CMC Regulatory Compliance Strategy For Biopharmaceuticals

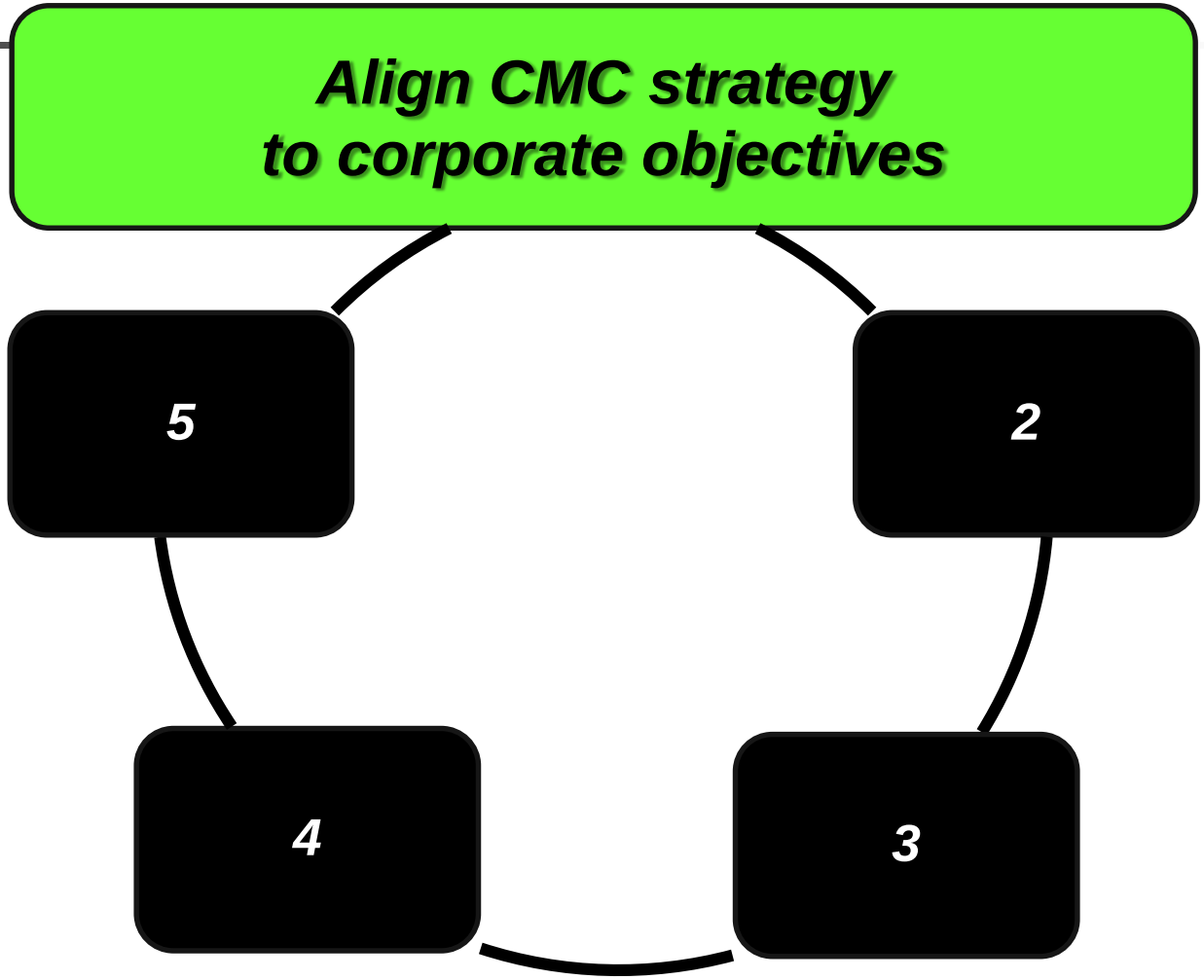
Course Outline

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

- ✓ *5 key design elements for an effective CMC strategy*
- ✓ *Managing the 'minimum CMC compliance continuum' throughout seamless clinical development stages and expedited clinical designations*

Composing an Effective Corporate CMC Regulatory Compliance Strategy for Biopharmaceuticals

5 Key Design Elements



Align CMC strategy to corporate objectives

Part 1 of 3: Acknowledge the full CMC picture

C Chemistry

product characterization, release and stability testing, …

M Manufacturing

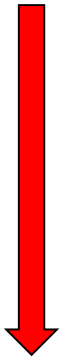
facilities, utilities, raw materials, process, …

C Controls

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

Part 2 of 3: Balance the CMC activities against the current, and potentially future, corporate objective

The level of maturity needed for the CMC compliance systems is dependent upon the corporate objective!



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

Increasing CMC resources and maturity of control systems

Caution: corporate objectives can always change!

Lots of acquisitions and mergers in this area!

Frequently, you must defend additional needed CMC resources to meet the corporate objective

Part 3 of 3: Recognize the corporate risk-tolerance level, and try to compensate for any concerns

Illustration of <u>Personal</u> Risk-Tolerance

Should I fly in an airplane?

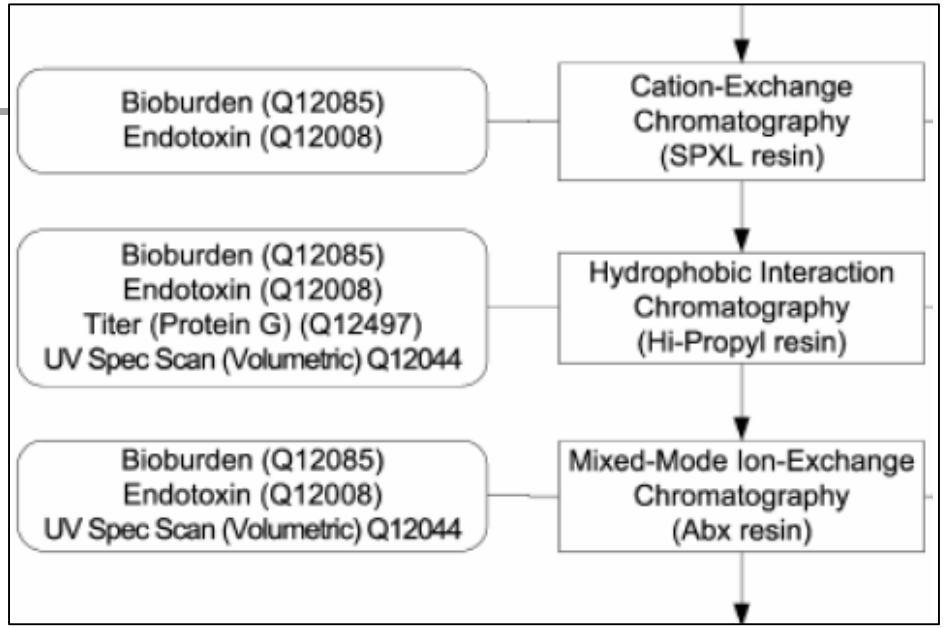
Risk Assessment (YOU):

- ***What is the highest severity if the airplane crashes?***
- ***What is the statistical probability of a crash?***
- ***What is the <u>perceived</u> probability of a crash?***

Acceptable risk to fly in an airplane?

Illustration of Corporate CMC Risk-Tolerance

Why are we spending so much resource when we test for bioburden at each purification step?
Let's consider testing for bioburden only at the DS!



Risk Assessment (QA/ QC/ Mfg/ Dev/ Reg Affairs):

- ***What is the highest severity if we only test at the DS?***
- ***What possible problems could result if we eliminate the in-process bioburden testing?***
- ***What is the perceived probability of such a problem occurring?***

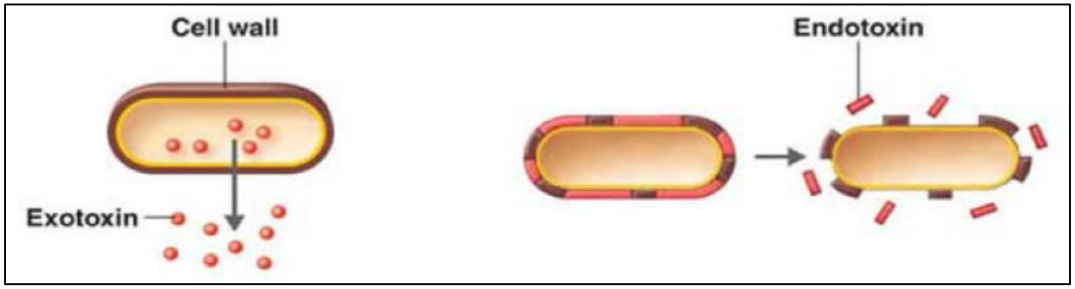
Acceptable to eliminate the in-process bioburden test?

Some biopharmaceutical companies are risk adverse – go slow

Some biopharmaceutical companies are 'cowboys' – go fast

Proper risk assessment requires obtaining ALL of the facts!

High bioburden load can release:



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

Peptidases can break down a recombinant protein or mAb during its shelf life

Regulatory authorities traditionally expect this testing, because of their experience

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

Case Example: high CMC risk tolerance coupled with a faulty risk assessment led to a very high level of risk!

(Genzyme story: 'can't happen to us')

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

- ***2006*: Evidence of widespread Vesivirus infections in cattle across a large area of the United States – biologic manufacturers who source US FBS put on notice**
- ***2006*: PCR test available to give a rapid detection of Vesivirus, but it was considered too costly by Genzyme – ~$2000 per sample**
- ***2008*: Genzyme encountered loss of cell productivity in both a 4000L bioreactor at their Belgium site, and a 2000L bioreactor at their US site – but manufacturing saw changes in cell growth profile and did not break bioreactor integrity – instead killed the cells and contamination inside the bioreactor – a virus suspected; if happened again, Genzyme believed that they would detect it early enough.**
- ***2009*: a nightmare hits! Genzyme confirms Vesivirus in a bioreactor, <u>but only after containment was broken!</u> Now, the virus was spread into the purification suite and throughout the entire facility!**
- ***June 2009*: Genzyme press release due to orphan drug supply – we have a fixable problem; will be back in operation within 1-2 months!**

REALITY

Genzyme Press Release Sept 2009

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

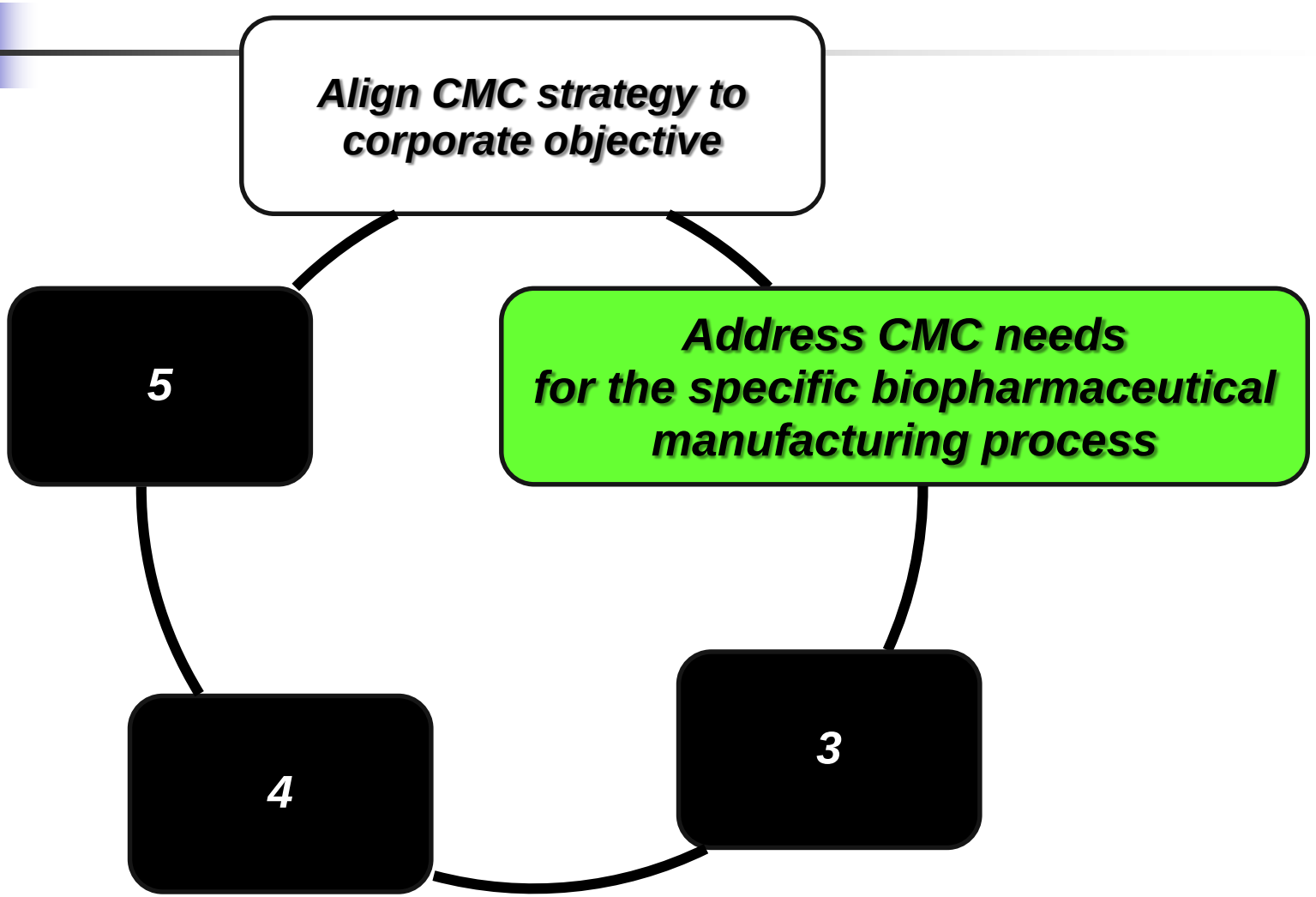
- The duration of the sanitization effort was almost 2 months and used approximately 2,236 gallons of solution and 1,488 cans of isopropyl alcohol for cleaning and sterilization.
- Outside contractors worked more than 40,000 service hours in this effort in June and July. At the height of the effort, 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.

For lack of a ~$2000 test!

Estimated impact on Genzyme ~$500 million

Composing an Effective Corporate CMC Regulatory Compliance Strategy for Biopharmaceuticals

5 Key Design Elements



Each Biopharmaceutical Manufacturing Process Has Its Uniqueness

Monoclonal antibody manufacturing
Roche

Cell-based biologic manufacturing
Novartis

ASSIGNMENT: As you watch, what 'adjectives' would you use to describe each of the two specific manufacturing processes?

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

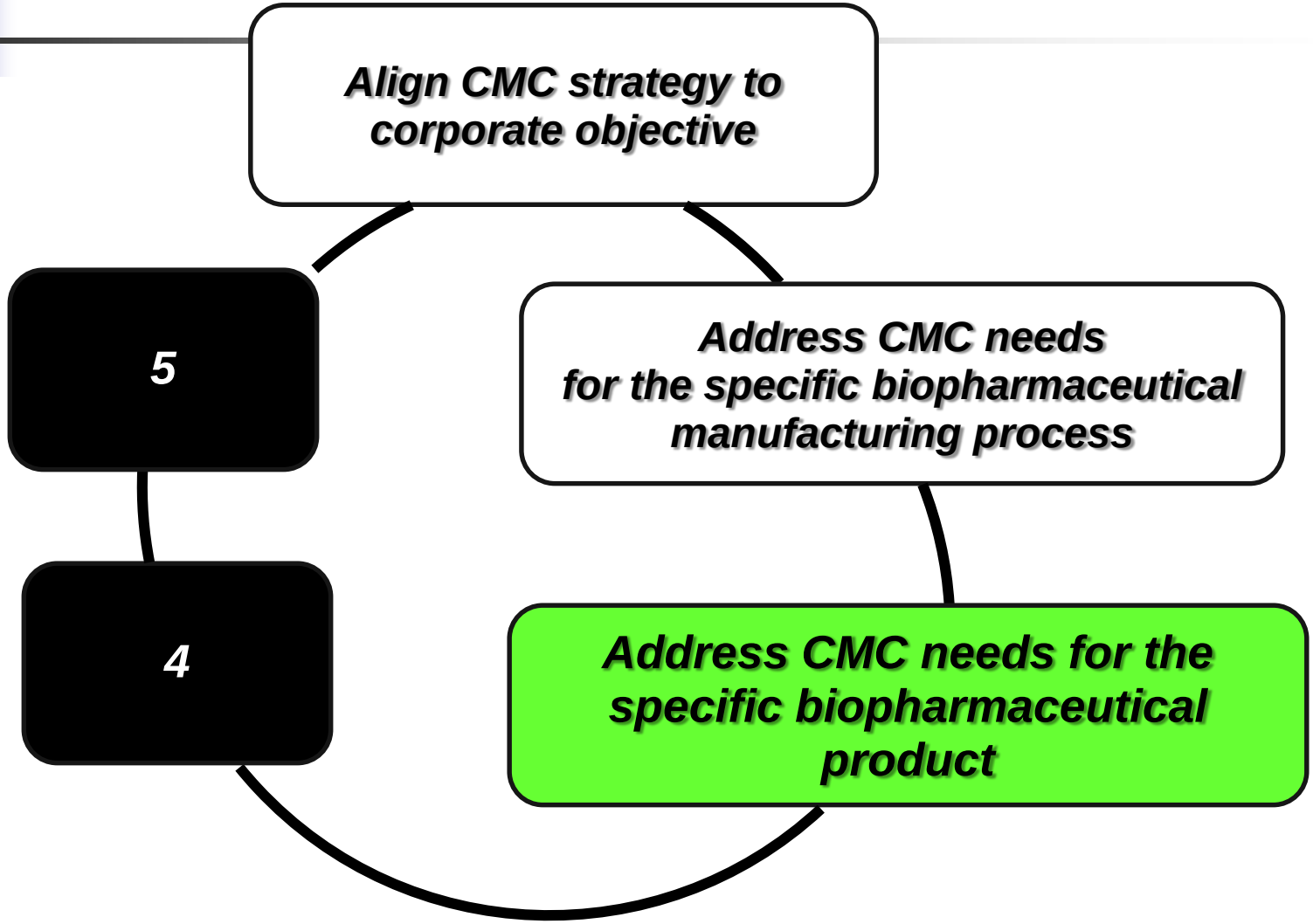
Many things in common, but no magic formula!

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

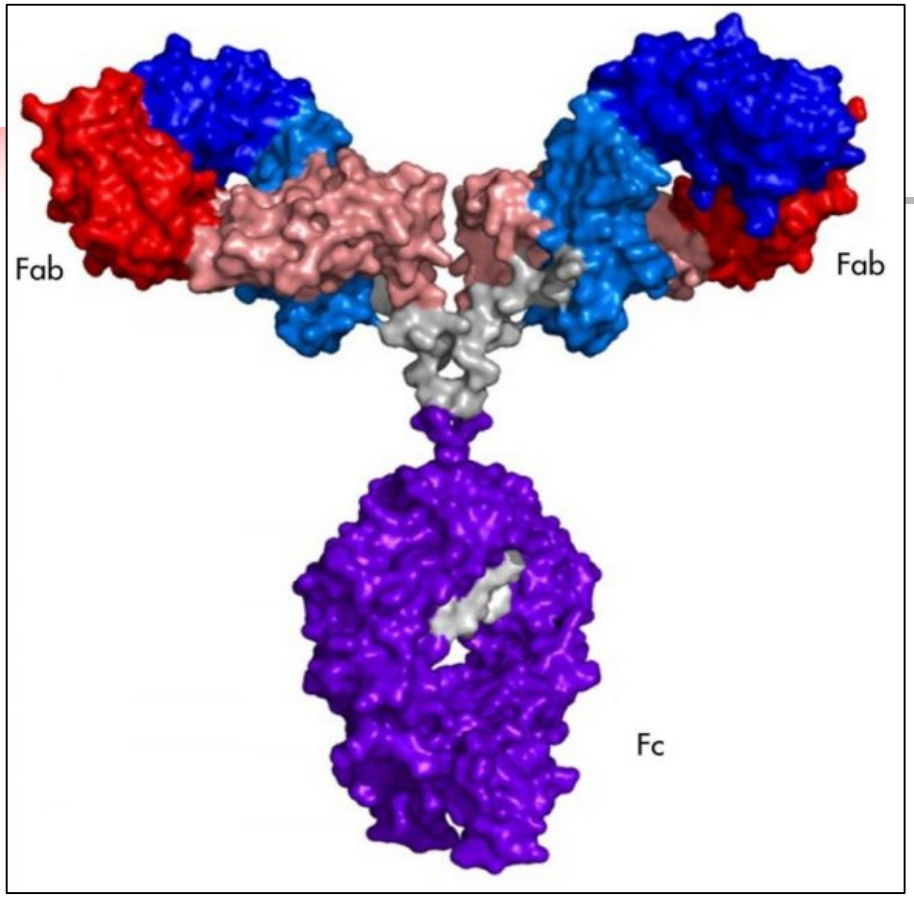
'platform' approach provides valuable insights

Composing an Effective Corporate CMC Regulatory Compliance Strategy for Biopharmaceuticals

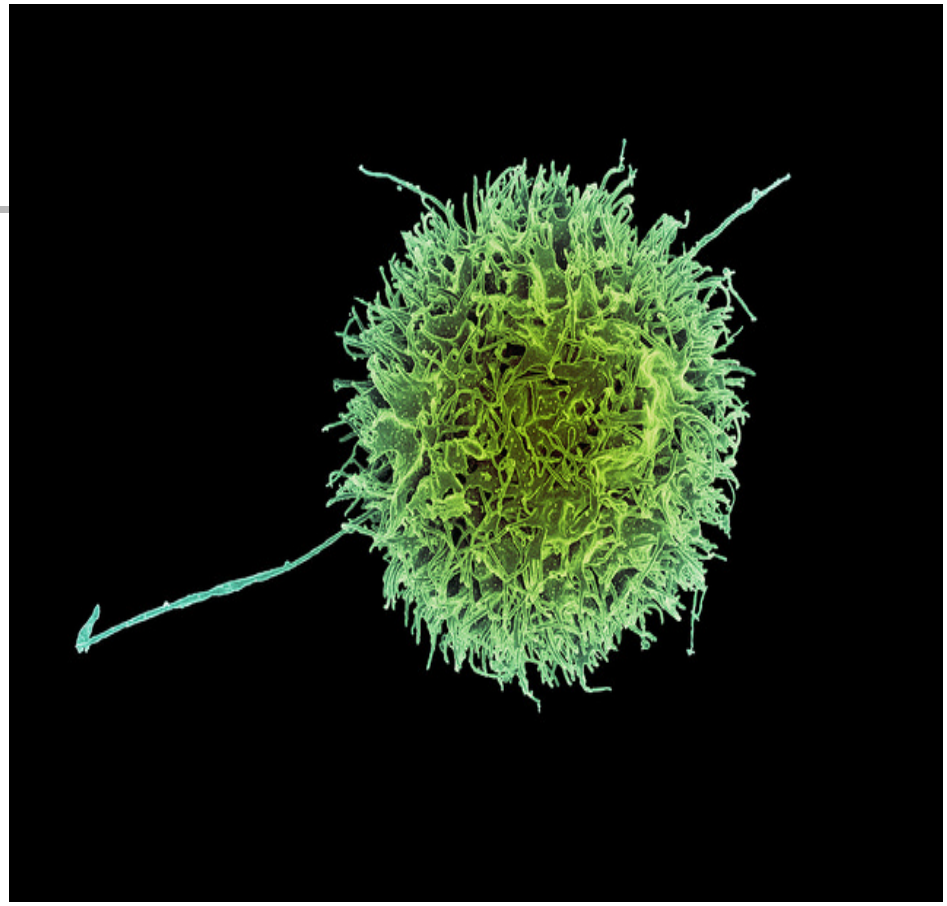
5 Key Design Elements



Each Biopharmaceutical Product Has Its Uniqueness

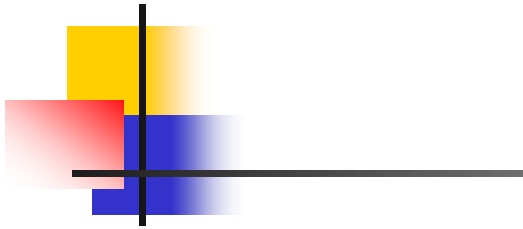


Monoclonal antibody
Roche



Cell-based biologic
Adaptimmune

ASSIGNMENT: <u>As you watch</u>, how would you determine the potency (therapeutic activity) for each of these two biopharmaceutical products?



17

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

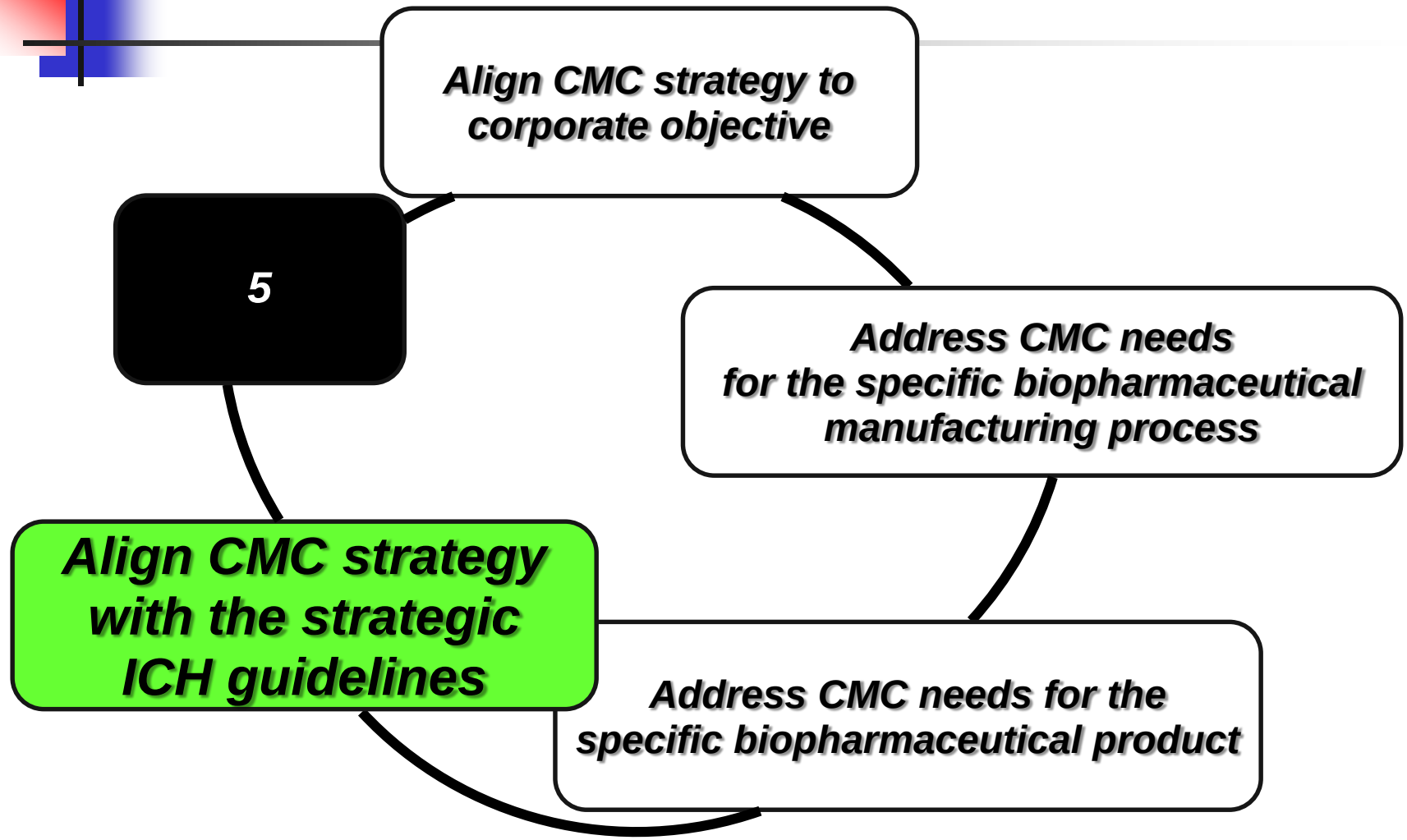
Many things in common, but no magic formula!

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

'platform' approach provides valuable insights

Composing an Effective Corporate CMC Regulatory Compliance Strategy for Biopharmaceuticals

5 Key Design Elements



International Council for Harmonisation

Q CMC

These ICH content guidelines have been a tremendous help in the CMC regulatory compliance arena for 2 decades!

(specific focus on recombinant proteins & mAbs)

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

(applicable to all biologics)

- **Q7** **GMP of Active Pharmaceutical Ingredients (APIs)** ***[2000]***
- **M4Q** **Common Technical Document (CTD) Format** ***[2000]***
- ***Q13 Continuous Manufacturing***
- ***Q14 Analytical Procedure Development***

ICH strategy guidelines are now also widely applied in the CMC regulatory compliance arena for biopharmaceuticals!

(look for term 'systematic' used in the guideline)

- ***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 Product Lifecycle Management (step 3)***

ICH Q8 *Pharmaceutical Development*

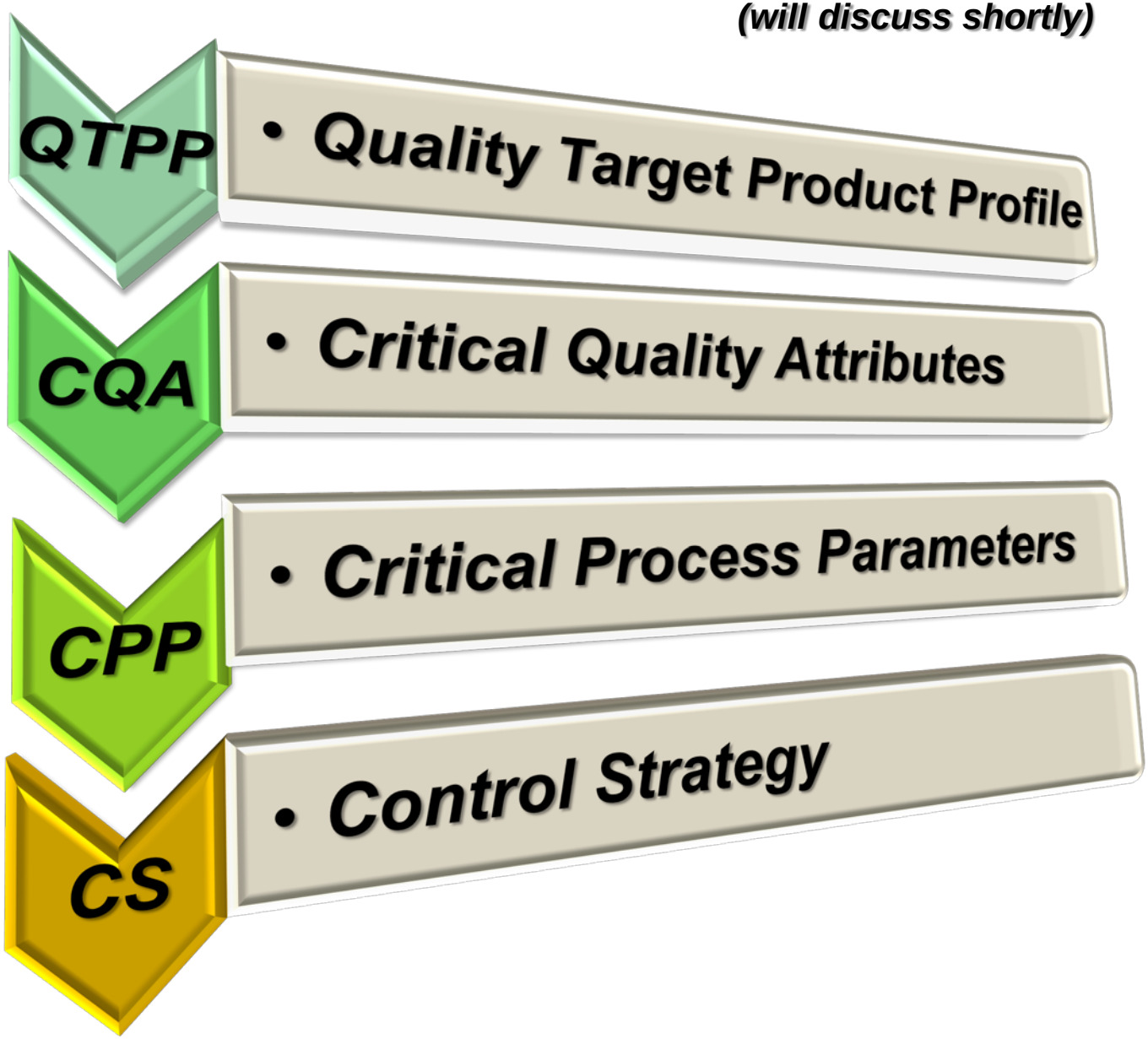
Quality by Design (QbD):

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.

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

ICH Q8: QbD – Four Steps to Implementation

(will discuss shortly)



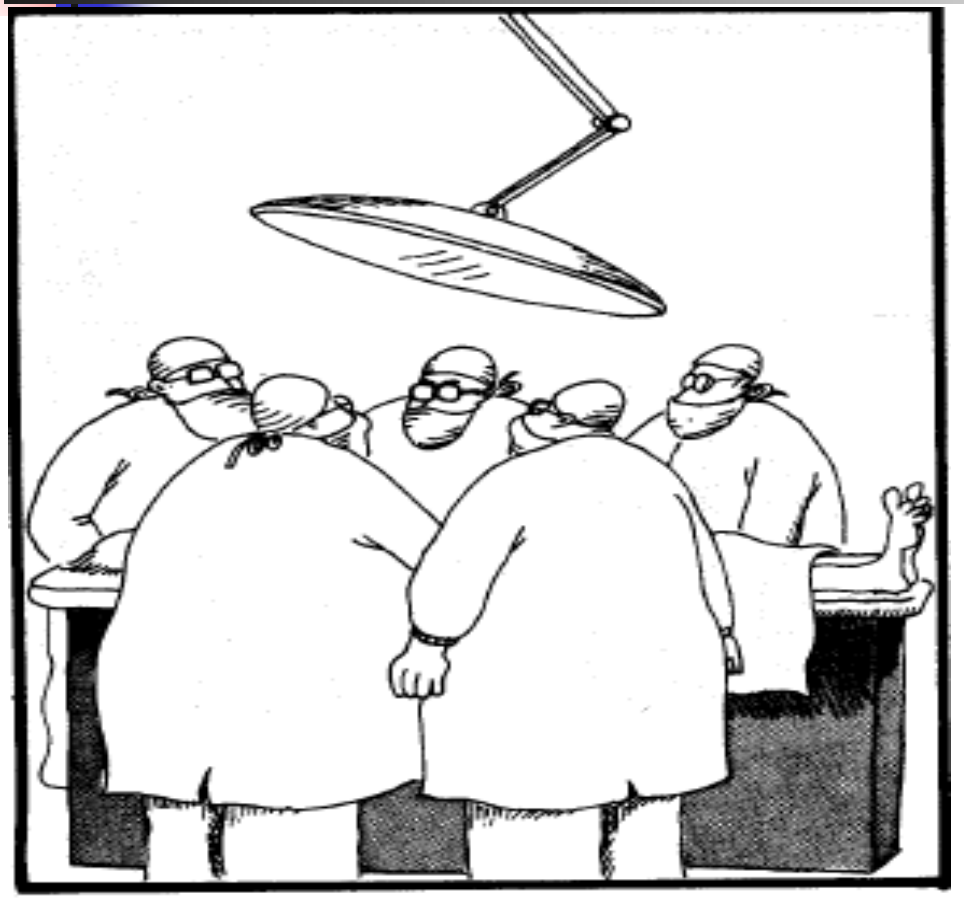
ICH Q9 QRM

Quality Risk Management:

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

***Focus*: How to prioritize and manage the higher risks in the quality design of the product and its manufacturing process**

Prioritization and management of risks to the product and manufacturing process is a major weak link in the biopharmaceutical industry

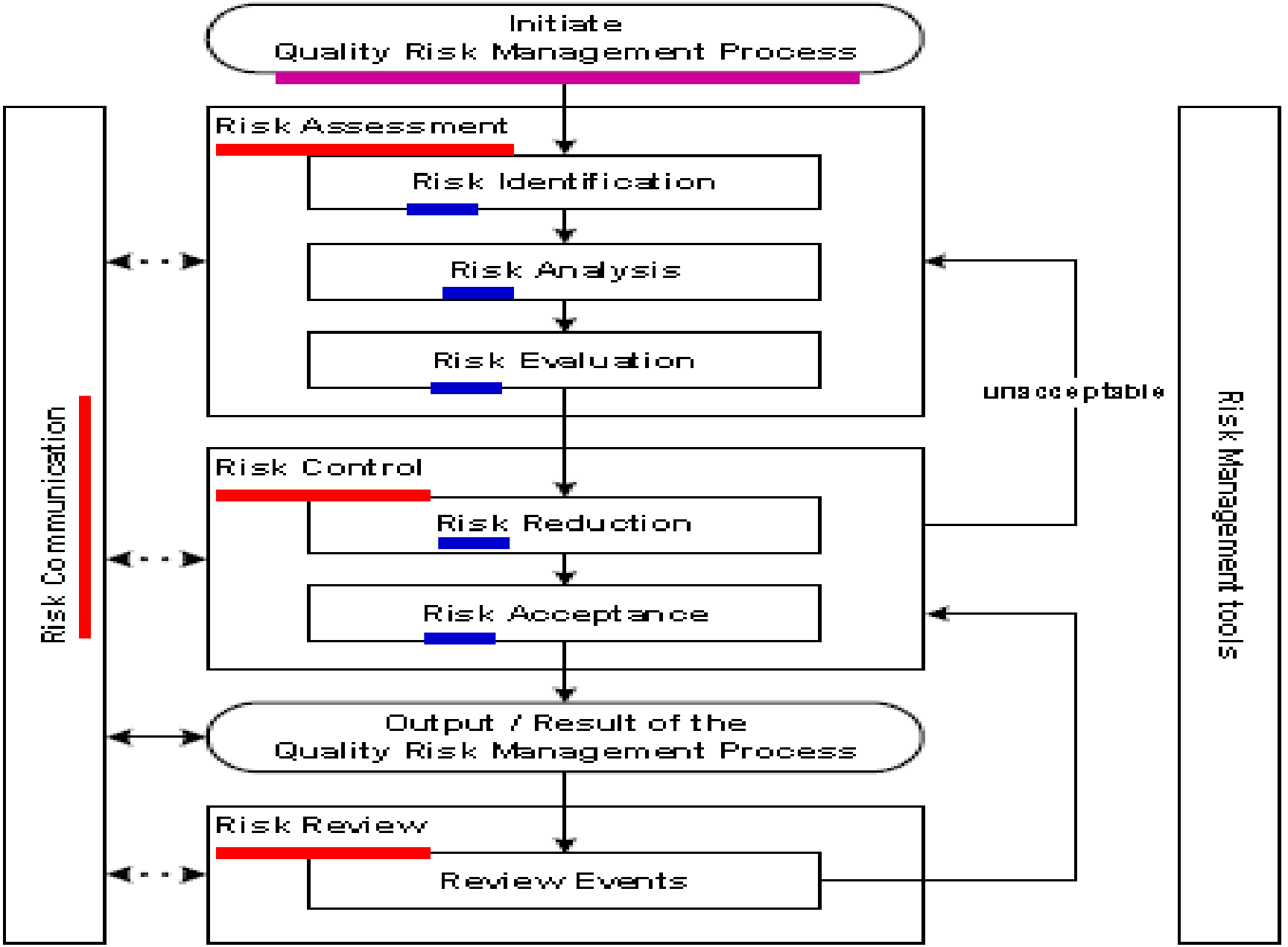


"Okay, Williams, we'll vote . . . how many here say the heart has four chambers?"

Reaching corporate consensus of the risks

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

CMC strategy people love Quality Risk Management (QRM)!



ICH Q9 introduces numerous QRM project management tools that can be used

Risk Ranking and Filtering* (RRF)

Failure Mode Effects Analysis (FMEA)

Preliminary Hazard Analysis (PHA)

ICH Q9 introduces numerous QRM analysis tools that can be used

Ishikawa Diagram (Fishbone)

Design of Experiments (DOE)

**** will be discussed shortly***

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".

Goal of Design of Experiments

many many process parameters known ***'process mapping'***	→	***the important process parameters identified*** ***'process understanding'***

OFAT for simple processes

(OFAT – 'one factor at a time')

$$OFAT = (Levels)^{(Process\ Parameters)}$$

Chemical Synthesis

3 Parameters

temperature
pressure
duration

3 Levels

low
medium
high

Levels (L)	Process Parameters (PP)	OFAT (total number of reactor runs needed)
3	3	27

Not that difficult … but … →

OFAT doesn't work for complex processes

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

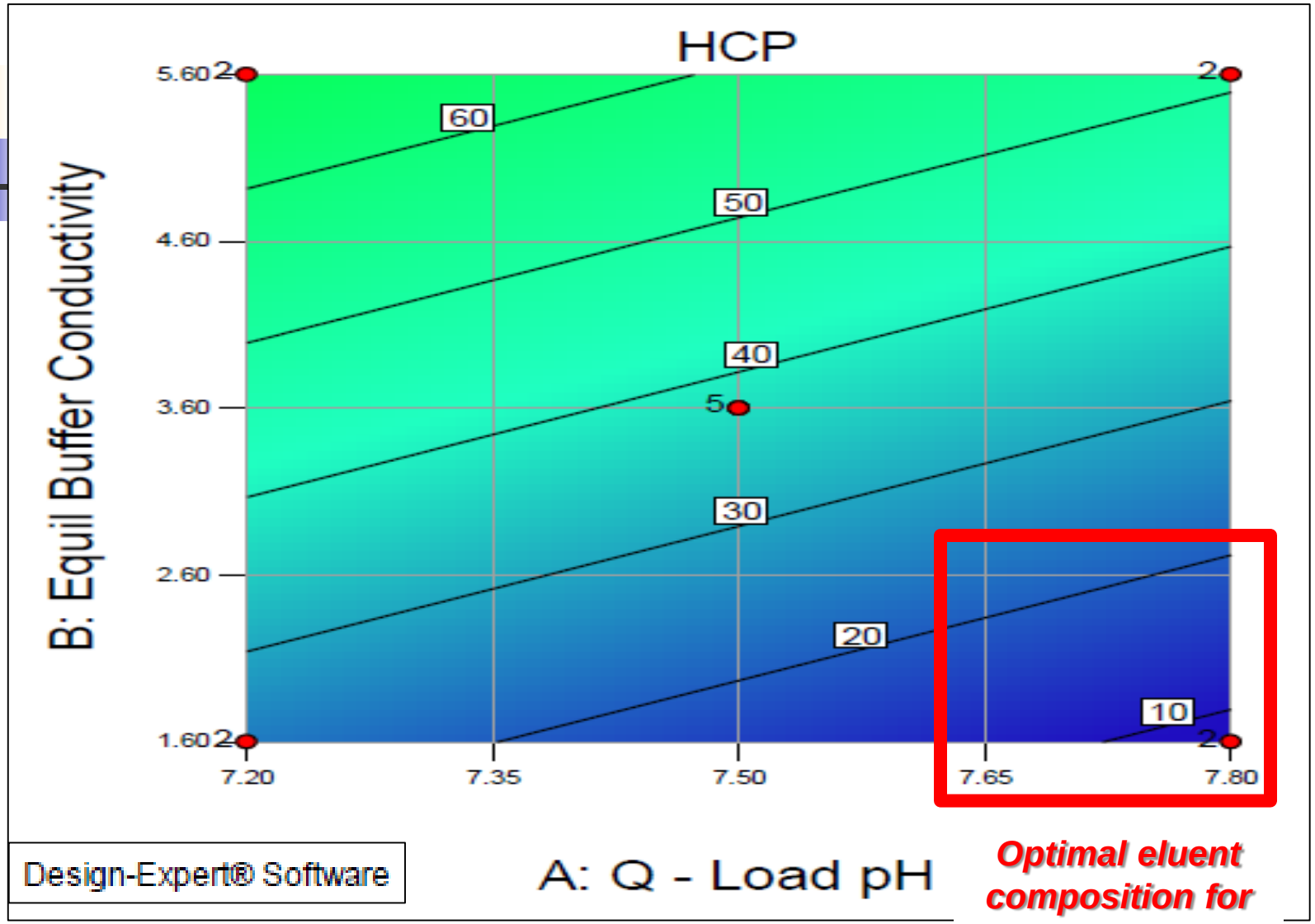
3 Levels

low
medium
high

Levels (L)	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!

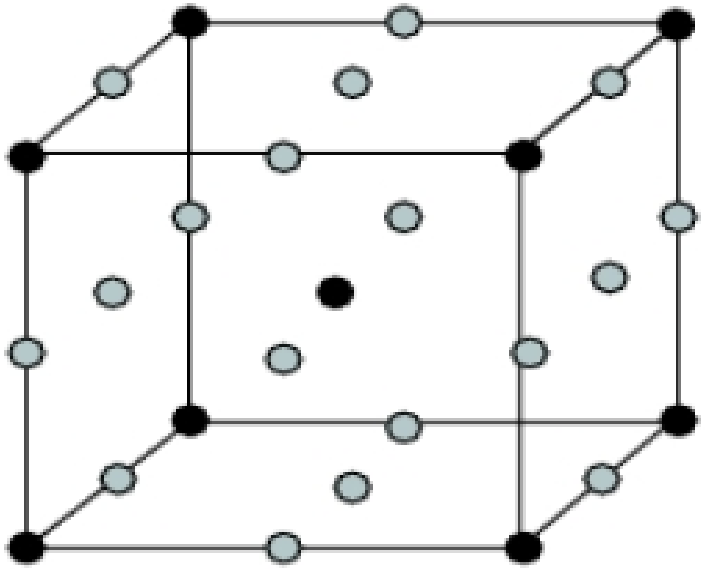
DOE can give impressive results



Optimal eluent composition for HCP removal

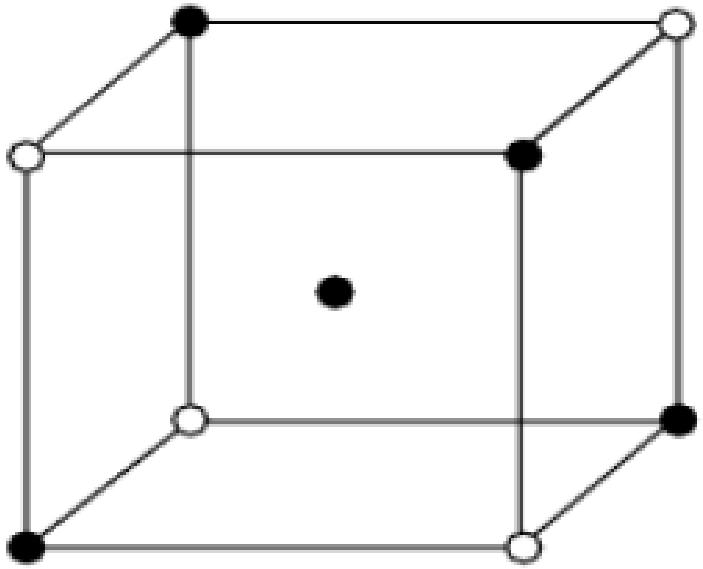
But DOE costs $$$

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



Full factorial

3^3 OFAT 27



Fractional factorial

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?

ICH Q10

Pharmaceutical Quality System

Knowledge Management: **(KM)**

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

Focus: Importance of 'passing forward' technical knowledge

KM is information in action – 'passing forward'

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

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

Edmund Burke, 1700's, Irish Statesman

Applies as well to the history of manufacturing development and product development – wastage of time and resources

There are known knowns; there are things we know we know.

We also know there are known unknowns; that is to say we know there are some things we do not know.

But there are also unknown unknowns — the ones we don't know we don't know

Donald Rumsfeld 2012

Ibn Yamin, 13th century Persian poet

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

Process change management will be discussed later

What is the overall impact of ICH Q8/Q9/Q10/Q11/Q12 on biopharmaceutical 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 – Four 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 (CS)***

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 biopharmaceutical processes!

case example

Quality by Design (QbD) elements such as risk assessment and multivariate experimental design were used during process characterisation. Results from multivariate (and univariate) experiments were used to evaluate process parameter criticality, but parameter ranges were mainly established based on historical development and manufacturing and no design space is claimed. The terminology and definitions used for the control strategy elements is mainly in line with ICH Q8(R2)/Q9/Q10/Q11 as regards CQAs, CPPs and non-CPPs. The applicant considers CPP acceptable ranges to be proven acceptable ranges (PARs). This is acceptable.

EMA European Public Assessment Report (EPAR) : Takhzyro (Lanadelumab)

18 October 2018
EMA/794314/2018

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]

[a] *Pharma Technical Development, Roche Diagnostics GmbH, Sandhofer Str. 116, 68305 Mannheim, Germany*
[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

QbD Approach

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***

What can a CMC team learn about the 'target' for this drug product?

Table 1
Example QTPP for a monoclonal antibody.

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

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 biopharmaceuticals?

- 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

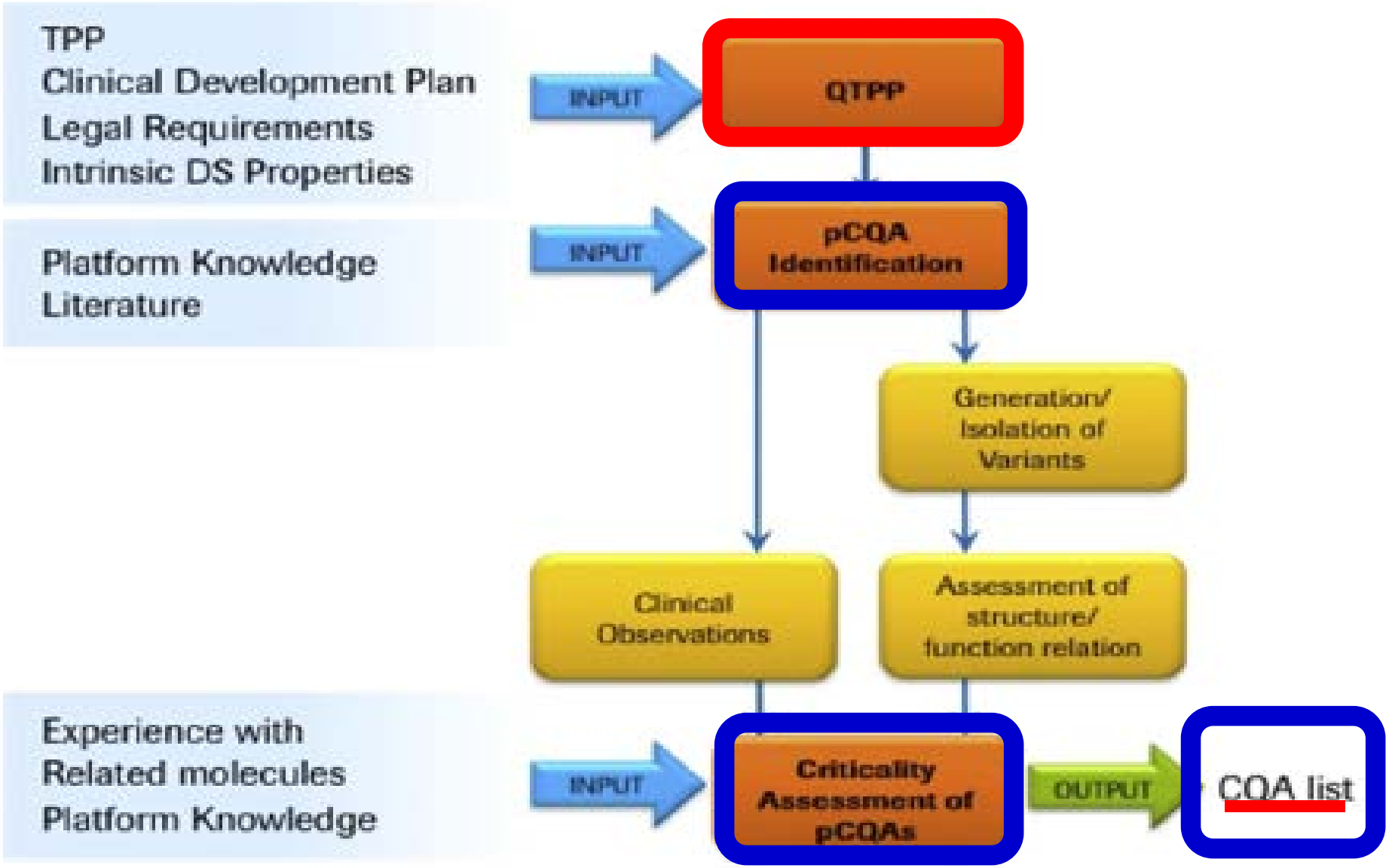


Fig. 2. Outline for workflow for COA identification.

3 Step Approach: QA → pCQA → CQA

Step 1: Identify all MAb molecular variants

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

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)

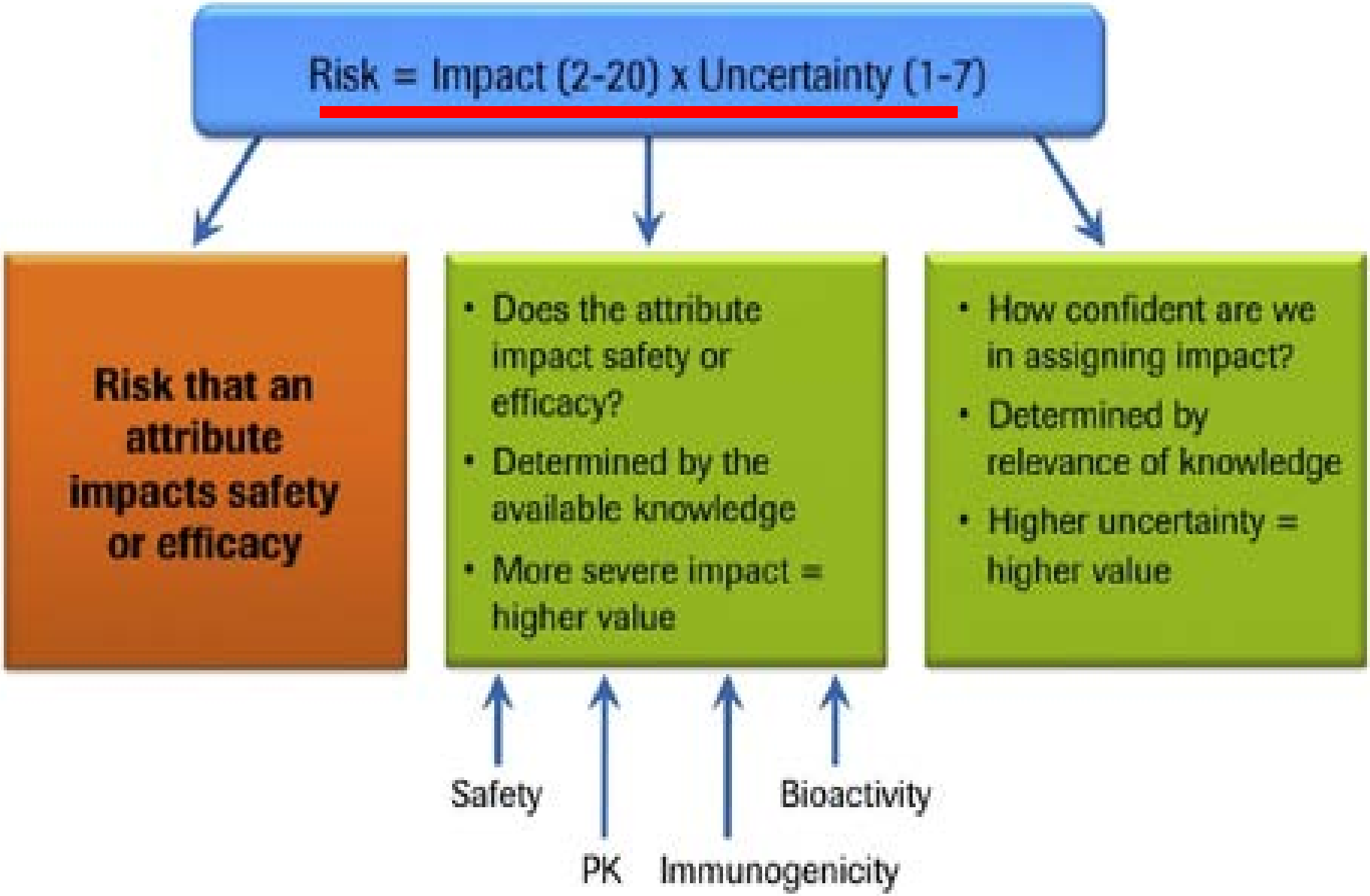


Fig. 3. Risk score defined by impact and uncertainty.

Risk Score (RS) = I x U

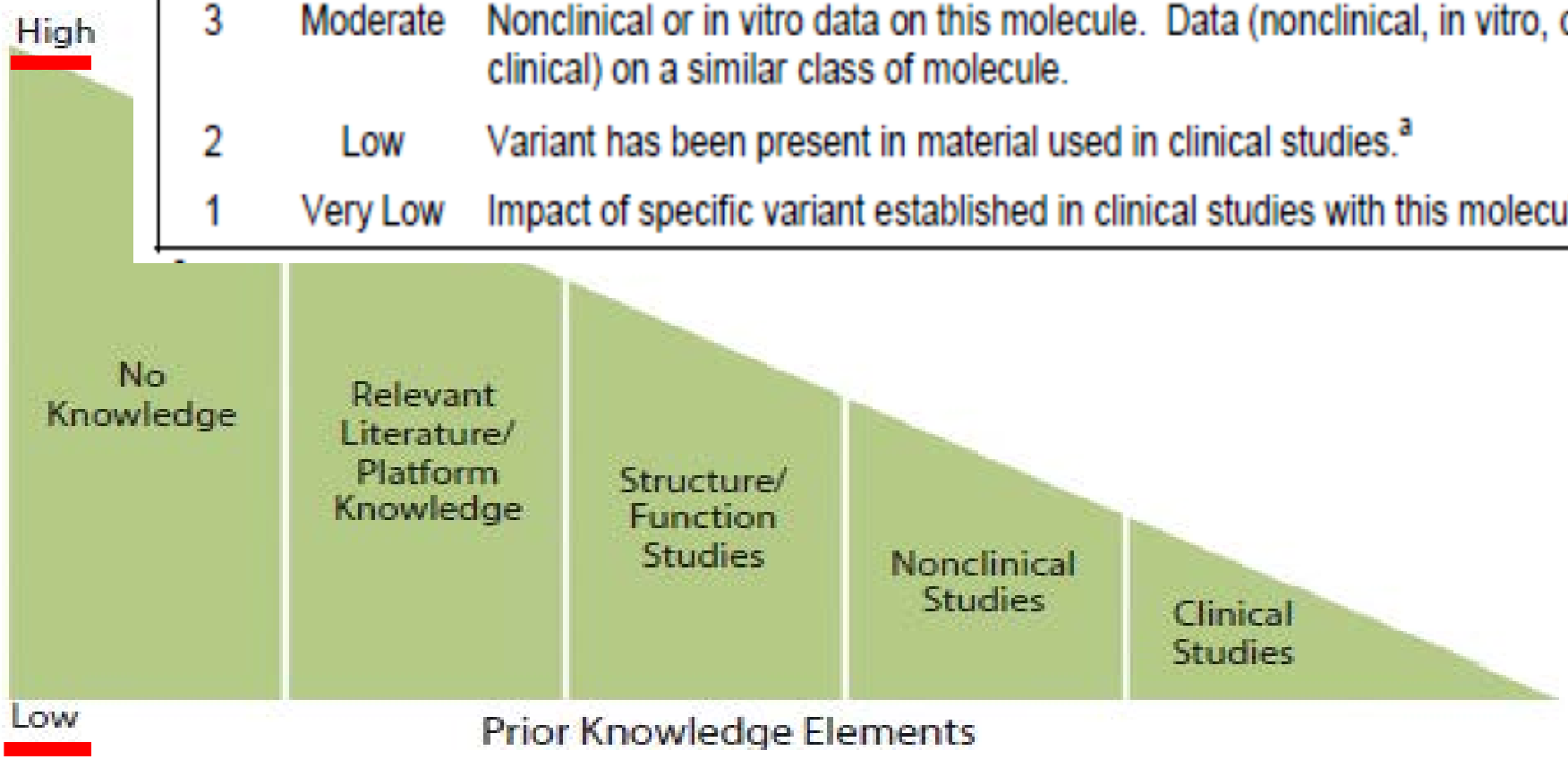
Impact = 2-20

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***
C-terminal lysine truncation	***4 (PK)***	***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
EDI < TTC → non-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: measured value > TTC → CQA
measured value < TTC → non-CQA

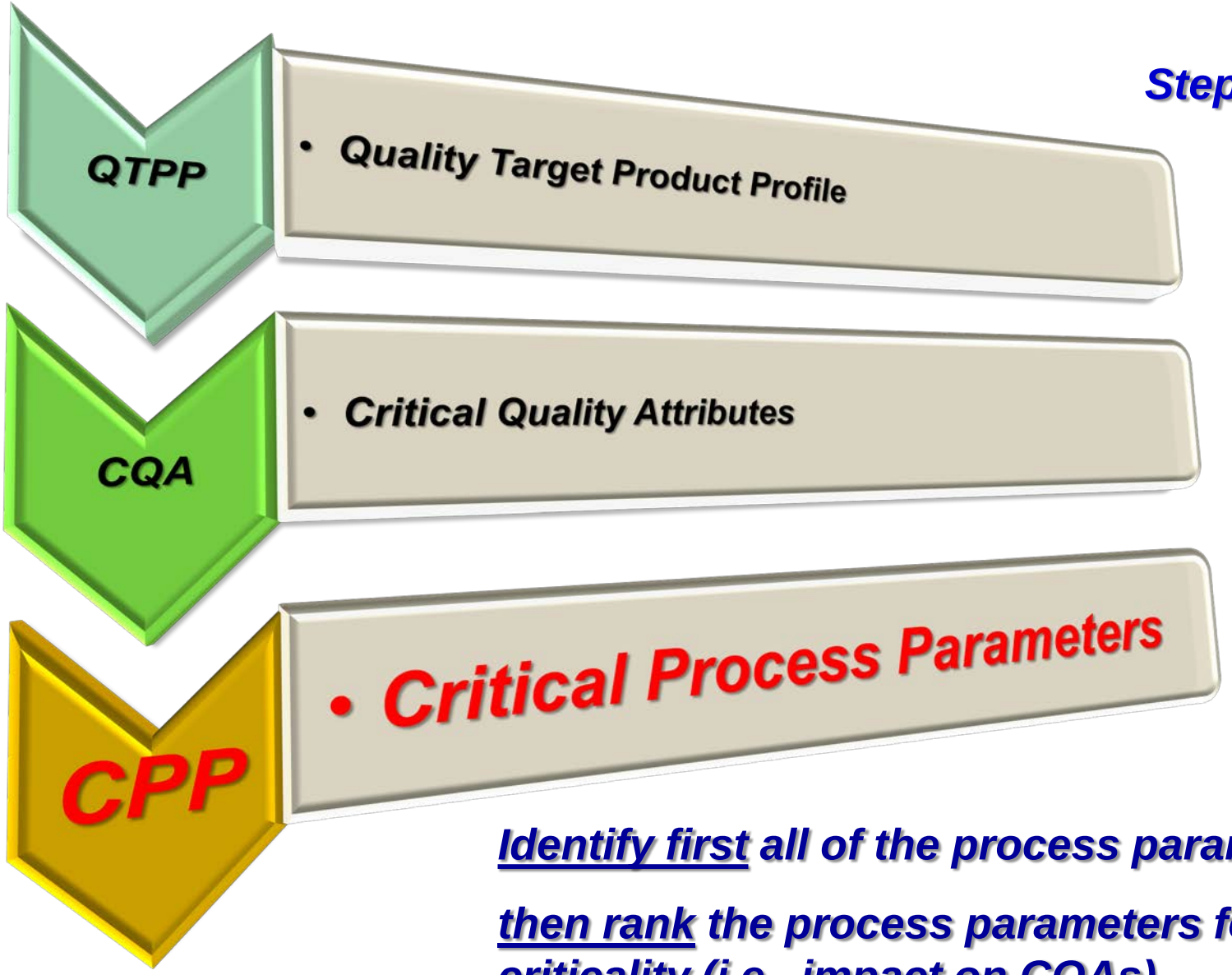
The approach for identification of leachables as CQAs is dependent on whether a specific compound can be detected in the final DS or DP. If a specific leachable is shown to exceed acceptable and safe levels, e.g. as determined based on ICH M7, that compound is designated as a CQA.

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

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

ICH 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

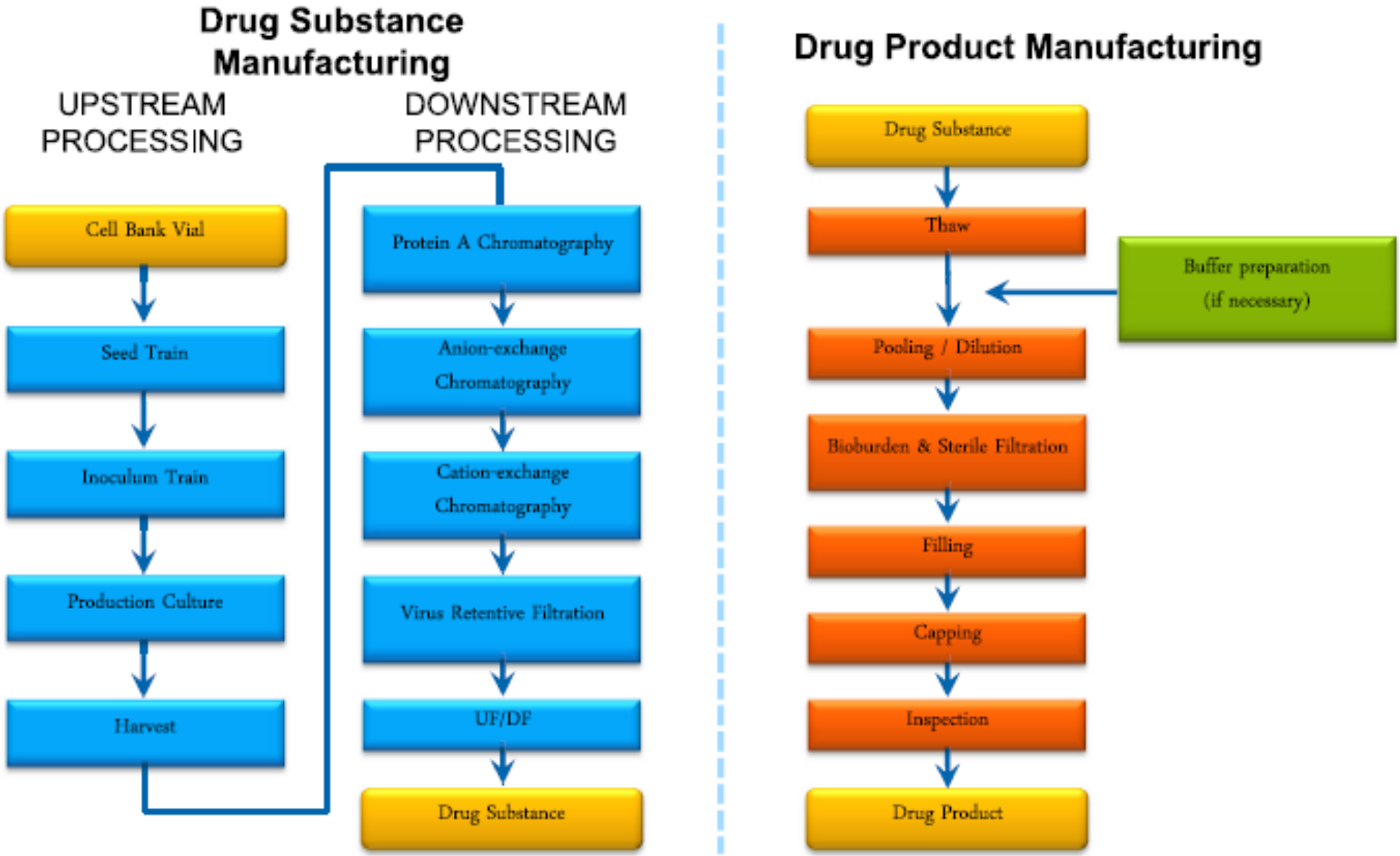


Fig. 3. Flow chart of a standard MAB manufacturing process.

Each process step has multiple process parameters!

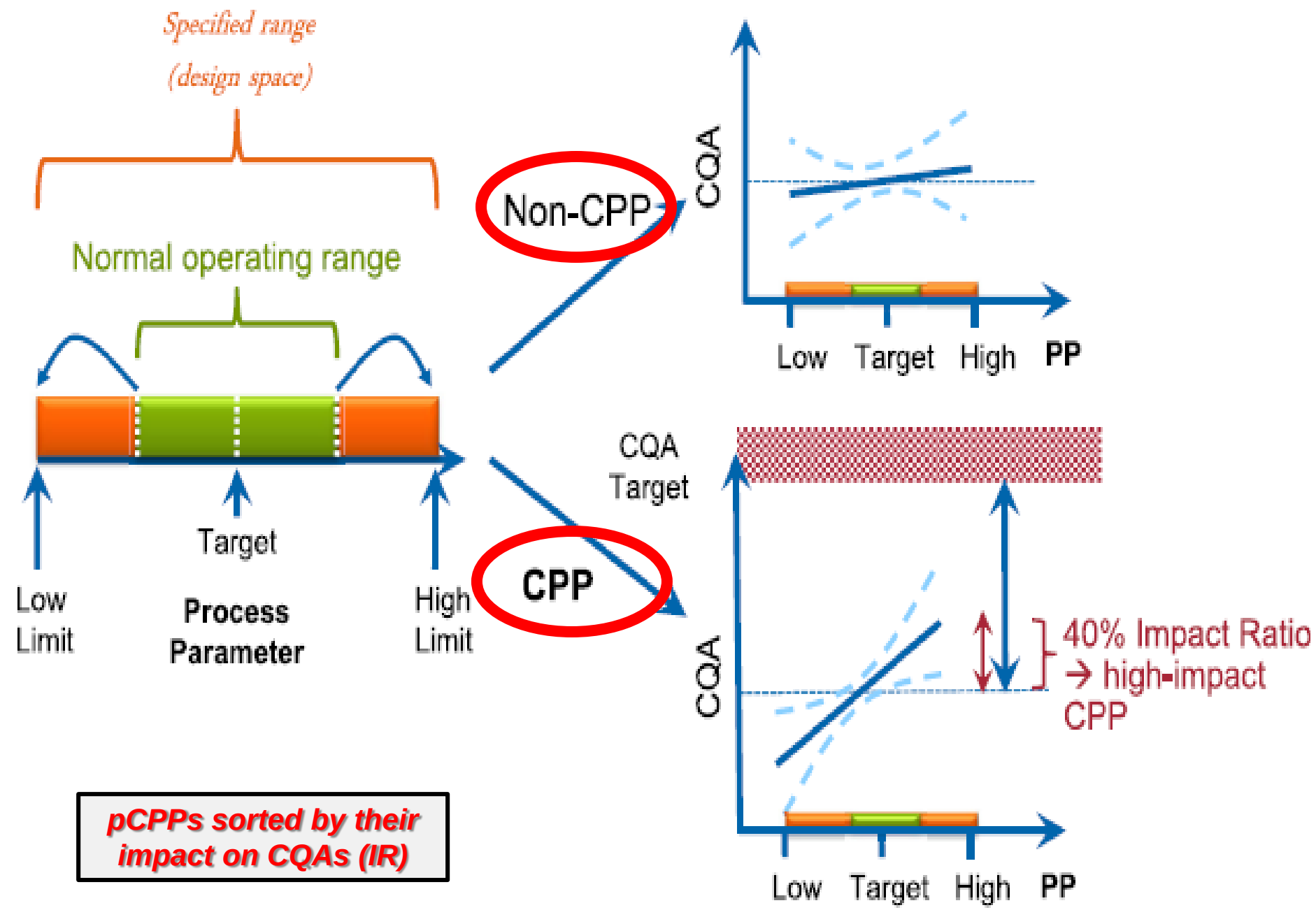
Step 1: Identify all process parameters (PPs)

↓

Step 2: Assign impact ratio (IR) to <u>each</u> process parameter (pCPPs)

↓

Step 3: Set impact ratio (IR) threshold – CPP vs non-CPP (arbitrary, but must be defendable)



pCPPs sorted by their impact on CQAs (IR)

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	[redacted]	
pO_2	0.06	0.07		
pH	0.05	0.06		
Temp	0.07	0.05		

CPP: if ≥ 0.10 CQA impact ratio

Non-CPP: if < 0.10 CQA impact ratio

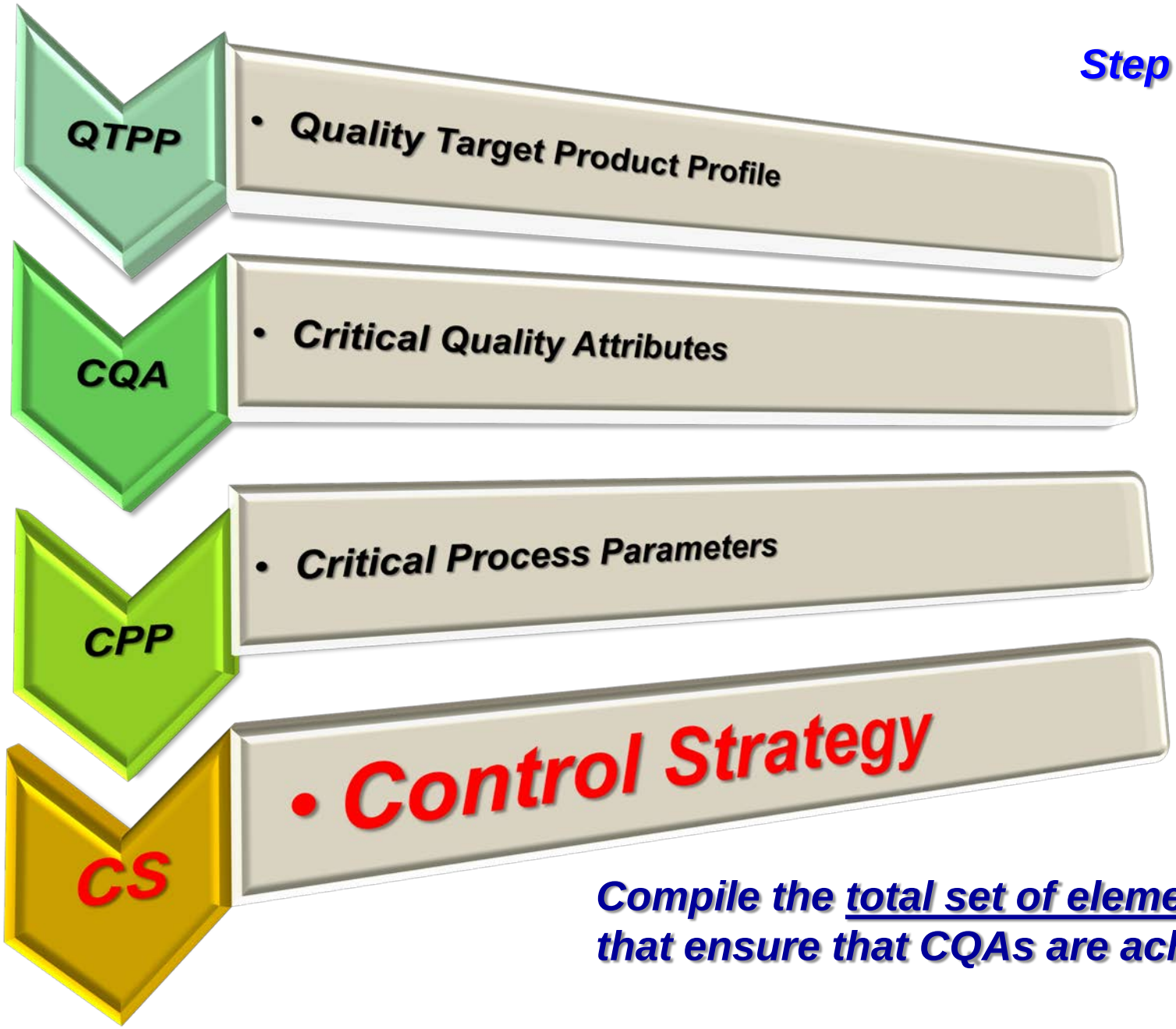
C. Hakemeyer et al. / Biologicals 44 (2016) 306–318

Question: Now, 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 if $\geq$ 0.10 CQA impact ratio
Non-CPP if < 0.10 CQA impact ratio

Illustrates the importance of looking across all CQAs!


Step 4
QTPP
• Quality Target Product Profile
CQA
• Critical Quality Attributes
CPP
• Critical Process Parameters
CS
• Control Strategy
Compile the total set of elements
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 materials for 'fit for use'

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.

4 Elements of a Complete Control Strategy

(ICH Q11 and ICH Q8)

#2 Process Design Control	**Optimize the design of the manufacturing process to obtain the required product quality** *Example: 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*
#3 In-Process Testing Control	**Utilize appropriate in-process testing with set limits** *Example: Action limits for bioburden, endotoxin* *Example: specified action limits or specifications for absence of virus or mycoplasma in cell culture process*
#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)*

Goal: use all control system elements that protect the quality of the biopharmaceutical!

Linking Control Strategy back to CQAs

Example for a Monoclonal Antibody Drug Substance

CQA	Risk	Origin	Control Strategy
Glycosylation Variants	Immunogenicity Efficacy impact	Cell culture/media Post-translational effects	Critical material control Batch release spec glycan map
Aggregates	Immunogenicity and PK Impact Efficacy impact	Bioreactor and purification conditions Post-translational effects	Identified CPPs (USP/DSP) In-process action limit Batch release spec
Potency	Efficacy Impact	Higher order structure (HOS) folding impacted by multiple bioreactor conditions and molecular variants	Cell-based bioassay spec release /stability
Endotoxin	Fever	Introduced through materials and handling during manufacturing process	Critical material control In-process bioburden control Batch release spec

Design Space (DS)

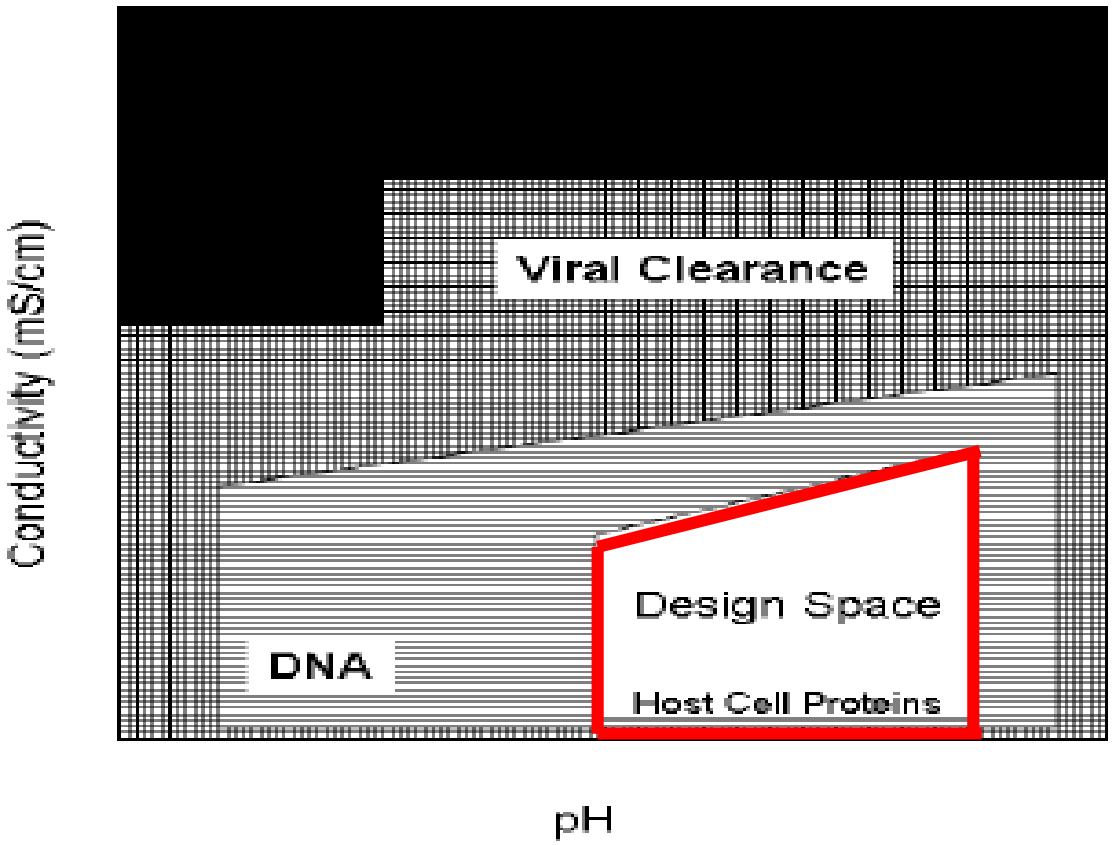
(ICH Q11 and ICH Q8)

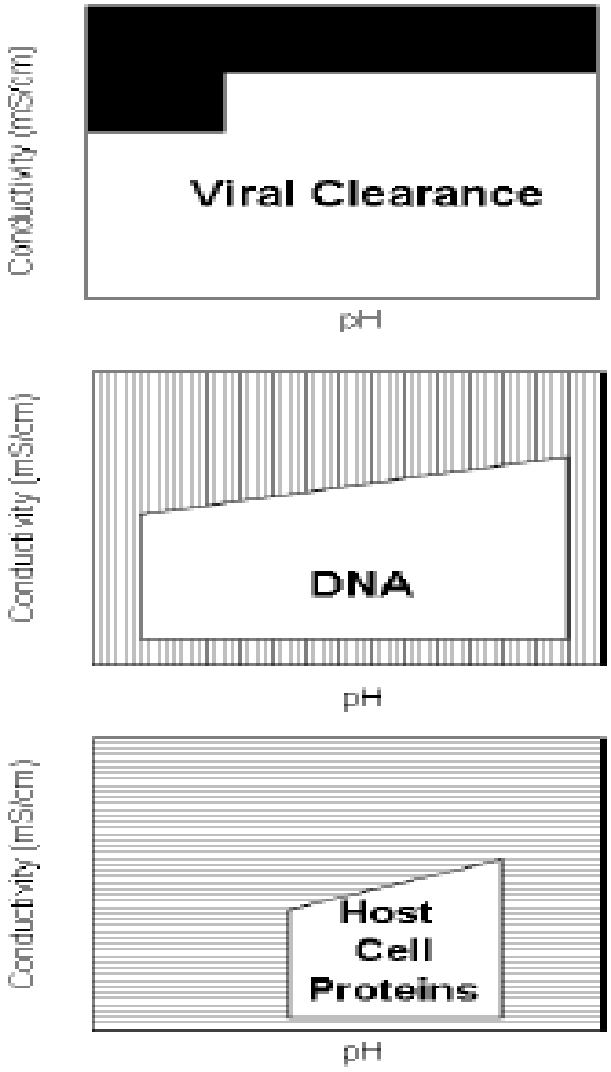
- ***Design space**: the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality*
- ***Working within the design space is not considered as a change ('regulatory freedom")***
- ***Design 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 Biologic Design Space – Individual Process Step

(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 Biopharmaceutical 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

The only biopharmaceutical reported to have achieved design space regulatory freedom

But if you address residual risk concerns …

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.

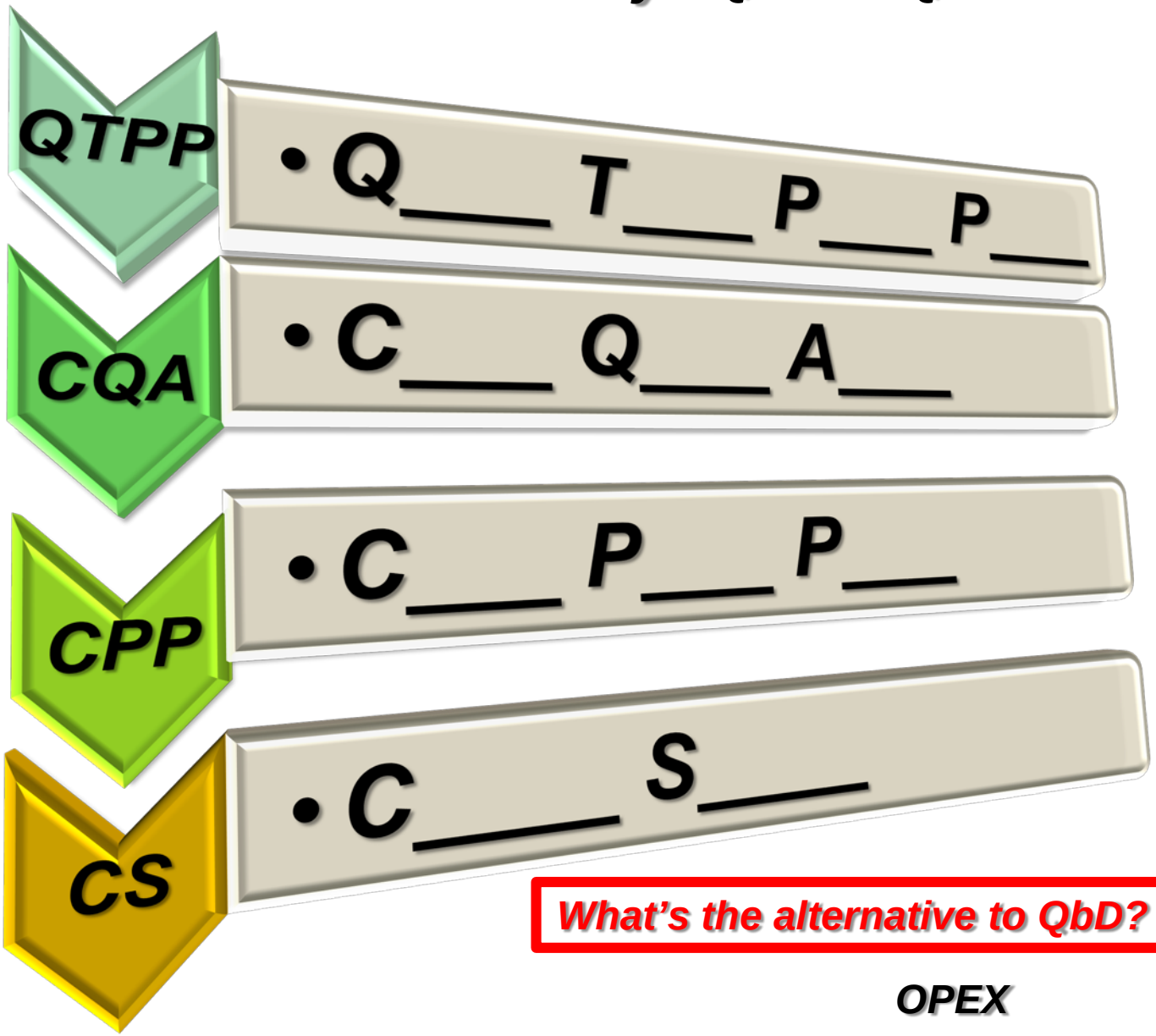
EMA achieved also

Traditional approach for potato chip manufacture

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

QbD

Summary - QUICK QUIZ



What's the alternative to QbD? QbC!

OPEX

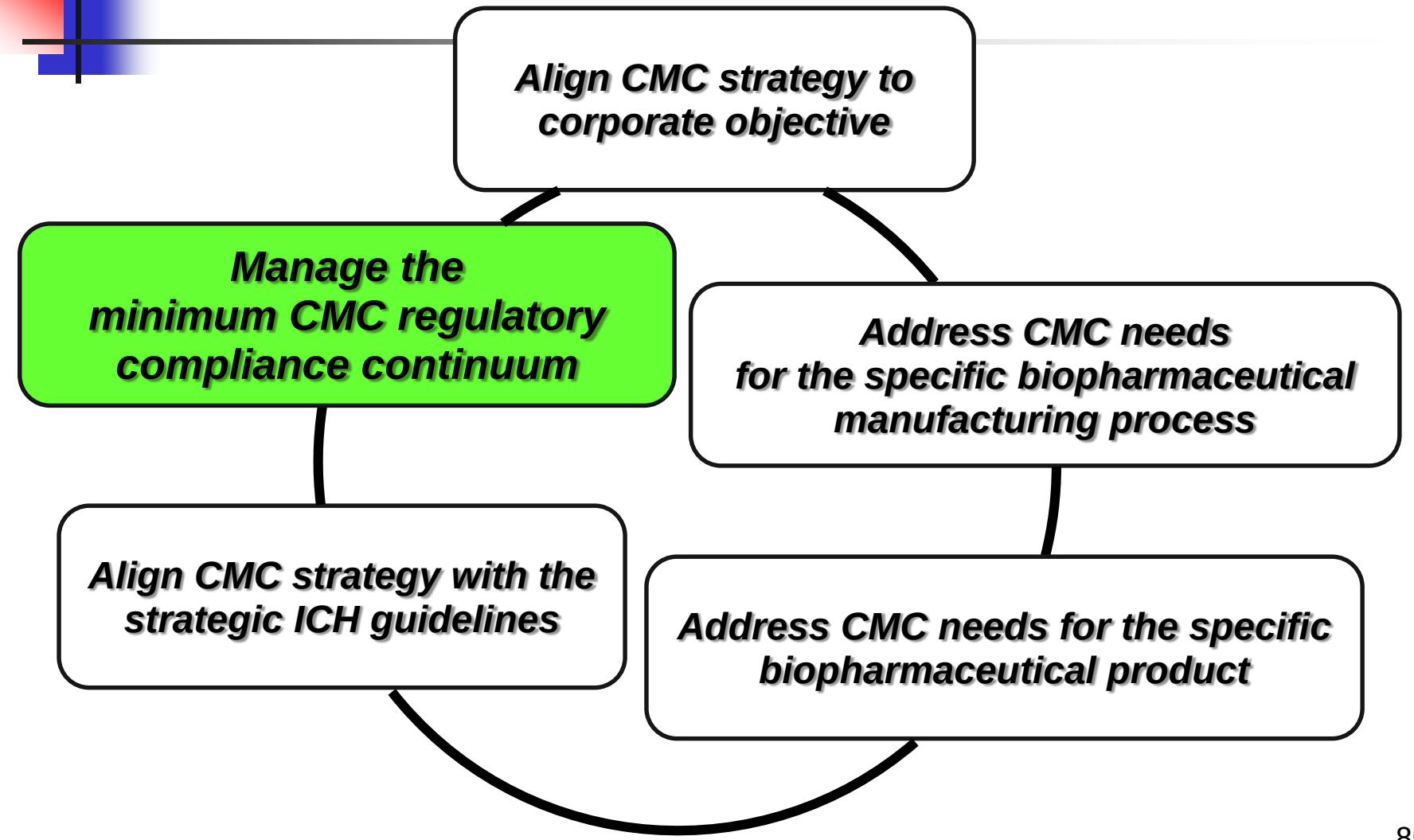
Don't underestimate the importance of each of the 4 QbD steps to a regulatory authority!

The Applicant distinguishes in-process controls (IPC) and in-process tests (IPT) whereas the latter are assigned no acceptance criteria and the respective results are collected for monitoring purposes. Criticality of the process parameters (and controls) is not stated in section 3.2.S.2.2 and 3.2.S.2.4. A list of the identified (and preliminarily established) CPPs is included in section 3.2.S.2.5 and 3.2.S.2.6 together with the statement, that the criticality assessment will be repeated following the production of 30 drug substance batches. Ongoing process verification is expected to ensure that the manufacturing process remains in a state of control. It is not the purpose of ongoing process verification to finalise an undeveloped control strategy which should be fixed at the point of authorisation and only then may it be subject to review under correct regulatory supervision as more process experience is gained. It is not acceptable to omit any clear (and legally binding) statement about critical process parameters or parameters for which it has been shown, or otherwise understood, to have to be satisfactorily controlled to limit their residual risk from the process description. Even though the main CPPs listed in sections S.2.5 and S.2.6, are reflected in the narrative process description, the Applicant should include these in a tabulated form in section S.2.2 and 2.4.

(corrected, EC approved 2019)

Composing an Effective Corporate CMC Regulatory Compliance Strategy for Biopharmaceuticals

5 Key Design Elements



Managing the minimum CMC regulatory compliance continuum

- ***Regulatory authorities recognize the need to manage CMC regulatory compliance throughout clinical development***
- ***But, they accept that flexibility is necessary***
- ***It is understand by the regulatory authorities, and the biopharmaceutical industry, that the minimum CMC regulatory compliance requirements would be broader and tighter as clinical development advances***
  - ***EMA***
  - ***FDA***
  - ***Biopharm Industry (PDA)***

Embraced by EMA

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

September 2018
EMA/CHMP/BWP/534898/2008

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 EMA

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

31 January 2019
EMA/CAT/852602/2018

CMC Area		Recognized R-B CMC Strategy
IMPD ***S.2.4***	***Control of Critical Steps***	***It is acknowledged that due to limited data at an early stage of development 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***

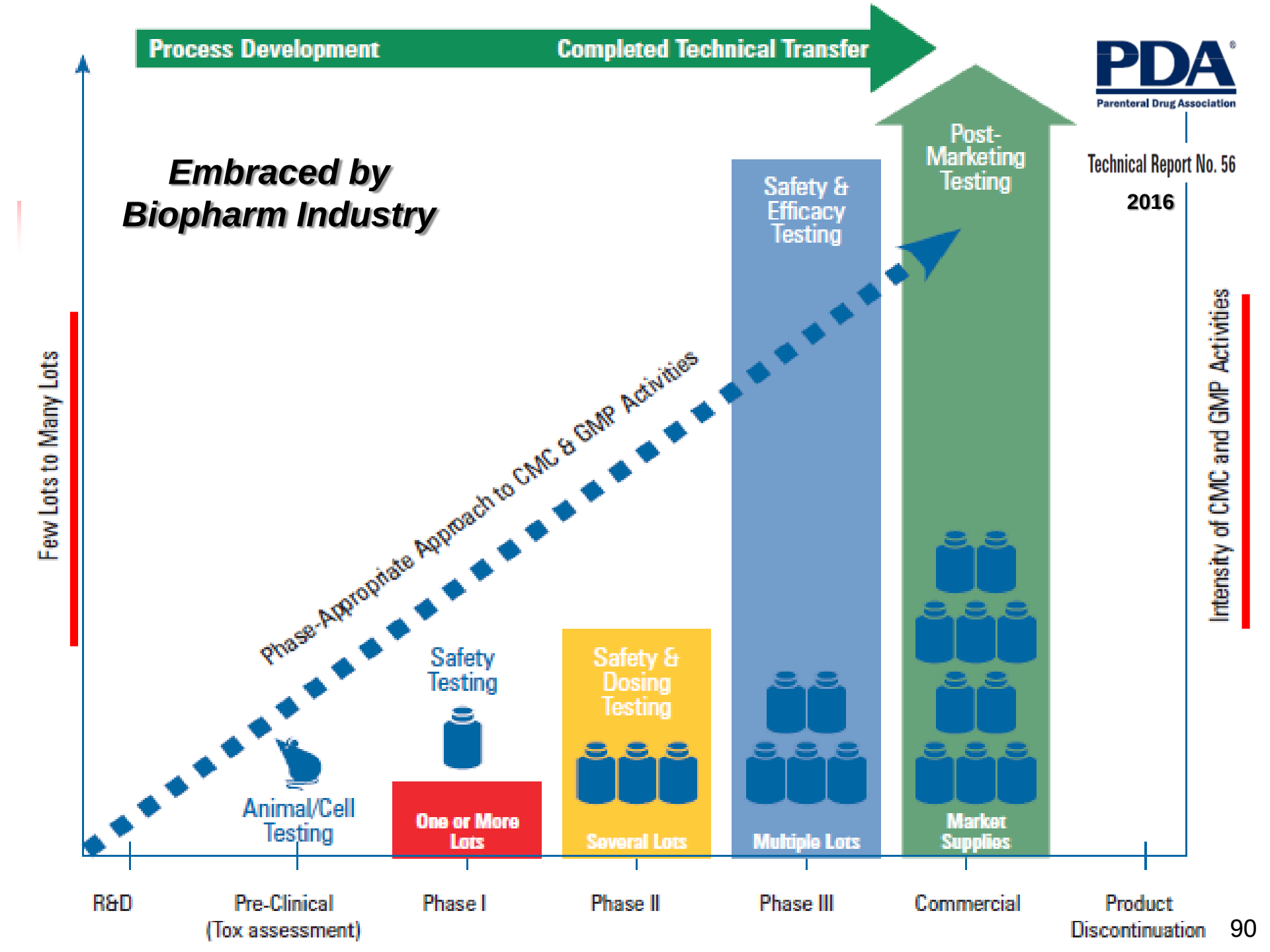
Embraced by FDA

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
CTD 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.


Process Development
Completed Technical Transfer
PDA
Parenteral Drug Association
Technical Report No. 56
2016
Embraced by Biopharm Industry
Post-Marketing Testing
Safety & Efficacy Testing
Few Lots to Many Lots
Intensity of CMC and GMP Activities
Phase-Appropriate Approach to CMC & GMP Activities
Safety Testing
Safety & Dosing Testing
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

Necessity for the risk-based approach today to a 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 attempts to avoid non-value-added CMC activities and focuses efforts on critical activities***
- ***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***
- ***A risk-based development plan actually enhances patient safety in early clinical stages, even when product understanding and resources may be limited***

Summary of Key Design Elements
QUICK QUIZ

Align CMC strategy to c_____ o_____

Manage the m___ CMC r ____ c_____ c_____

Address CMC needs for the specific biopharmaceutical m_____ p_____

Align CMC strategy with the s_____ ICH guidelines

Address CMC needs for the specific b_____ p_____

***Expedited* clinical pathways are changing the clinical development landscape …**

… and stretching the capability of the CMC team to respond fast enough!

Migration to a Shorter, 'Seamless' Clinical Development Program

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 instead carrying it out after market approval)

FDA is concerned about the capability of 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.

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

FDA's major concerns for CMC due to clinical expediting

recognized CMC regulatory compliance 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

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

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

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

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

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

EMA has identified its major concerns for CMC due to clinical expediting

CMC issues to be discussed prior to PRIME designation

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***
- ***Product characterization, including CQAs and biological potency***
- ***Manufacturing process development, including process changes and upscaling plan for commercial purposes and timing in relation to launch***
- ***… (a great laundry list of CMC concerns)***

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

Always a danger if going too fast!

Comments? Questions?