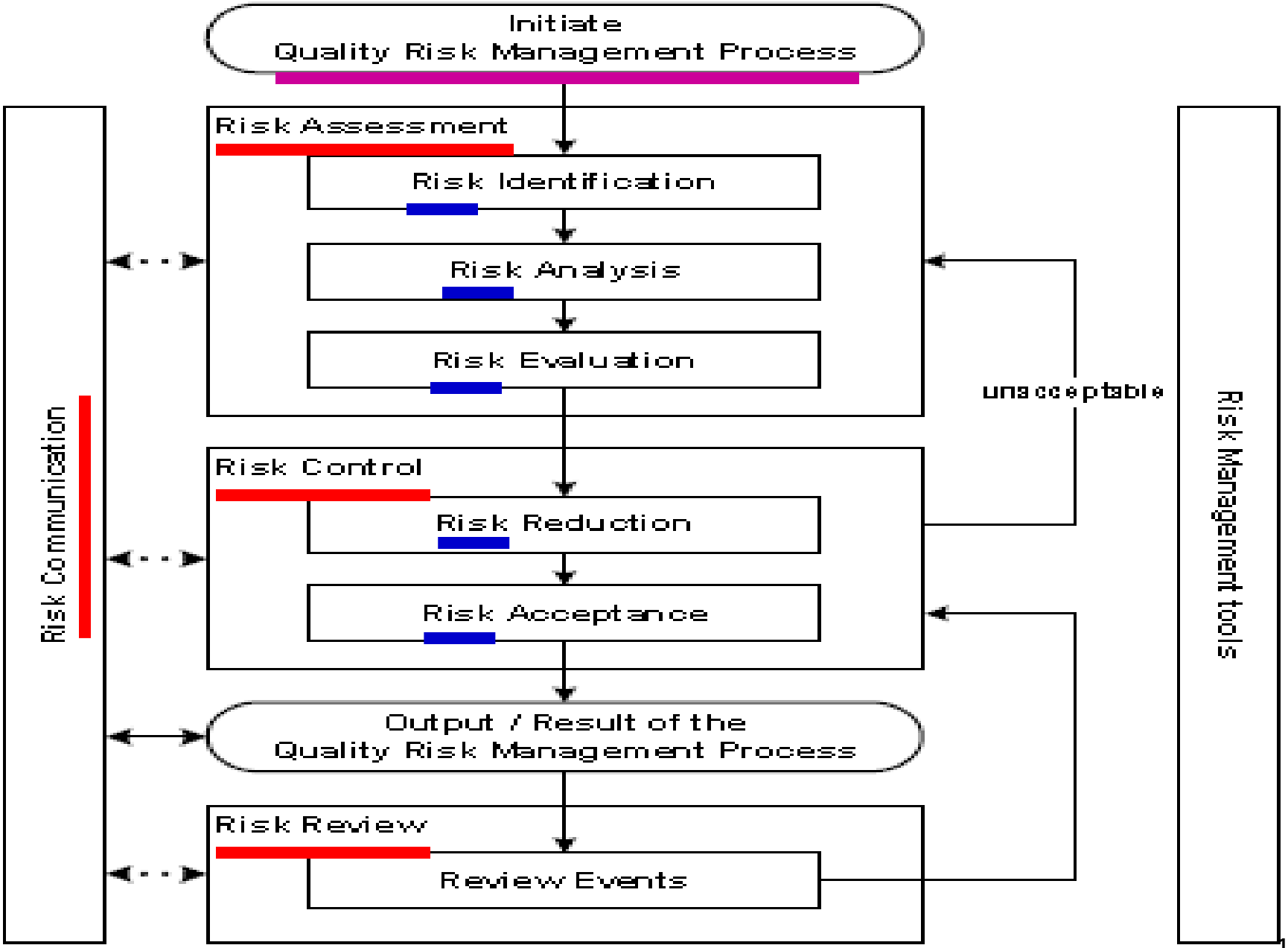


ICH Q9

Quality Risk Management: (QRM)

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

CMC strategy people love Quality Risk Management (QRM)!



ICH Q9 introduces numerous QRM risk prioritization tools that can be used

Risk Ranking and Filtering* (RRF)

Failure Mode Effects Analysis (FMEA)

Preliminary Hazard Analysis (PHA)

ICH Q9 introduces numerous QRM statistical analysis tools that can be used

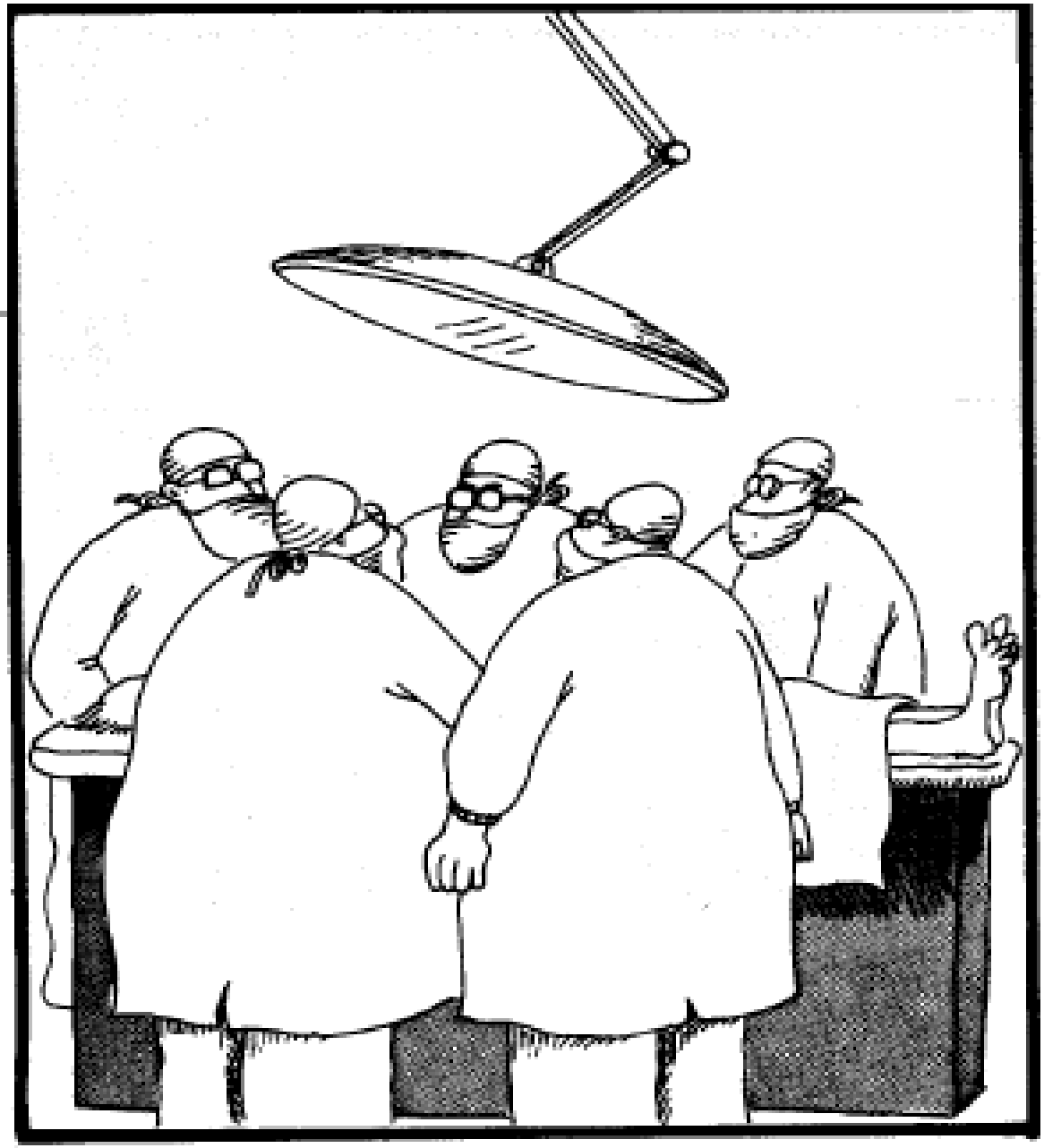
Ishikawa Diagram (Fishbone)

Design of Experiments* (DOE)

**** will be discussed shortly***

Risk prioritization weakest link:

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



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

DOE

Formal Experimental Design:

A structured, organized method for determining the relationship between factors affecting a process and the output of that process. Also known as "Design of Experiments".

many many process parameters

'process mapping'

→ ***DOE*** →

important process parameters identified

'process understanding'

OFAT for simple processes

(OFAT – 'one factor at a time')

$OFAT = L^{PP}$

3 Parameters

temperature
pressure
duration

Chemical Synthesis

Levels (L) [low, medium, high]	Process Parameters (PP)	OFAT (total number of reactor runs needed)
3	3	27

Not that difficult … but . →

OFAT doesn't work for complex processes

OFAT = L^{PP}

Bioreactor Culture Production

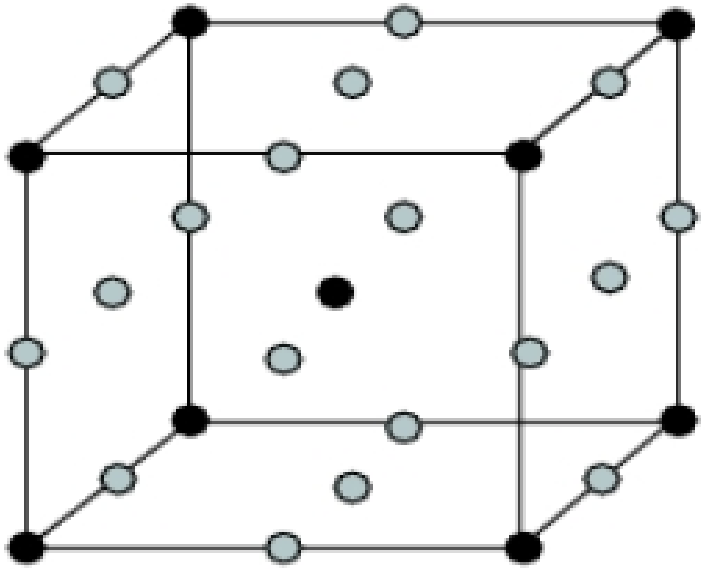
9 Parameters

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

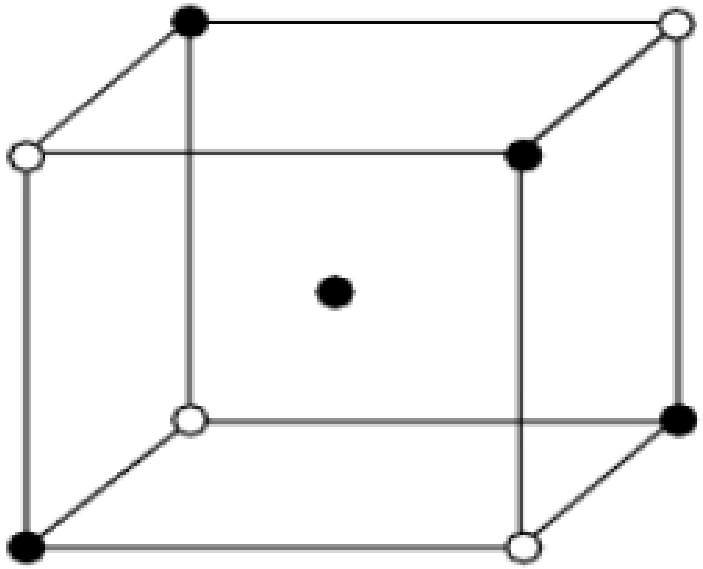
Levels (L) [low, medium, high]	Process Parameters (PP)	OFAT (total number of bioreactor runs needed)
3	9	19,683

Try explaining to senior management why you need to run 20,000 experiments!

Goal of DOE: maximum amount of understanding among operational parameters with minimum amount of scientific studies



Full factorial



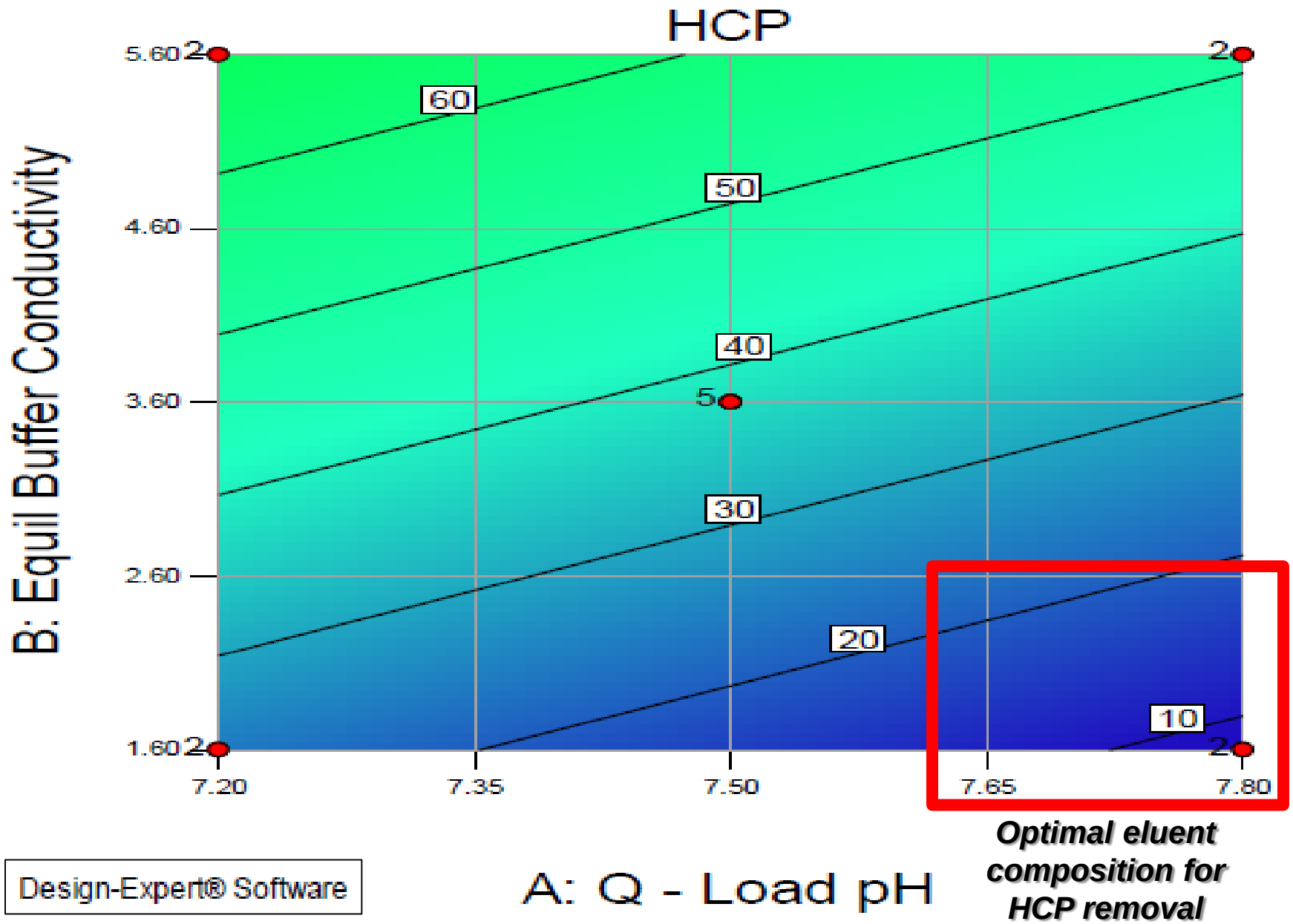
Fractional factorial

OFAT 27

DOE 9

Will you get <u>full</u> understanding of the biologic process with DOE?
Can you get <u>adequate</u> understanding of the biologic process with DOE?

DOE can give impressive visual results ***<u>But</u> DOE costs $$$***



Optimal eluent composition for HCP removal

ICH Q10

Pharmaceutical Quality System (PQS):

Management system to direct and control a pharmaceutical company with regard to quality. (ICH Q10 based upon ISO 9000:2005)

Knowledge Management: **(KM)**

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

- ***Importance of 'passing forward' technical knowledge***

KM is information in action

(getting information to the right people, at the right time, and in the right format)

As a biologic industry, we need to do a better job!

- ***What do you know about the history of your Master Cell Bank? How was genetic engineering carried out? How was the single starting clone selected 5-15 years ago?***
- ***What do you know about the history of your formulated biologic? How were excipients selected? How were the amounts of each excipient determined?***

"Those who don't know history are destined to repeat it"

Edmund Burke, 1700's, Irish Statesman

ICH Q11

DEVELOPMENT AND MANUFACTURE OF DRUG SUBSTANCES (CHEMICAL ENTITIES AND BIOTECHNOLOGICAL/BIOLOGICAL ENTITIES)

Q11 2012

ICH Q11 provides further clarification on the principles and concepts described in ICH Q8, Q9 and Q10 applied to the development and manufacture of drug substances

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

CQAs and CPPs will be discussed shortly

ICH Q12

Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

Core Guideline

Draft version

November 2017

POST-APPROVAL CMC CHANGES

ESTABLISHED CONDITIONS (ECs)

PRINCIPLES OF CHANGE MANAGEMENT

Illustrative Examples Annex I B: Biological Product

What is the overall impact of ICH Q8/Q9/Q10/Q11/Q12 on biologic regulatory compliance strategy?

- ***Be prepared to know not only the 'WHAT' but also the 'WHY' (justify, justify, justify, ….)!***
- ***Gone are the old formulas – preset targets independent of manufacturing process capability, 'industry standard', 3 run rule for process validation***
- ***Learning never ends – keep your eyes open for early warning signs of CMC issues; work toward <u>real</u> corrections and <u>effective</u> preventative actions!***

QbD – Five Steps to Implementation

QbD is not mandatory, but QbD principles are expected to be described in market approval application dossiers!

Reviewers should ensure that applications contain at least the minimum information on pharmaceutical development described by ICH Q8(R2) as "At a minimum, those aspects of drug substances, excipients, container closure systems, and manufacturing processes that are critical to product quality should be determined and control strategies justified."

- ***Namely, applications should include the following minimal elements delineated in the ICH Q8(R2) Annex:***
  - ***Quality target product profile (QTPP).***
  - ***Critical quality attributes (CQAs) of the drug product.***
  - ***CQAs of the drug substance and excipients.***
  - ***Selection of an appropriate manufacturing process.***
  - ***Control strategy***

FDA CDER Manual of Policies & Procedures (MAPP): 5016.1 Applying ICH Q8(R2), Q9 and Q10 Principles to CMC Review (May 2016)

QbD is not mandatory, but QbD principles are expected to be applied to commercial biological processes!

case example

During the procedure a major objection was raised in relation to the proposed manufacturing process control strategy. The Applicant was requested to provide more information on the manufacturing process control strategy to ensure quality of the active substance. The applicant provided a more thorough discussion of the development of the manufacturing process control strategy with the provision of extensive background information. The basis for defining the current CQAs is now appropriately described including an updated risk assessment matrix, explanation of the relationship between CQAs and the elaboration of CPPs/MPPs/IPCs for the process. The applicant also provided a detailed explanation of how criticality of process parameters and in-process controls was determined.

EMA European Public Assessemnt Report (EPAR) : Oxervate (Cenegermin) Recombinant human nerve growth factor (May 2017)

QbD requires 'risky' investment in development before clinical success!

Table 2. 2013 Successful Progression Rates [1]

Phase Progression	Therapeutic Category	Molecule Classification	Probable Success Rate
Phase I-Phase II	Oncology	Small Molecule NME	66%
		Peptides/Proteins	48%
		Monoclonal Antibodies	68%
	Non-Oncology	Small Molecule NME	65%
		Peptides/Proteins	65%
		Monoclonal Antibodies	72%
Phase II-Phase III	Oncology	Small Molecule NME	29%
		Peptides/Proteins	31%
		Monoclonal Antibodies	29%
	Non-Oncology	Small Molecule NME	29%
		Peptides/Proteins	42%
		Monoclonal Antibodies	47%

Nature Biotechol. 2014; 32, 40-51

(will use graphics from these published articles on QbD applied to commercial mAbs)

Biologicals 44 (2016)

Determination of critical quality attributes for monoclonal antibodies using quality by design principles

Nadja Alt [a, *], Taylor Y. Zhang [d], Paul Motchnik [e], Ron Taticek [d], Valerie Quarmby [f], Tilman Schlothauer [b], Hermann Beck [c], Thomas Emrich [b], Reed J. Harris [d]

[a] *Pharma Technical Development, Roche Diagnostics GmbH, Nonnenwald 2, 82377 Penzberg, Germany*
[b] *Pharma Research and Early Development, Roche Innovation Center Munich, Roche Diagnostics GmbH, Nonnenwald 2, 82377 Penzberg, Germany*
[c] *Pharma Technical Development Biotech Europe, F. Hoffmann-La Roche Ltd, 4070 Basel, Switzerland*
[d] *Pharma Technical Development, Genentech, South San Francisco, CA 94080, USA*
[e] *Biologics Quality Control, Genentech, South San Francisco, CA 94080, USA*
[f] *Research and Early Development, Genentech, South San Francisco, CA 94080 USA*

Process characterization and Design Space definition

Christian Hakemeyer [a, *], Nathan McKnight [c], Rick St. John [c], Steven Meier [c], Melody Trexler-Schmidt [c], Brian Kelley [c], Frank Zettl [b], Robert Puskeiler [d], Annika Kleinjans [b], Fred Lim [c], Christine Wurth [d]

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[b] *Pharma Technical Development, Roche Diagnostics GmbH, Nonnenwald 2, 82377 Penzberg, Germany*
[c] *Pharma Technical Development, Genentech, South San Francisco, CA 94080, USA*
[d] *Pharma Technical Development Biotech Europe, F. Hoffmann-La Roche Ltd, 4070 Basel, Switzerland*

Step 1

QTPP • Quality Target Product Profile

Traditional Approach

Develop a process → Add 'quality' into the process → Adjust process to fix 'quality'

QbD Approach

Pre-define the quality target (QTPP) → Develop a process to meet the QTPP → Confirm QTPP has been achieved

Quality Target Product Profile (QTPP)

Quality Target Product Profile (QTPP):

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

The QTPP sets the corporate 'forward target' for the drug product

(focus to keep all team members heading in the same direction)

- ***Development***
- ***Manufacturing***
- ***Quality Control/Assurance***
- ***Regulatory Affairs***
- ***Clinical***
- ***Marketing***

Table 1
Example QTPP for a monoclonal antibody

Attribute	Target
Indication	Non-Hodgkin's Lymphoma (indolent & aggressive NHL) Chronic Lymphocytic Leukemia (CLL) Diffuse Large B-Cell Lymphoma (DLBCL)
Mechanism of Action	B-cell depletion: - antibody-dependent cellular cytotoxicity (ADCC) - antibody-dependent cellular phagocytosis (ADCP) - direct cell death induction (apoptosis-like)
Critical Features Impacting MoA	Type II CD20 binding, ADCC activation
Dosage Form	Sterile, preservative-free liquid for infusion
Dosage Strength	1000 mg per vial, 40 mL at 25 mg/mL
Mode of Administration	Intravenous, diluted with isotonic saline, max. 1000 mg/h
Drug Product Primary Container	50 mL type 1 borosilicate glass vials, fluoro-resin laminated stopper
Drug Product Shelf-Life	Minimal claim at submission ≥30 months (target) at 2–8 °C)
Compatibility with Application Devices and Stability during Administration	Compatibility with intravenous bags and application lines in concentrations of 0.4–20 mg/mL and at infusion speed ≥ 4 mL/h without requirement of inline filter. Stable solution for 24 h at room temperature
Drug Product Quality Requirements	Meets pharmacopoeial requirements for parenteral dosage forms (PhEur, USP, JP)
Degradants and Impurities	Acceptable patient risk due to process-related and product-related impurities in relation to the benefit

TPP

When should the QTPP be established?

- As early as possible (although many blanks will be there)
- Changeable – but should be change controlled (QA)

What is the value of the QTPP for biologics?

- Avoids last minute surprises!

Personal case examples from participating in BLA preparation meetings with senior management where no QTPP had been established

- Clinical very upset that drug product presentation was only in a vial; really wanted a user friendly pre-filled syringe for the submission
- Marketing very upset that refrigeration temp shelf life was to be the labeled claim; really wanted room temp label claim all along to be competitive

Step 2

***Identify first* all the quality attributes (molecular, functional, compositional properties)**

***then rank* the quality attributes for criticality (i.e., importance to patient efficacy or safety)**

***then set threshold* for CQA vs non-CQA!**

Critical Quality Attribute (CQA)

Quality Attribute (QA):

A physical, chemical, biological or microbiological property or characteristic

Quality risk assessments (ICH Q9) are performed to rank quality attributes ***('non-critical → critical' is a continuum)***

Critical Quality Attribute (CQA):

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

ICH Q8

The challenge of determining CQAs for biopharmaceuticals (ICH Q11)

- ***In the case of biotechnological/biological products, most of the CQAs of the drug product are associated with the drug substance and thus are the result of the design of the drug substance or its manufacturing process***
- ***The identification of CQAs for complex products can be challenging. Biotechnological/biological products, for example, typically possess such a large number of quality attributes that it might not be possible to fully evaluate the impact on safety and efficacy of each one.***

Example 1: Product Molecular Variants

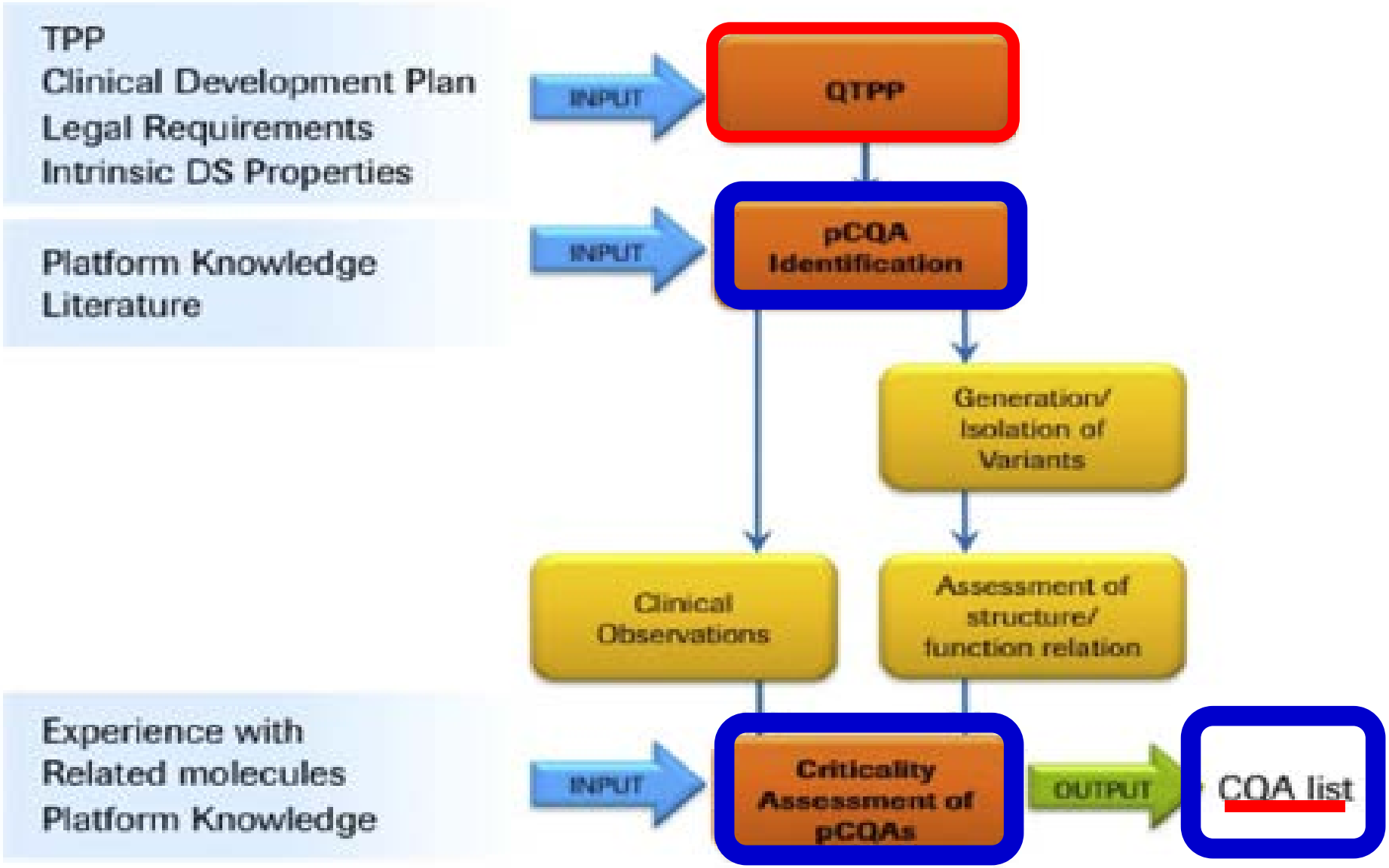


Fig. 2. Outline for workflow for COA identification.

Example 1: Product Molecular Variants

3 Step Approach: QA → pCQA → CQA

Step 1: Identify all MAb molecular variants

Table 2
List of molecular variant pCQAs for a monoclonal antibody.

Category	Quality attribute[a]
Size-related Variants	High Molecular Weight Species (HMWS)
	Low Molecular Weight Species (LMWS)
Charge-related Variants (Acidic)	Deamidation in CDR
	Deamidation in Non-CDR
	Glycation in CDR
	Glycation in Non-CDR
Charge-related Variants (Basic)	Aspartic Acid Isomerization in CDR
	Aspartic Acid Isomerization in Non-CDR
	N-Terminal Leader Sequence (may be molecule specific)
	N-Terminal Pyroglutamic Acid
	C-Terminal Lysine
	C-Terminal Proline (IgG1) or Leu (IgG4) Amidation
Oxidation-related Variants	Oxidation in CDR (Met, Trp)
	Oxidation in Non-CDR (Met, homo-variant)
	Oxidation in Non-CDR (Met, hetero-variant)
Fc Glycosylation	Afucosylation
	Galactosylation
	High-Mannose
	Sialylation (NANA, NGNA)
	Non-Glycosylated Heavy Chain
Structural Variants	Cysteine Forms
	Sequence Variants
	Protein Structure

[a] Certain low abundance variants may need to be added to the list of general known variants such as advanced glycation end-products, hydroxylysine, or oxidative carbonylation.

23

Step 1: Identify all MAb molecular variants (23)

↓

Step 2: Assign risk score (RS) to <u>each</u> MAb molecular variant
(Q9 risk ranking/filtering method; pCQAs)

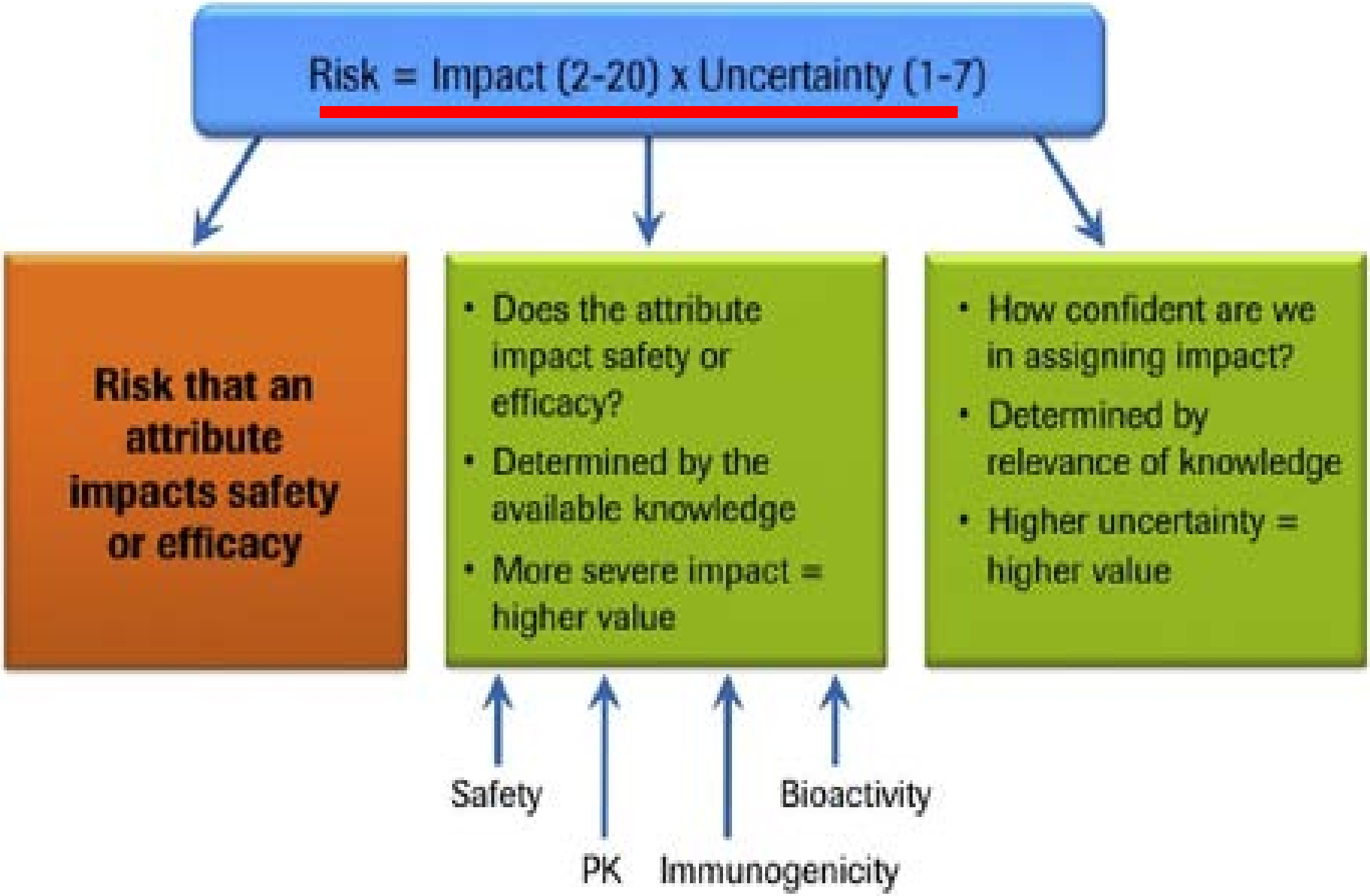


Fig. 3. Risk score defined by impact and uncertainty.

Risk Score (RS) = I x U

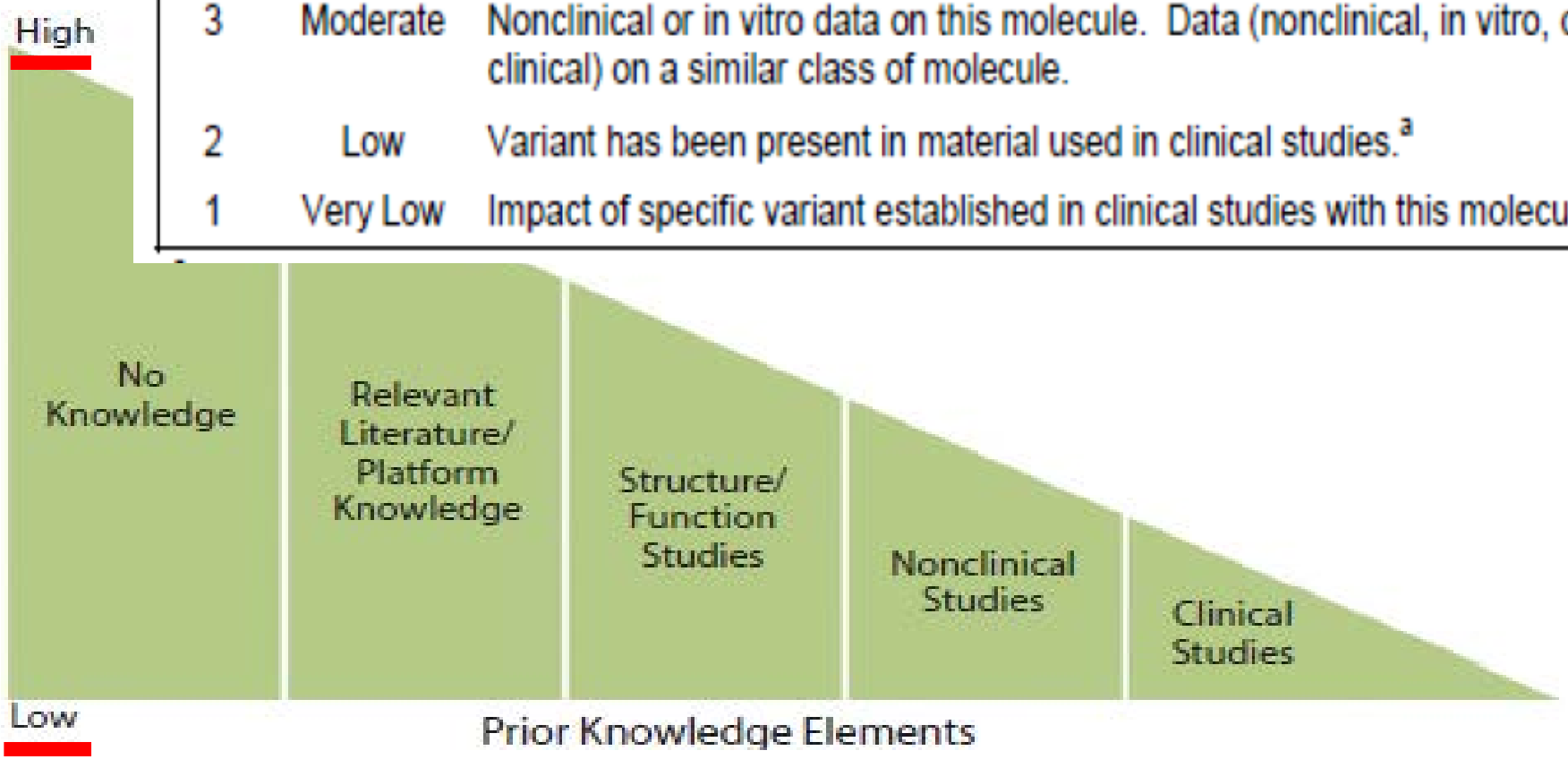
Impact = 2-20

Impact and Rating	Biological Activity[a]	PK[b]	Immunogenicity[c]	Safety
Very High (20)	> 100% change	> 40% change	ATAs detected that may be life threatening	Irreversible or life-threatening AEs and/or life-threatening loss of efficacy
High[d] (16)	40%–100% change	20%–40% change with impact on PD	ATAs detected that may be associated with non-life-threatening loss of efficacy	Reversible AEs and/or loss of efficacy that is not life threatening
Moderate (12)	20%–40% change	20%–40% change with no impact on PD	ATAs detected with effect that can be managed by clinical treatment (i.e., dose titration, medication, etc.)	AEs that can be managed by clinical treatment (i.e., dose titration, medication, etc.)
Low (4)	<20% change	<20% change with no impact on PD	ATAs detected with effect on PK or PD, but no effect on safety or efficacy	Safety or efficacy effect with minimal clinical significance
None (2)	No change	No impact on PK or PD	ATAs not detected or ATAs detected with no effect on PK, PD, safety, or efficacy	No effect on safety or efficacy

Risk Score (RS) = I x U

Uncertainty = 1-7

Rank	Uncertainty	Description (Product Variants and Host Cell–Derived Impurities)
7	Very High	No information (new variant).
5	High	Published external literature on variant in related molecule.
3	Moderate	Nonclinical or in vitro data on this molecule. Data (nonclinical, in vitro, or clinical) on a similar class of molecule.
2	Low	Variant has been present in material used in clinical studies.[a]
1	Very Low	Impact of specific variant established in clinical studies with this molecule.



Step 1: Identify all MAb molecular variants (23)

↓

Step 2: Assign risk score (RS) to each MAb molecular variant (Q9 risk ranking/filtering method; pCQAs)

↓

Step 3: Set risk score (RS) threshold – CQA vs non-CQA (arbitrary, but must be defendable)

Identifying which molecular variants are …

CQAs	*RS > 12*
non-CQAs	*RS ≤ 12*

Quality Attribute	*Impact Rank*	*Uncertainty Rank*	*Risk Score*
Afucosylation (absence of the core fucose residue on the GlcNAc carbohydrate residue)	*16 (biological activity)*	*3*	*48*
Glycation in CDR (reaction of reducing sugars with amino groups of lysine residues)	*16 (biological activity)*	*3*	*48*
C-terminal lysine truncation	*4 (PK)*	*3*	*12*
Free thiols (unpaired cysteines)	*4 (biological activity)*	*3*	*12*

Example 2: Obligatory CQAs

Pharmacopeia Requirements

DS/DP obligatory CQAs:

- ***Protein Content***
- ***Osmolality***
- ***pH***
- ***Appearance (Color, Opalescence, Clarity)***
- ***Buffer Content***
- ***Excipient Content***
- ***Surfactant Content***

Adventitious agents obligatory CQAs:

- ***Viruses***
- ***Microbiological impurities (Bacteria, Mycoplasma)***
- ***Bacterial endotoxins***

DP specific obligatory CQAs:

- ***Subvisible Particles***
- ***Visible Particles***
- ***Extractable Volume***
- ***Sterility***

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

Example 3: Raw Material Residuals

Toxicological: EDI > TTC → CQA

Raw materials used in the drug substance manufacturing process are evaluated for toxicity by considering a theoretical estimated daily intake (EDI), compared to a threshold of toxicological concern (TTC), provided by a toxicologist. This EDI value is derived by summing up the complete amount of the respective raw material that is introduced into the process, divided by the minimum yield. This approach is very conservative because it does not take into account any removal of a raw material in unit operations after the ones in which they are introduced into the process. The obtained value is multiplied with the maximum dose for the product to obtain the final EDI value.

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

Example 4: Leachables

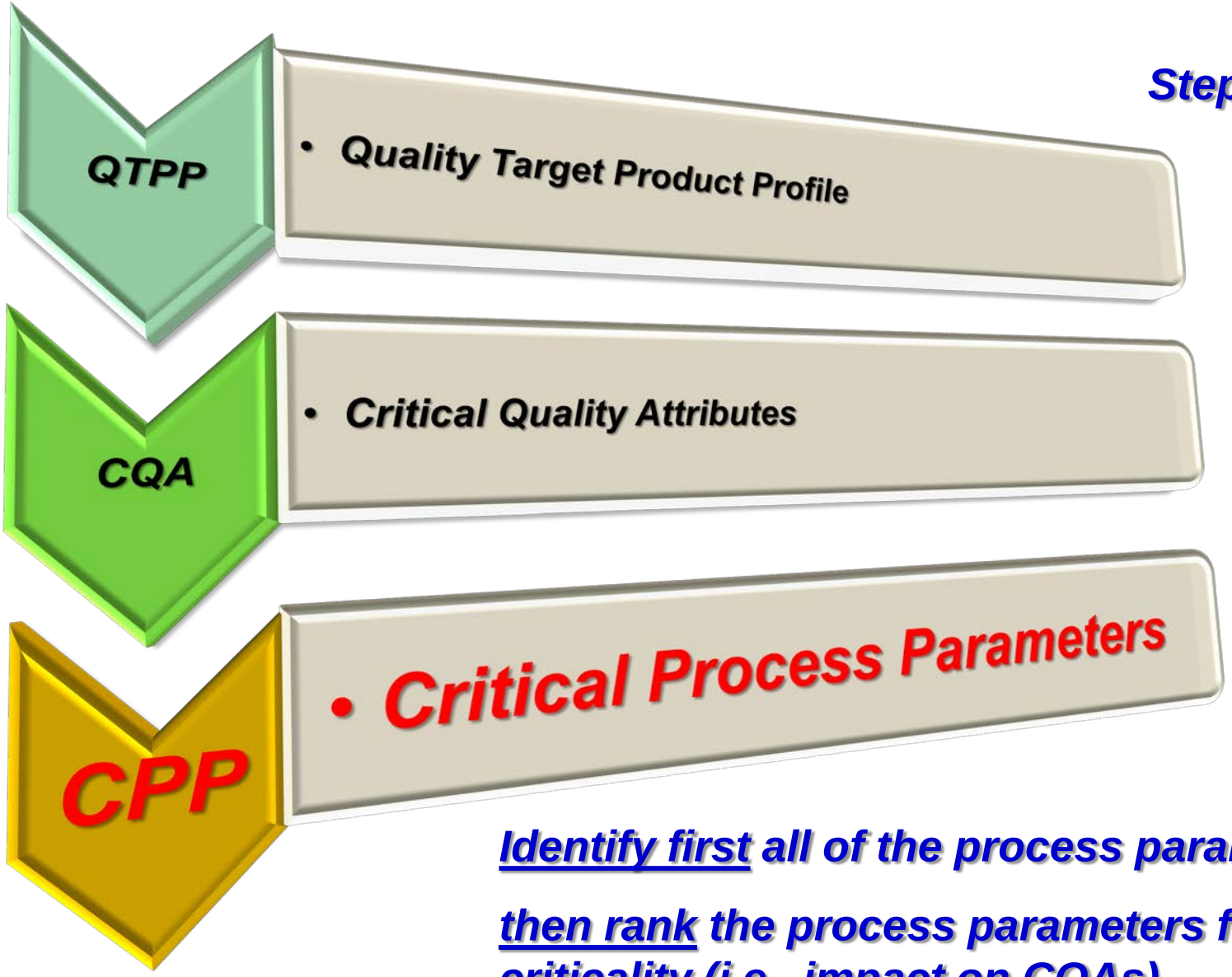
Toxicological: > TTC → CQA

The approach for identification of leachables as CQAs is dependent on whether a specific compound can be detected in the final DS or DP. If a specific leachable is shown to exceed acceptable and safe levels, e.g. as determined based on ICH M7, that compound is designated as a CQA.

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

ASSESSMENT AND CONTROL OF DNA REACTIVE (MUTAGENIC) IMPURITIES IN PHARMACEUTICALS TO LIMIT POTENTIAL CARCINOGENIC RISK **M7**

Threshold of Toxicological Concern (TTC)



Step 3

Identify first all of the process parameters

then rank the process parameters for criticality (i.e., impact on CQAs)

then set threshold for CPP vs non-CPP!

Critical Process Parameter (CPP)

Process Parameter (PP):

An element of process control

Quality risk assessments (ICH Q9) are performed to rank process parameters ('non-critical → critical' is a continuum)

Critical Process Parameter (CPP):

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

ICH Q8

[KPP – Key Process Parameter – a process parameter that impacts performance but not a CQA]

Example: Manufacturing Process Parameters

3 Step Approach: PP → pCPP → CPP

Step 1: Identify all process parameters
(could be hundreds of PPs)

C. Hakemeyer et al. / Biologicals 44 (2016) 306–318

How many manufacturing process parameters for a biopharmaceutical?

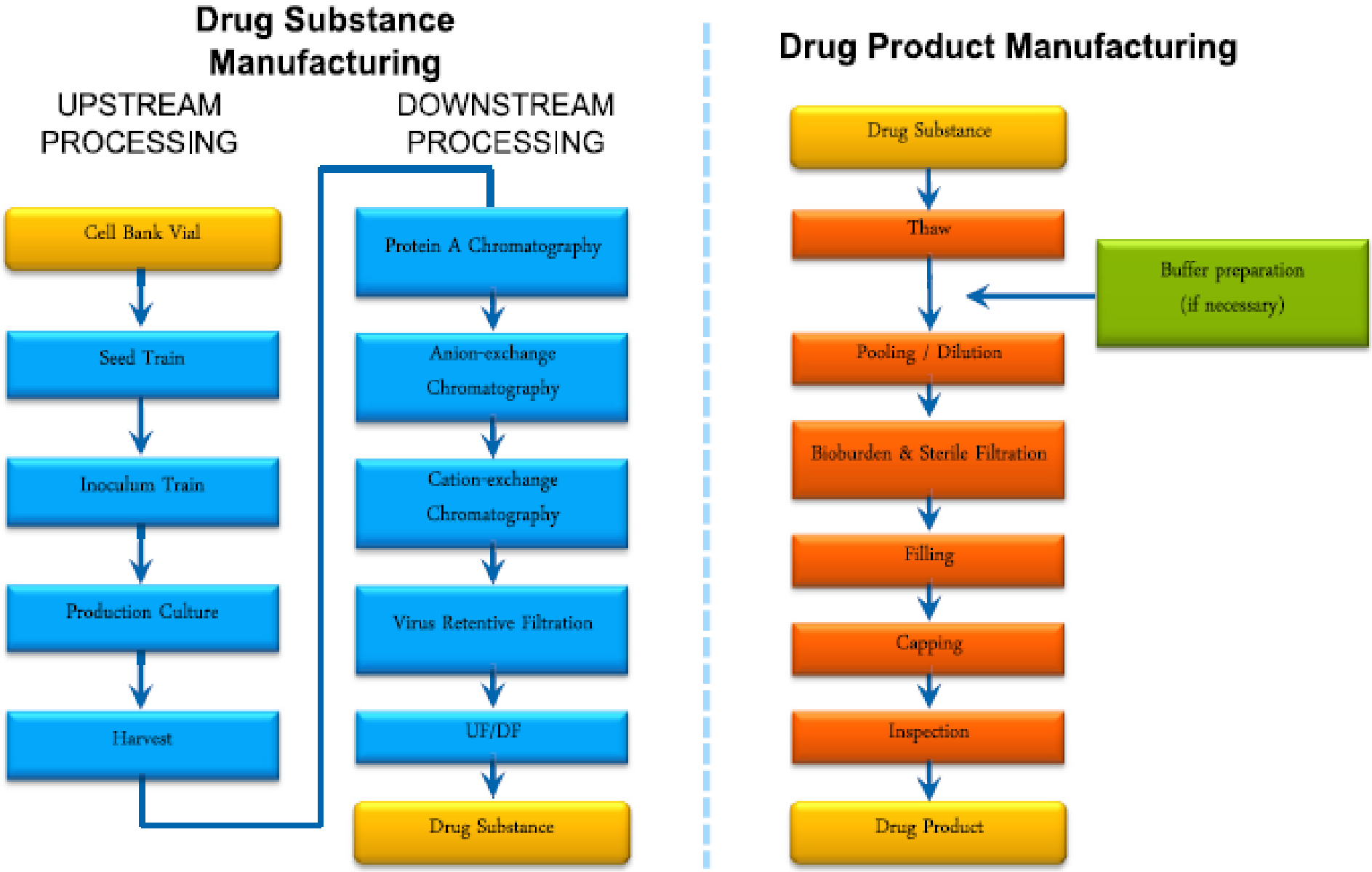


Fig. 3. Flow chart of a standard MAB manufacturing process.

Step 1: Identify all process parameters (PPs)

↓

Step 2: Assign risk score (RS) to <u>each</u> process parameter

(Q9 risk ranking/filtering method, pCPPs)

Step 1: Identify all process parameters (PPs)

↓

Step 2: Assign risk score (RS) to <u>each</u> process parameter (Q9 risk ranking/filtering method, pCPPs)

↓

Step 3: Set risk score (RS) threshold – CPP vs non-CPP

(arbitrary, but must be defendable)

Process parameters are ultimately categorized as high-impact CPPs, low-impact CPPs, or non-CPPs, in order to better categorize their relative criticality. For each parameter, an Impact Ratio is calculated for each CQA. The highest Impact Ratio is compared to the following criteria:

- High Impact CPP: Impact Ratio > 0.33
- Low Impact CPP: 0.33 ≥ Impact Ratio ≥ 0.10
- Non-CPP: Impact Ratio < 0.10

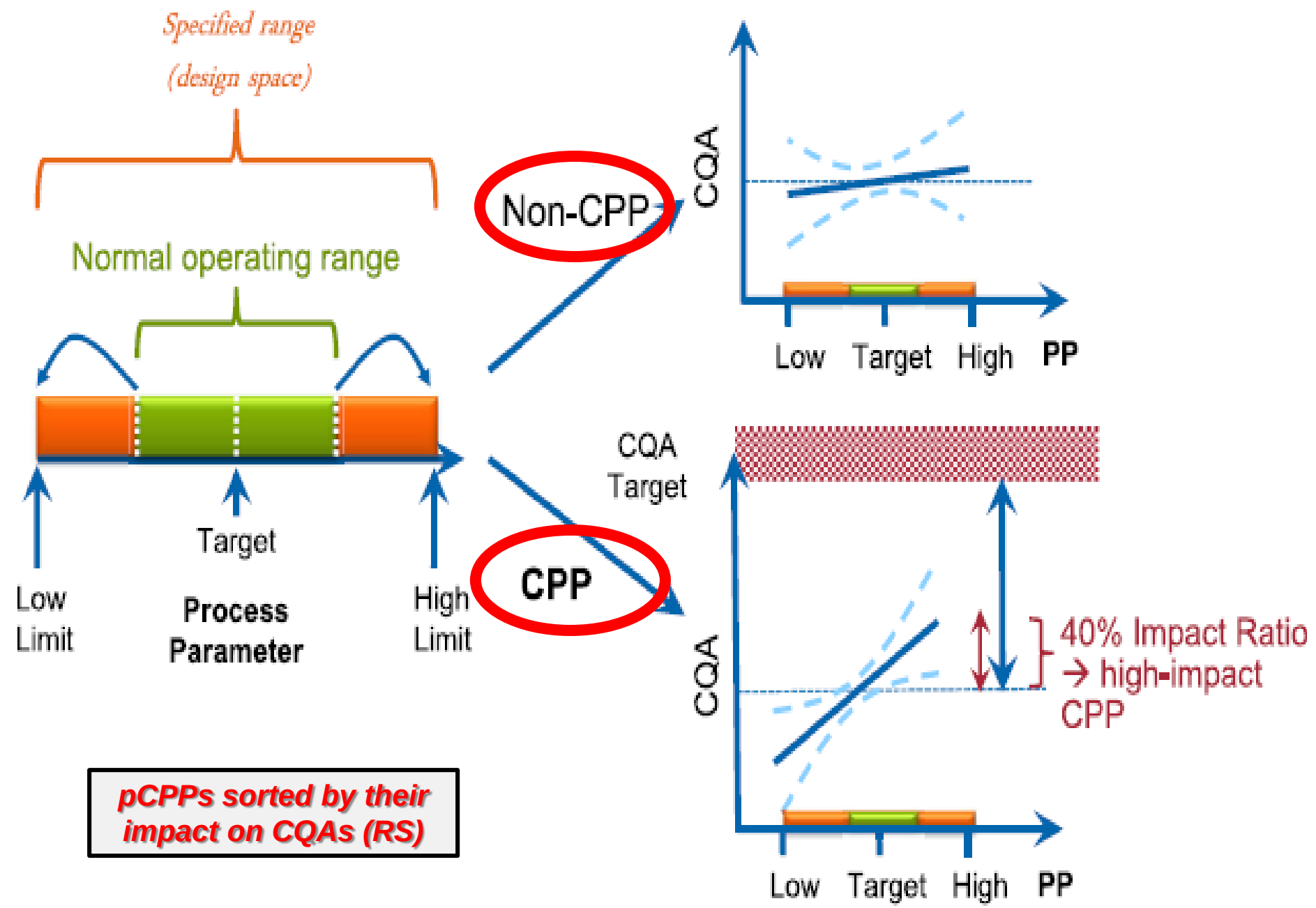


Fig. 6. Illustration of impact ratio calculation.

Question: Which process parameters are CPP?

Process Parameter	*Monoclonal Antibody CQA Impact Ratio*			*CPP or non-CPP?*
	Acidic Region	*Oxidation*		
pO_2	*0.06*	*0.07*		
pH	*0.05*	*0.06*		
Temp	*0.07*	*0.05*		

CPP ≥ 0.10 CQA impact ratio
Non-CPP < 0.10 CQA impact ratio

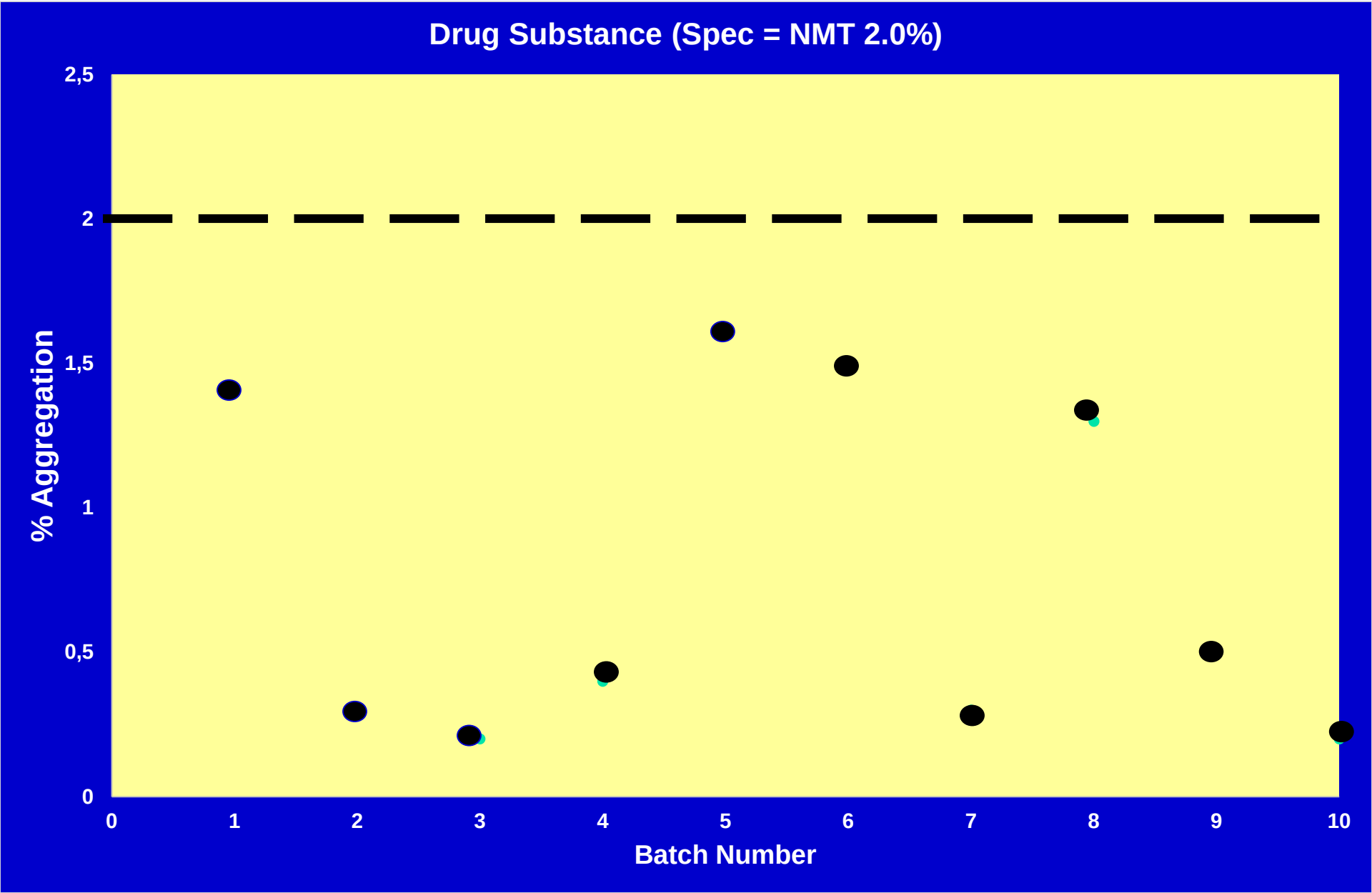
Question: Which process parameters are CPP?

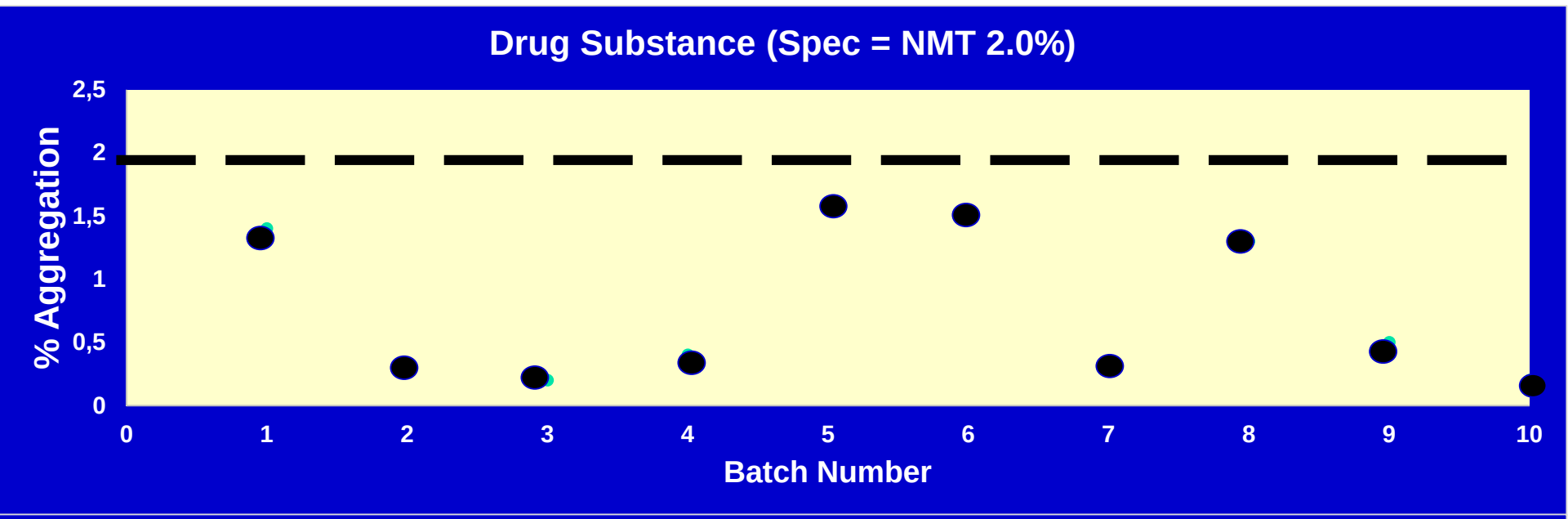
Process Parameter	Monoclonal Antibody CQA Impact Ratio				CPP or non-CPP?
	Acidic Region	Oxidation	Basic Region	Glyco-Structures	
pO_2	0.06	0.07	0.04	0.35	
pH	0.05	0.06	0.08	0.40	
Temp	0.07	0.05	0.15	0.28	

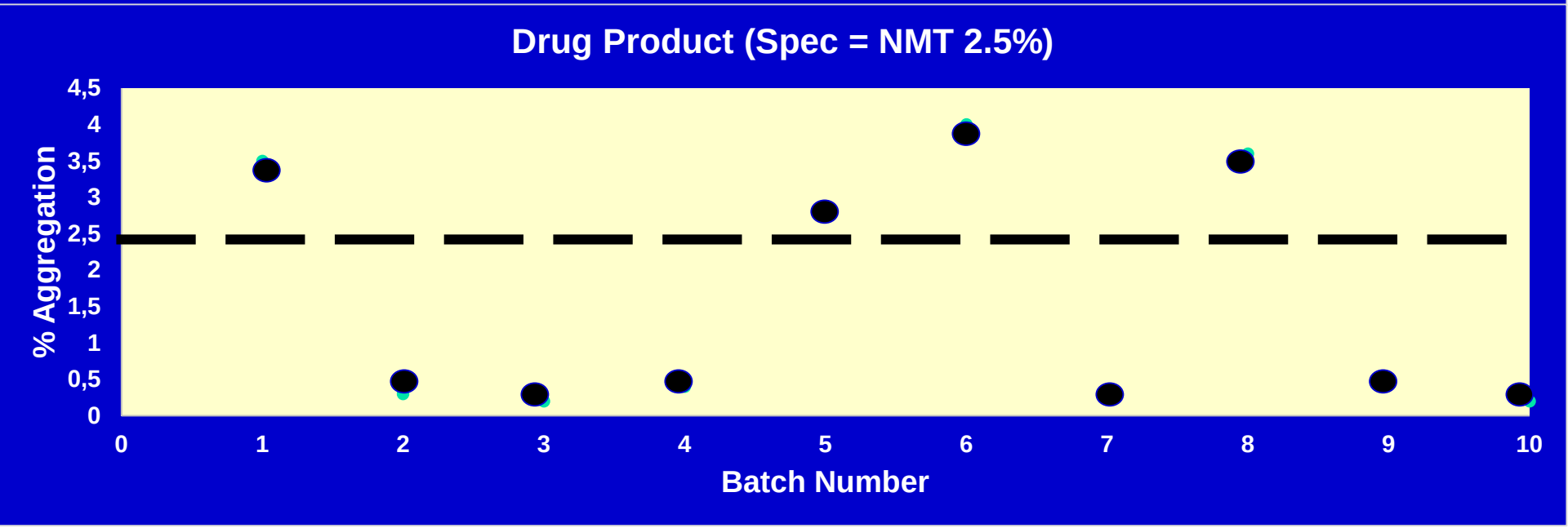
CPP $\geq$ 0.10 CQA impact ratio
Non-CPP $<$ 0.10 CQA impact ratio

Illustrates the importance of looking across <u>all</u> CQAs!

First impressions can be misleading!

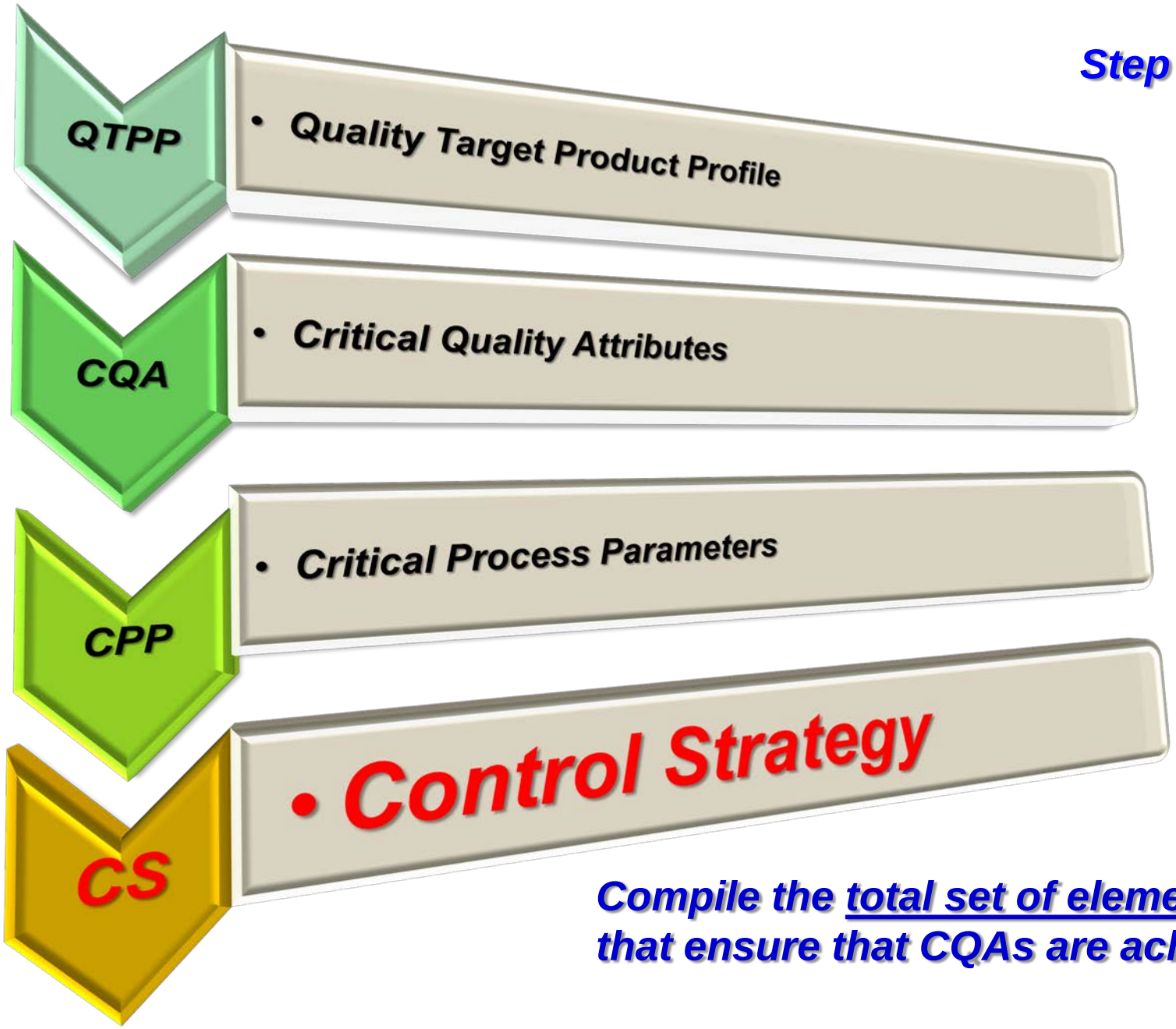






Missing CPP found!

IP HT (hr):	***12***	***0***	***0***	***0***	***10***	***14***	***0***	***12***	***0***	***0***



Step 4

Compile the <u>total set of elements</u> that ensure that CQAs are achieved

Control Strategy

Control Strategy:

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

Control strategy is much more than product release specifications!

4 Elements of a Complete Control Strategy

(ICH Q11 and ICH Q8)

#1 Critical Material Control	Identify Critical Material Attributes (CMAs) and control critical raw materials, starting materials, intermediates, reagents, excipients, primary packaging materials that can impact CQAs

The manufacturing process development program should identify which material attributes (e.g., of raw materials, starting materials, reagents, solvents, process aids, intermediates) and process parameters should be controlled. Risk assessment can help identify the material attributes and process parameters with the potential for having an effect on drug substance CQAs. Those material attributes and process parameters that are found to be important to drug substance quality should be addressed by the control strategy.

ICH Q11

Evaluate raw materials for 'fit for use'

Case example of a CMA in cell culture medium impacting molecular variant formation CQA

Prolia (Denosumab) Amgen EPAR 2010

Manufacture

The manufacture of the drug substance takes place mainly at two sites: Amgen Inc. (ACO) located in Boulder, Colorado and Boehringer Ingelheim Pharma GmbH & Co. Kg (BI Pharma or BIP in Biberach an der Riss, Germany).

According to most of the analytical results, the materials derived from the two sites were comparable. However, a difference in charge profile was found in the extended biochemical characterisation in the comparability analysis. The root cause was found to relate to a component of the culture medium. The variant forms are clinically qualified, because the clinical experience of the C-terminal variants, spans the range of the observed variability. Nevertheless, the applicant has committed to further harmonize the process, as performed at the two sites.

Case example of a CMA in cell culture medium impacting glycosylation composition CQA

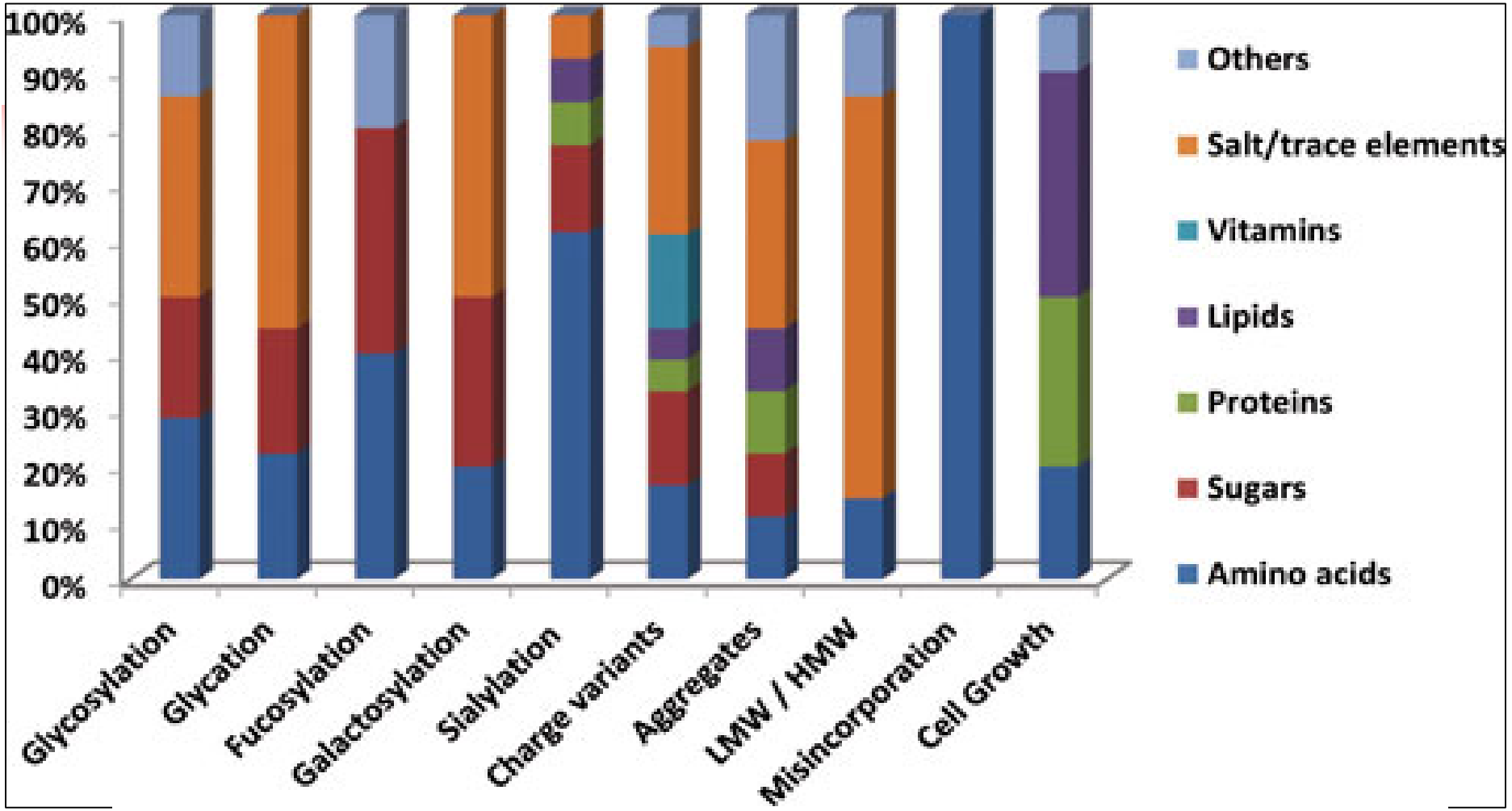
Ocrevus (ocrelizumab) Roche EPAR 2017

9 November 2017
EMA/790835/2017

Studies concluded that the manganese level in the production cell culture medium contributed to the glycosylation differences observed. The ocrelizumab glycoform distribution is sensitive to manganese (Mn) levels in the production culture medium. Manganese levels in the production medium can vary based on contributions from multiple sources.

To ensure process consistency, two measures of potency testing (CDC and ADCC), as well as the correlated glycan attributes (G0 and G0-F), are included on the control system.

Impact (percentage wise distribution) of media components upon CQAs of monoclonal antibodies



Impact of Media Components on CQAs of Monoclonal Antibodies

(The authors review how media components modulate the quality of monoclonal antibody products)

BioPharm International Volume 30, Issue 9, 40–46 Sep 01, 2017

Anurag Rathore, Rajinder Kaur, Dipankar Borgayari

4 Elements of a Complete Control Strategy

(ICH Q11 and ICH Q8)

1 Critical Material Control	Identify and control Critical Material Attributes (CMAs)
#2 Process Design Control	Optimize the design of the manufacturing process to obtain the required product quality (examples: – effectively control the cell culture process to obtain the desired cell productivity – extended duration of the cell culture process can result in additional production of product, but also can increase cell lysis impurities (HCDNA HCP), placing pressure on the downstream purification process steps – adequate number/type and proper sequence of chromatographic steps to effectively control impurity profile in biologic product – effective viral clearance capability designed into the purification process

4 Elements of a Complete Control Strategy

(ICH Q11 and ICH Q8)

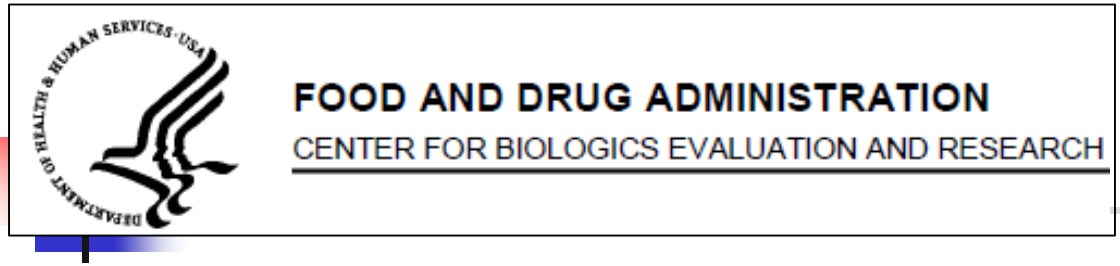
1 Critical Material Control	Identify and control Critical Material Attributes (CMAs)
2 Process Design Control	Optimize the design of the manufacturing process to obtain the required product quality
#3 In-Process Testing Control	Utilize appropriate in-process testing with set action limits (examples: – Action limits (bioburden, endotoxin) – Specified action limits or specifications (absence of virus or mycoplasma in cell culture process)

4 Elements of a Complete Control Strategy

(ICH Q11 and ICH Q8)

1 Critical Material Control	Identify and control Critical Material Attributes (CMAs)
2 Process Design Control	Optimize the design of the manufacturing process to obtain the required product quality
3 In-Process Testing Control	Utilize appropriate in-process testing with either set action limits or specifications
#4 Product Testing Control	Set release and/or stability testing with assigned specifications (this is the most common control element, but it is only 1 of 4 controls)

Case example: multi-element control strategy → impurity profile



RIXUBIS 2013

Final CMC Review of Baxter's original BLA application for Coagulation Factor IX (Recombinant)

- ***Process design control*** *– 'purification process has been developed specifically to clear the process- and product-related impurities'; 'adequate capability of the process to remove and reduce the levels impurities has been demonstrated through process validation studies'*
- ***Product testing control*** *– 'meaningful specifications were developed'; 'consistent purity of batches has been demonstrated through the process validation and scale-comparability exercises'; 'side-by-side comparison between Rixubis and licensed products demonstrated comparable or improved impurity profile in Rixubis'*

Linking Control Strategy to CQAs

Illustration for a Monoclonal Antibody Drug Substance

CQA	Risk	Origin	Control Strategy
Molecular Variants	Immunogenicity, Possible impact on efficacy	Incomplete antibody assembly during production, heat exposure, high pH	Release and stability testing
Glycosylation Variants	None expected	Monoclonal antibody does not have any activity associated with the Fc region	Extensive validation to remove testing at release
Potency	Efficacy	Antibody folding is impacted by bioreactor conditions	Cell-based bioassay spec at release and stability
Endotoxin	Safety	Introduced during manufacturing process	Bioburden control, release and stability testing

Design Space (DS)

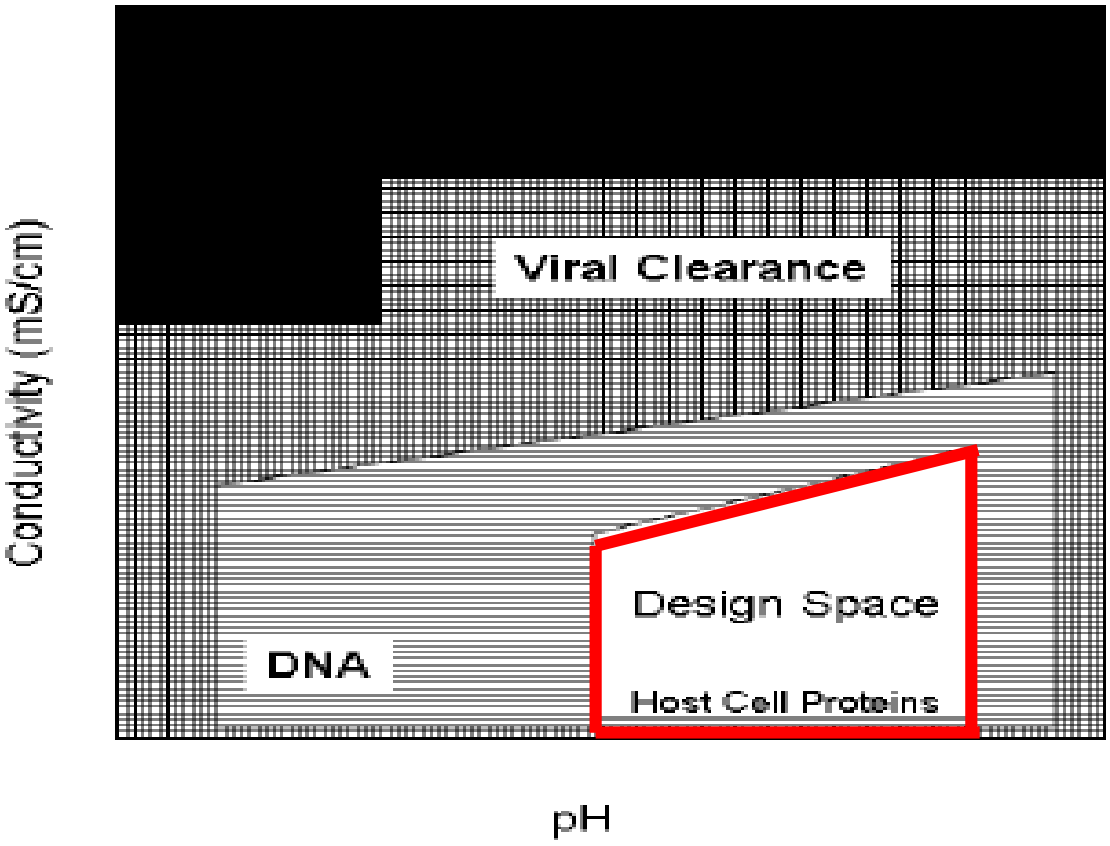
(ICH Q11 and ICH Q8)

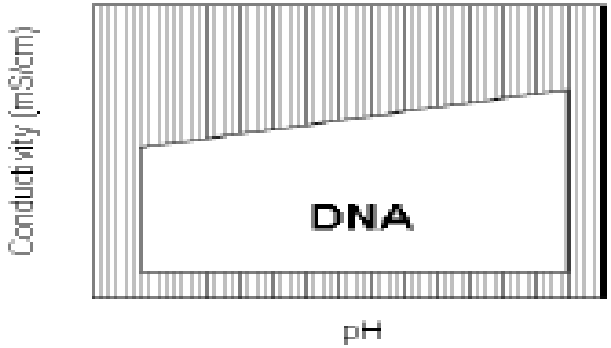
- ***Design space is the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality***
- ***Working within the design space is not considered as a change***
- ***Design space is proposed by the applicant and is subject to regulatory assessment and approval***
- ***A design space might be determined per unit operation … or a combination of selected unit operations***

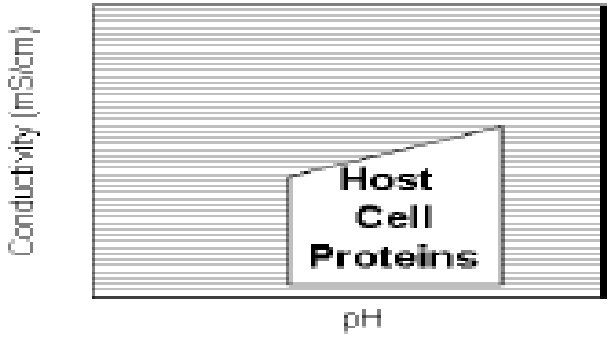
Example of Design Space Determination

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

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







Major Challenge for Design Space of Biologic Manufacturing Processes

Residual Risk

- ***Residual risk: potential for unexpected changes to CQAs based on uncertainties***
- ***Design space 'regulatory flexibility' is inversely proportional to residual risk***

DEPARTMENT OF HEALTH AND HUMAN SERVICES

But if you address residual risk concerns …

The only biologic reported to have achieved design space regulatory freedom

Food and Drug Administration
Silver Spring MD 20993

BLA 125486/0

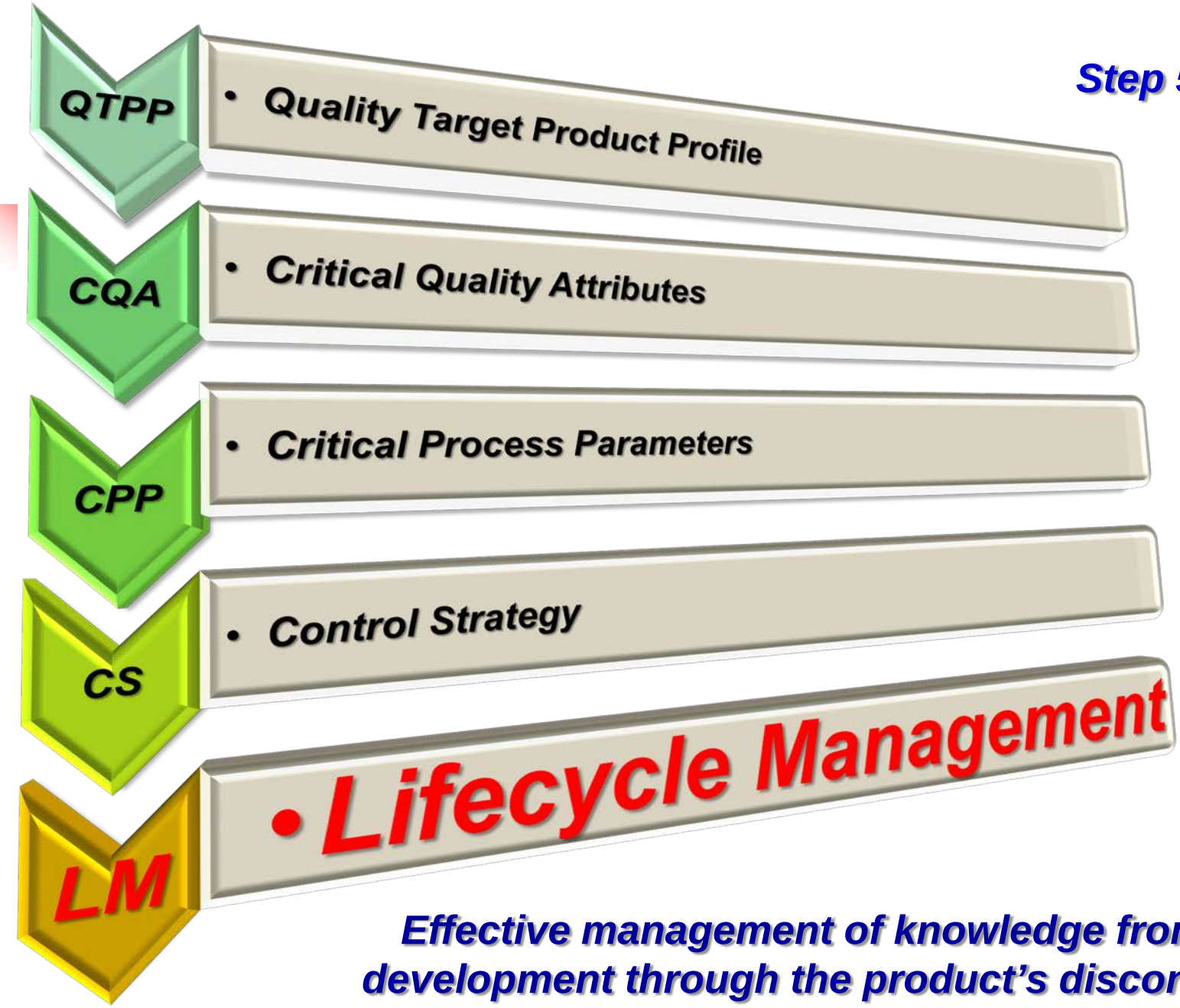
GAZYVA (obinutuzumab)

BLA APPROVAL

11/01/2013

Genentech, Inc.

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


Step 5
QTPP
• Quality Target Product Profile
CQA
• Critical Quality Attributes
CPP
• Critical Process Parameters
CS
• Control Strategy
LM
• Lifecycle Management
Effective management of knowledge from initial development through the product's discontinuation

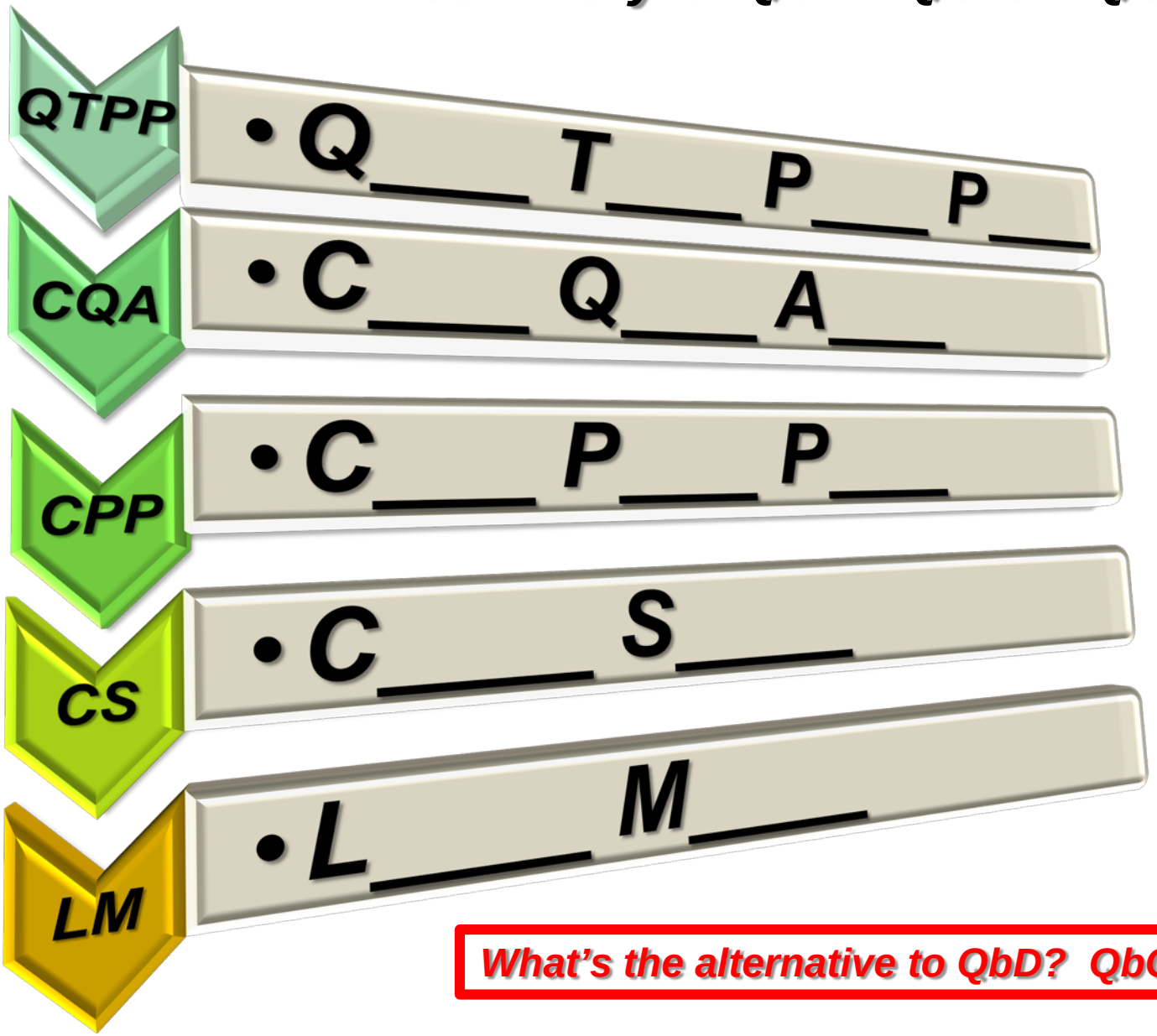
Lifecycle Management

ICH Q11

There should be a systematic approach to managing knowledge related to both drug substance and its manufacturing process throughout the lifecycle. This knowledge management should include but not be limited to process development activities, technology transfer activities to internal sites and contract manufacturers, process validation studies over the lifecycle of the drug substance, and change management activities. The knowledge and process understanding should be shared as needed to perform the manufacturing process and implement the control strategy across sites involved in manufacturing the drug substance.

knowledge management; continuous process improvement

Summary of QbD - QUICK QUIZ



What's the alternative to QbD? QbC!

The biopharmaceutical industry has embraced QbD

- Recombinant proteins
- Monoclonal antibodies →
- Biosimilar manufacturers
- Genetically engineered viruses →
- Genetically engineered cells

Monoclonal Antibody

Hemlibra (Emicizumab)

Development, characterization, and validation of the emicizumab process are based on a Quality by Design (QbD) approach. … The QbD strategy has been discussed in detail. The applicant has built a series of risk assessment tools aimed at analyzing, categorizing, and ensuring appropriate mitigation and management of risk to product efficacy and safety related to the production process. In combination, these elements form a comprehensive risk and science based program to assess the criticality of product attributes and rationally design a process and product control strategy.

- ***Identification of critical quality attributes (CQAs) for the active substance and finished product using CQA risk ranking and filtering (RRF) was refined iteratively during development as more product knowledge was accumulated;***
- ***Process design, assessment of potential critical process parameters (pCPPs) to be included in process validation (PV) studies, and analysis and categorization of study results to identify CPPs were refined continuously over the process development life cycle;***

EMA European Public Assessment Report (EPAR) : Hemlibra (January 2018)

Genetically Engineered Virus

Luxturna (Voretigene Neparvovec-rzyl)

A risk assessment was performed on each manufacturing process step to identify process parameters that impact safety and/or efficacy of the product. An evaluation of historical manufacturing at CHOP and Spark was used to identify a set of provisional critical process parameters (CPPs) and critical in-process controls (CIPCs) for the production of Drug Substance, and their associated control range. The process parameters and their corresponding Process Performance Qualification (PPQ) acceptance criteria were based on an Interim Control Strategy developed from a Failure Mode and Effects Analysis (FMEA) ….

FDA Vaccines, Blood & Biologics: Licensed Biologic Products With Supporting Data – Luxturna (Voretigene Neparvovec-rzyl) – Approval History, Letters, Reviews, and Related Documents – CMC Review (December 2017)

Traditional approach for potato chip manufacture

By QbD, how do they make the exact, perfect shape every time?

Video

Pringles – Enhanced Approach (QbD) – using continuous manufacturing – any CQAs? CPPs?

Warning: Don't play games with QbD!

Control of manufacturing process

Withdrawal Assessment Report

The general approach to assure a consistent and reliable manufacturing process is in compliance with ICH Q6B. However, the control strategy was not sufficiently defined for the manufacturing of DS. This was regarded as a major objection at D120. The Company has determined the control steps according to quality by design (QbD) principles without applying QbD. The performance parameters are categorized into in-process controls, in-process limits, and in-process specifications. Based on an FMEA risk assessment, each process parameter was ranked from 1-10 on the severity, probability of occurrence, and the ability to detect an excursion and/or the impact of an excursion outside of the normal operating range (NOR). The categorization of a process parameter as critical or non-critical followed a risk based approach without a proper argumentation of the criticality of the parameters and this was not considered appropriate.

IXinity (formerly IB1001)

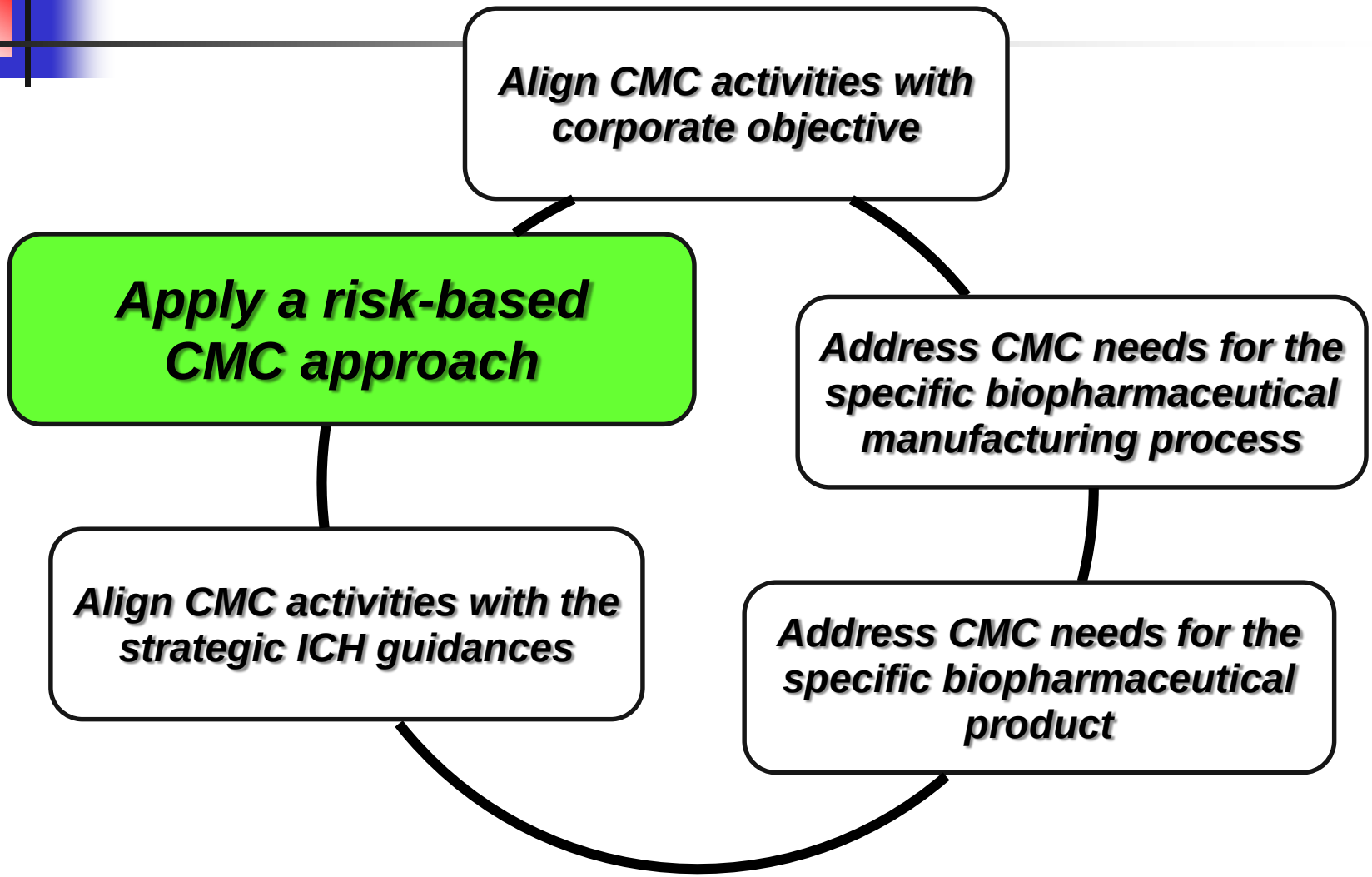
Inspiration Biopharmaceuticals

International non-proprietary name: Recombinant coagulation factor IX (trenonacog alfa)

London, 20 September 2012
EMA/CHMP/598935/2012

Composing an Effective Corporate CMC Regulatory Compliance Strategy

5 Key Design Elements



Apply a risk-based approach to your CMC regulatory compliance strategy

- ***A risk-based approach focuses the CMC activities on aspects that, directly or indirectly, may affect the safety and efficacy of the product***
- ***A risk-based approach does not mean doing less to ensure safety and efficacy but doing the right amount of CMC activity at the right time based on the understanding of the risks to product quality and patient safety***
- ***Thus, a risk-based development plan actually enhances patient safety in early clinical stages, even when product understanding and resources may be limited***

(also referred to as 'Phase-Appropriate' approach)

A risk-based approach attempts to avoid non-value-added CMC activities and focuses efforts on critical activities

The risk-based CMC regulatory compliance approach through the clinical development phases is recognized and embraced by the regulatory authorities and the biopharmaceutical industry:

- ***EMA***
- ***FDA***
- ***Biopharm Industry (PDA)***

Embraced by EMA

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

14 September 2017
EMA/CHMP/BWP/534898/2008 rev. 1

CMC Area		Recognized R-B CMC Strategy
S.2.4	Control of Critical Steps	It is acknowledged that due to limited data at an early stage of development (phase I/II) complete information may not be available
S.2.5	Process Validation	Process validation data should be collected throughout development
S.2.6	Manufacturing Process Development	During early phases of non-clinical and clinical studies, comparability testing is generally not as extensive as for an approved product
S.4.1	Specifications	As the acceptance criteria are normally based on a limited number of development batches and batches used in non-clinical and clinical studies, they are by their nature inherently preliminary and may need to be reviewed and adjusted during further development
S.4.3	Validation of Analytical Procedure	Validation of analytical procedures during clinical development is seen as an evolving process

Embraced by FDA

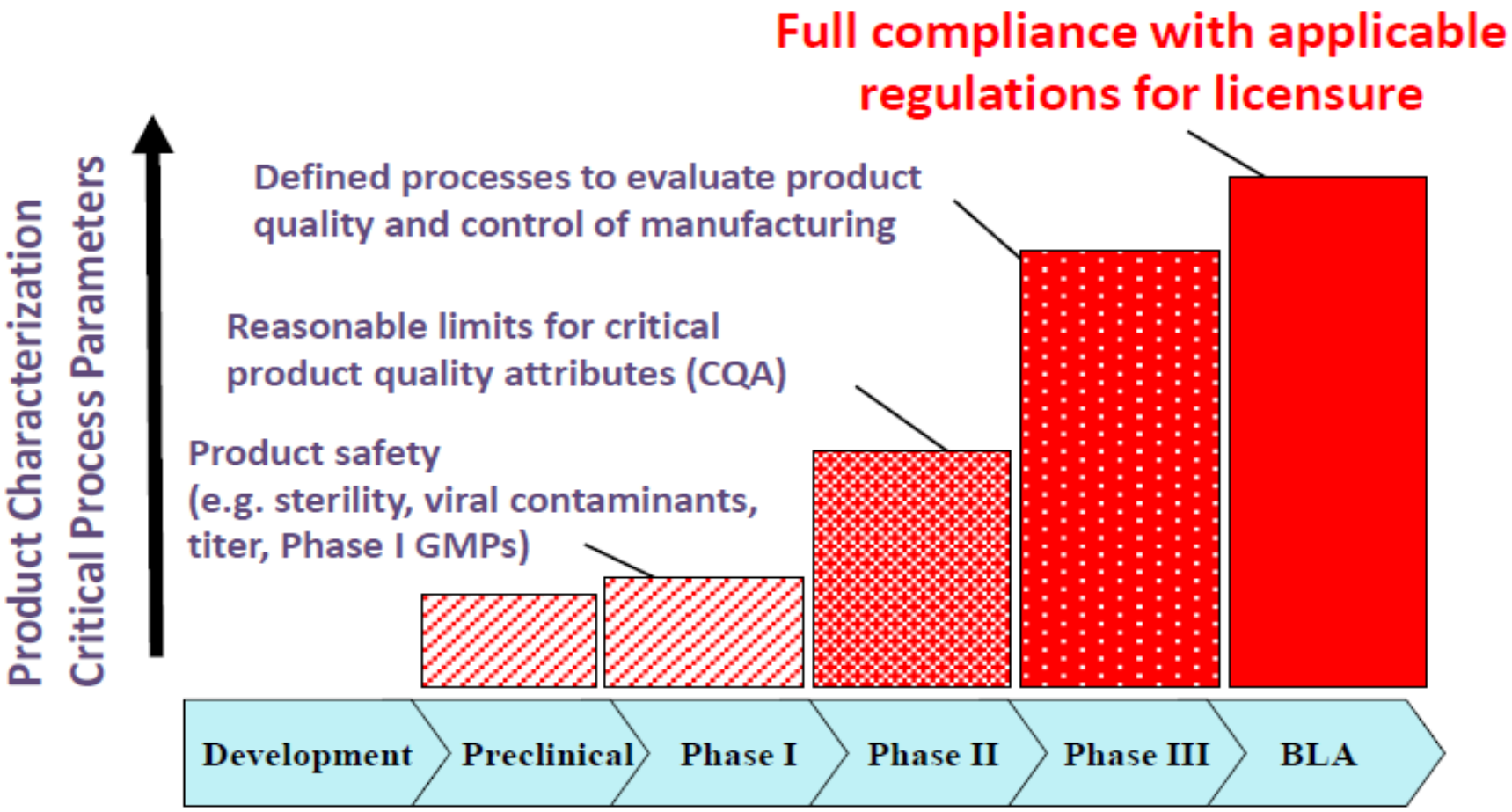
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
July 2018

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

Draft Guidance for Industry

CMC Area		Recognized R-B CMC Strategy
3.2.S.2.5	Process Validation	Process validation studies are generally or typically not required for early stage manufacturing, and thus, most original IND submissions will not include process performance qualification. We recommend that you use early stage manufacturing experience to evaluate the need for process improvements and to support process validation studies in the future.
3.2.S.4.1	Specifications	For products in the early stages of clinical development, very few specifications are finalized, and some tests may still be under development.
3.2.S.4.3	Validation of Analytical Procedure	Validation of analytical procedures is usually not required for original IND submissions for Phase 1 studies; however, you should demonstrate that test methods are appropriately controlled.

Expectations For Product Development Are Phased In During Development Stages



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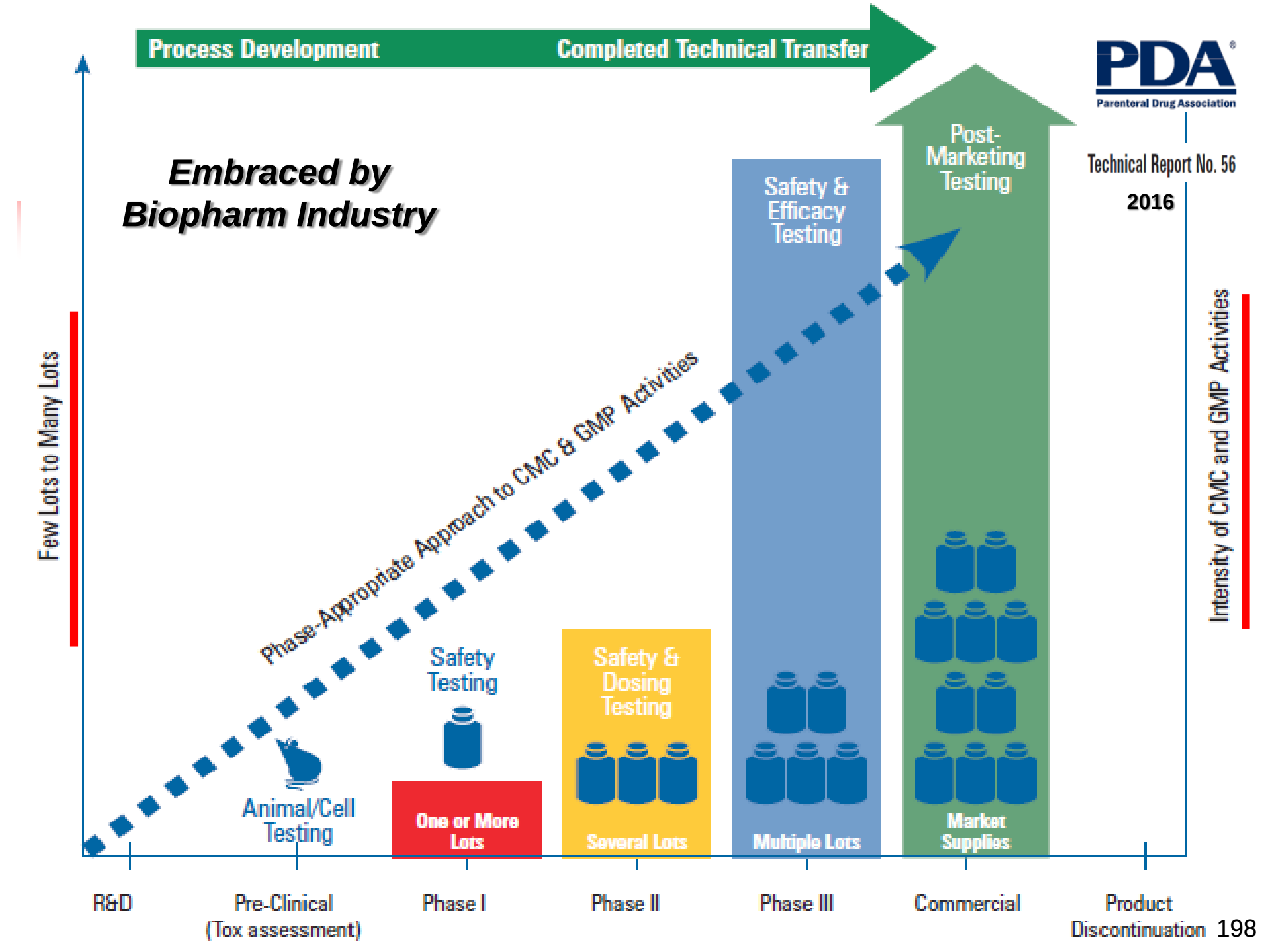
PDA/FDA Joint Regulatory Conference
Sept. 11, 2017


Process Development
Completed Technical Transfer
PDA
Parenteral Drug Association
Technical Report No. 56
2016
Embraced by Biopharm Industry
Post-Marketing Testing
Safety & Efficacy Testing
Safety & Dosing Testing
Safety Testing
Phase-Appropriate Approach to CMC & GMP Activities
Few Lots to Many Lots
Intensity of CMC and GMP Activities
Animal/Cell Testing
One or More Lots
Several Lots
Multiple Lots
Market Supplies
R&D
Pre-Clinical (Tox assessment)
Phase I
Phase II
Phase III
Commercial
Product Discontinuation

Caution Ahead!

Impacts to Risk-Based Approach to CMC Regulatory Compliance

1) Expedited clinical pathways

2) Biosimilars

3) Gene therapy biopharmaceuticals

1) Expedited clinical pathways are moving the clinical development into a 'seamless phase'

FDA expedited clinical pathways:

- ***accelerated approval – use of surrogate endpoints***
- ***priority review***
- ***fast track designation***
- ***breakthrough therapy designation***
- ***regenerative medicine advanced therapy (RMAT) designation***

EMA expedited clinical pathways:

- ***accelerated assessment***
- ***conditional marketing authorization***
- ***primary medicine (PRIME) designation***

Under the expedited clinical pathways, the clinical development teams have the opportunity to move fast through the clinical phases, even at times not having to carry out a Phase 3 pivotal clinical program for market approval (but needing to carry it out after market approval)

FDA is concerned about the CMC team if expedited clinical pathway is granted!

The sponsor of a product that receives an expedited drug development designation may need to pursue a more rapid manufacturing development program to accommodate the accelerated pace of the clinical program.

When sponsors receive an expedited drug development designation, they should be prepared to propose a commercial manufacturing program that will ensure availability of quality product at the time of approval.

The proposal should consider estimated market demand and the commercial manufacturing development plan. The proposal should also consider manufacturing facilities and a lifecycle approach to process validation. Additionally, the proposal should include a timeline for development of the manufacturing capabilities with goals aligned with the clinical development program.

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

Case Example

FDA CMC Breakthrough Meeting Minutes

Janssen Darzalex (daratumumab)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 100638

Meeting Type:	Type B
Meeting Category:	Breakthrough Therapy

MEETING MINUTES

Janssen Research & Development, LLC

We also refer to the meeting between representatives of your firm and the FDA on July 31, 2013. The purpose of the meeting was to discuss a comprehensive overview of the planned development program for daratumumab, including planned clinical studies and Phase 3 Chemistry Manufacturing and Controls (CMC) plans for the development of daratumumab and the proposed comparability strategy between Phase 1/2 and Phase 3 clinical/commercial material.

FDA Drug Databases: Drugs@FDA – FDA Approved Drug Products – Darzalex (Daratumumab) – CDER Memorandum of Meeting Minutes – Breakthrough Therapy Daratumumab (Janssen Biotech) (July 31, 2013)

Where the FDA was willing to give some CMC relief: specs

Question 8:

Does the Agency agree that the proposed approach for setting commercial specifications that utilizes a combination of Janssen mAb process experience, daratumumab clinical batch experience and product knowledge, and the results of available structure- function studies is sufficient to support the BLA submission?

FDA Response to Question 8:

Commercial specifications are based on lots used in clinical studies, manufacturing consistency, and stability data. Knowledge of critical quality attributes for daratumumab can support establishing specifications for licensure. FDA acknowledges limited data may be available at the time of licensure and would support re-evaluating specifications once sufficient commercial manufacturing experience is gained.

Where the FDA was not willing to give some CMC relief: stability

Question 9c:

Further, does the Agency agree that available stability results for PPQ batches would be submitted to FDA with the Clinical Safety update during the BLA review period and subsequent updates in the BLA Annual Report for this product?

FDA Response to Question 9c:

No, per the PDUFA V legislation, limited components of the BLA submission may be submitted within 30 days of the BLA submission. Any available stability data for the drug product PPQ batches should be submitted with the BLA submission. With respect to the submission of additional stability data to support a proposed expiry period, the FDA may request a 'simple stability update'. A simple stability update is defined as stability data and analyses performed under the same conditions and for the same drug product batches in the same container closure system(s) as described in the stability protocol provided in the original submission; it will use the same tabular presentation as in the original submission as

FDA concerns for CMC due to clinical expediting

recognized CMC pressure points

- CQA assessment and product characterization
- Formulation development
- Cell line cloning, master cell bank development and characterization
- Assay development (e.g. potency, host cell protein assay, immunogenicity assays)
  - Bridging early assays to commercial assays
  - Suitable assays in place for process performance qualification
  - Suitable assays in place for pivotal trials
- Timing of process scale-ups and site transfers

CDER presentation, WCBP 2017

EMA is concerned about the CMC team if expedited clinical pathway (PRIME) is granted!

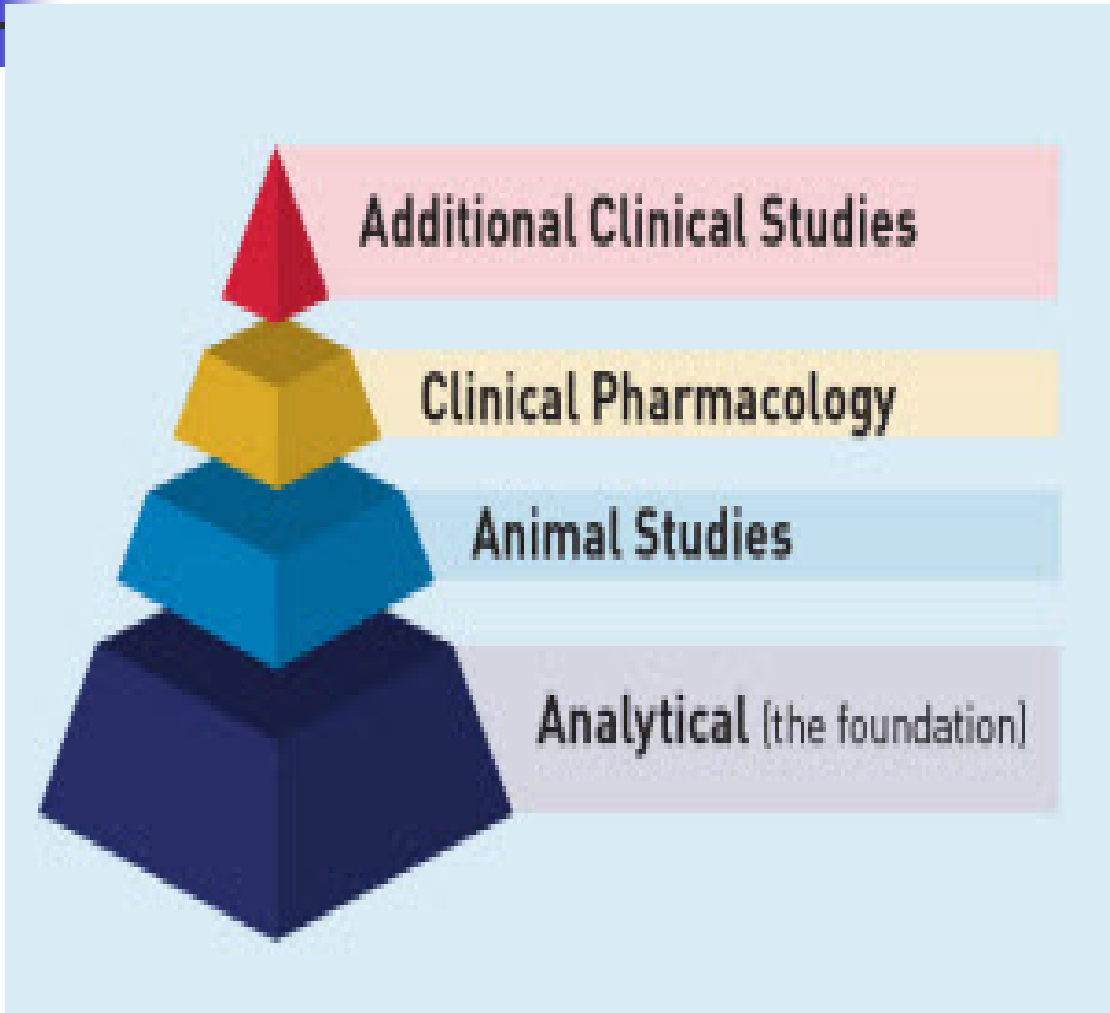
When preparing the document, the applicant should consider key pharmaceutical aspects in relation to the active substance and finished product that need to be highlighted to support the discussion during the meeting.

Examples of such aspects/issues are included below:

- ***Cell line development and cell banking strategy, as applicable***
- ***Product characterisation including critical quality attributes and biological potency***
- ***Manufacturing process development including process changes and upscaling plan for commercial purposes and timing in relation to clinical data generation/launch (discuss any issues and bridging data in case of different manufacturing sites) …***

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

2) Biosimilars – foundational importance of CMC biosimilarity



If Step 1 (CMC Biosimilarity) is not achieved, steps 2 and 3 are not pursued

Mature CMC systems are needed at the outset of biosimilar development!

3) Gene therapy biopharmaceuticals – heightened importance of CMC

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

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

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

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

NO EXCUSES – CMC risk-based approach should never endanger patients!

FDA investigated the U.S. National Institutes of Health (NIH) and discovered that the gene therapy cells that they were preparing were not properly aseptically processed – putting the clinical patients at risk

In light of serious problems identified in the NIH Clinical Center Pharmaceutical Development Section last year, NIH launched a multifaceted effort to ensure that processes for patient safety and quality of care at the hospital are of the highest standards. Accordingly, NIH hired two companies specializing in quality assurance for manufacturing and compounding – Working Buildings and Clinical IQ – to evaluate all of its facilities producing sterile or infused products for administration to research participants. This evaluation is underway and preliminary findings have identified facilities not in compliance with quality and safety standards, and not suitable for the production of sterile or infused products. As a result, production has been suspended in two facilities: a National Cancer Institute laboratory engaged in cell therapy production and a National Institute of Mental Health facility producing positron emission tomography (PET) materials.

April 19, 2016

Summary of Key Design Elements
QUICK QUIZ

Align CMC activities with c_____ o_____

Apply a r___-b_____ CMC approach

Address CMC needs for the specific biopharmaceutical m_____ p_____

Align CMC activities with the s_____ ICH guidances

Address CMC needs for the specific b_____ p_____