

Leaders Summit

22-23 Feb. 2010. London, England



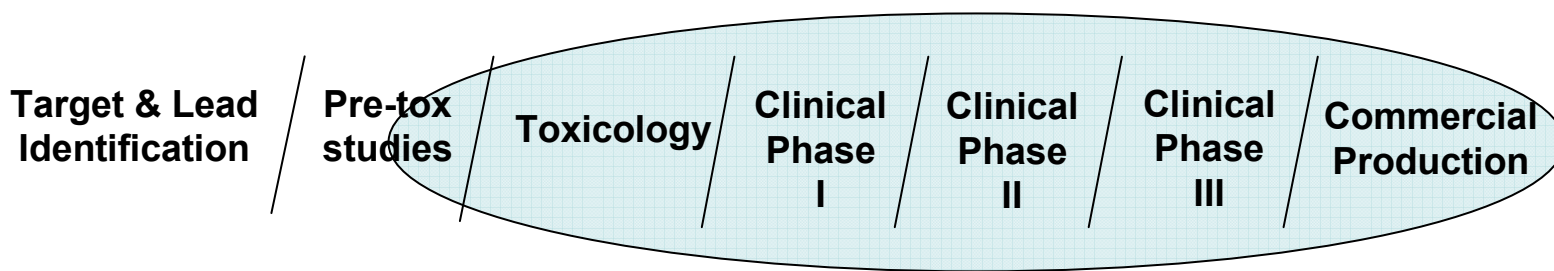
FDA's new Process Validation Guideline

*Can Process validation be
a value adding activity*

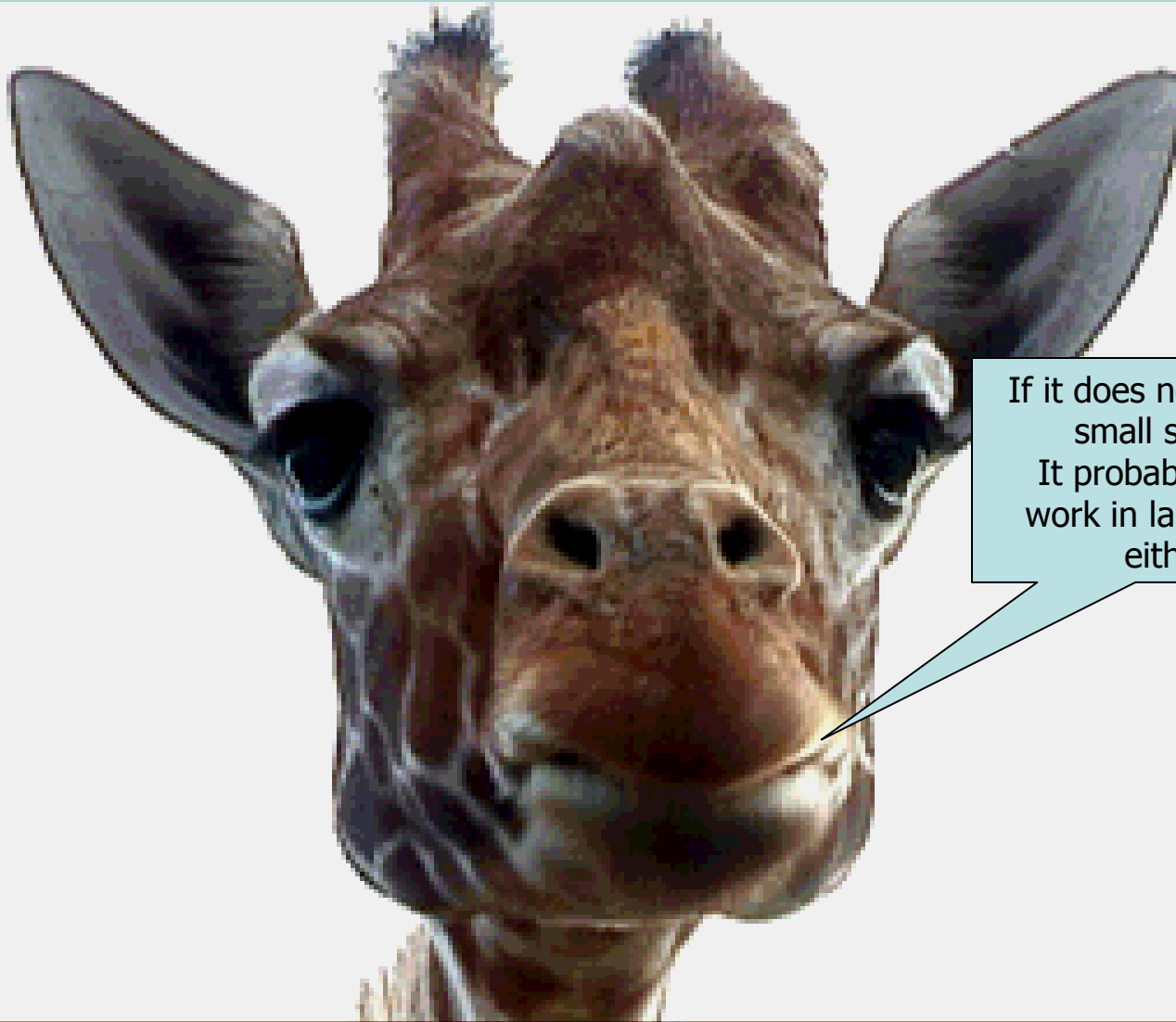
Morten Munk, VP
CMC Biologics A/S

Chemistry
Manufacturing
Control

DNA to API
Pre-tox to Commercial
Regulatory Compliance



**Biopharmaceutical Contract
Manufacturing Based On
MAMMALIAN CELL CULTURE
& MICROBIAL FERMENTATION**



If it does not work in
small scale !
It probably won't
work in large scale
either

- » **The Guidance covers the subject of Process Validation across the Product Lifecycle**
 - » **Stage 1. Process Design**
 - » Lab, pilot, small scale and commercial scale studies to establish process
 - » **Stage 2. Process Qualification**
 - » Facility, Utilities and Equipment
 - » Performance Qualification (confirm commercial process design)
 - » **Stage 3. Continued Process Verification**
 - » Monitor, collect information, assess during commercialization
 - » Maintenance, continuous verification, and process improvement

Guidance for Industry

Process Validation: General Principles and Practices

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

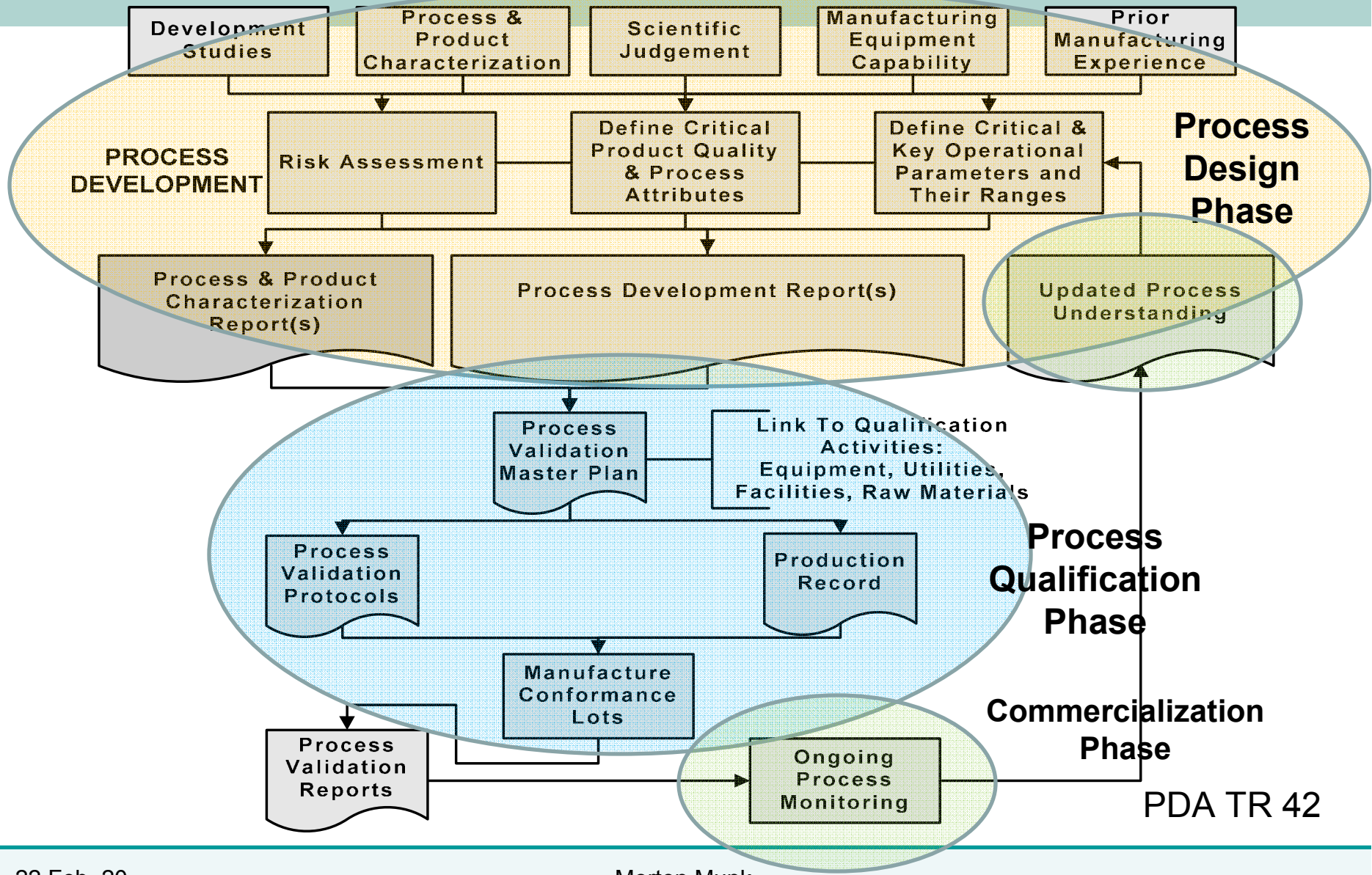
Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Brian Hasselbalch or Grace McNally (CDER) 301-796-3286 or 301-796-3279, Christopher Joneckis (CBER) 301-827-0373, or Dennis Bensley (CVM) 301-827-6956.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)

November 2008
Current Good Manufacturing Practices (CGMP)

Validation Work Flow



PDA TR 42

- » Fosters Innovation; Promoting manufacturing science
- » Changing Process Validation Paradigm
 - » Process Validation is “umbrella term”
 - » Process Validation is not a check-list activity
 - » Not a package to “put a ribbon around”
- » A “broad, balanced review of reality.”

Based on Grace E. McNally (FDA) presentation

» Lifecycle

- » Overall validation is not “completed” but ongoing
 - » Necessitates comprehensive process design to understand sources of variability and achieve process understanding
 - » Incorporates risk management
 - » Recognizes that more knowledge will be gained during commercialization
 - » How do I demonstrate that my process works as intended?
- » Both during development and marketed production, the document encourage use of:
- » DoE, trending and all other relevant statistical tools
 - » PAT, QbD
 - » Risk based approach

Based on Grace E. McNally (FDA) presentation

1987 PV Guidance

- » Documented evidence
- » Critical
- » Focus on conf. lots (PQ)
- » Supported 3 lots strategy
- » Limited requirements for statistical tools
- » Minimize changes after PV

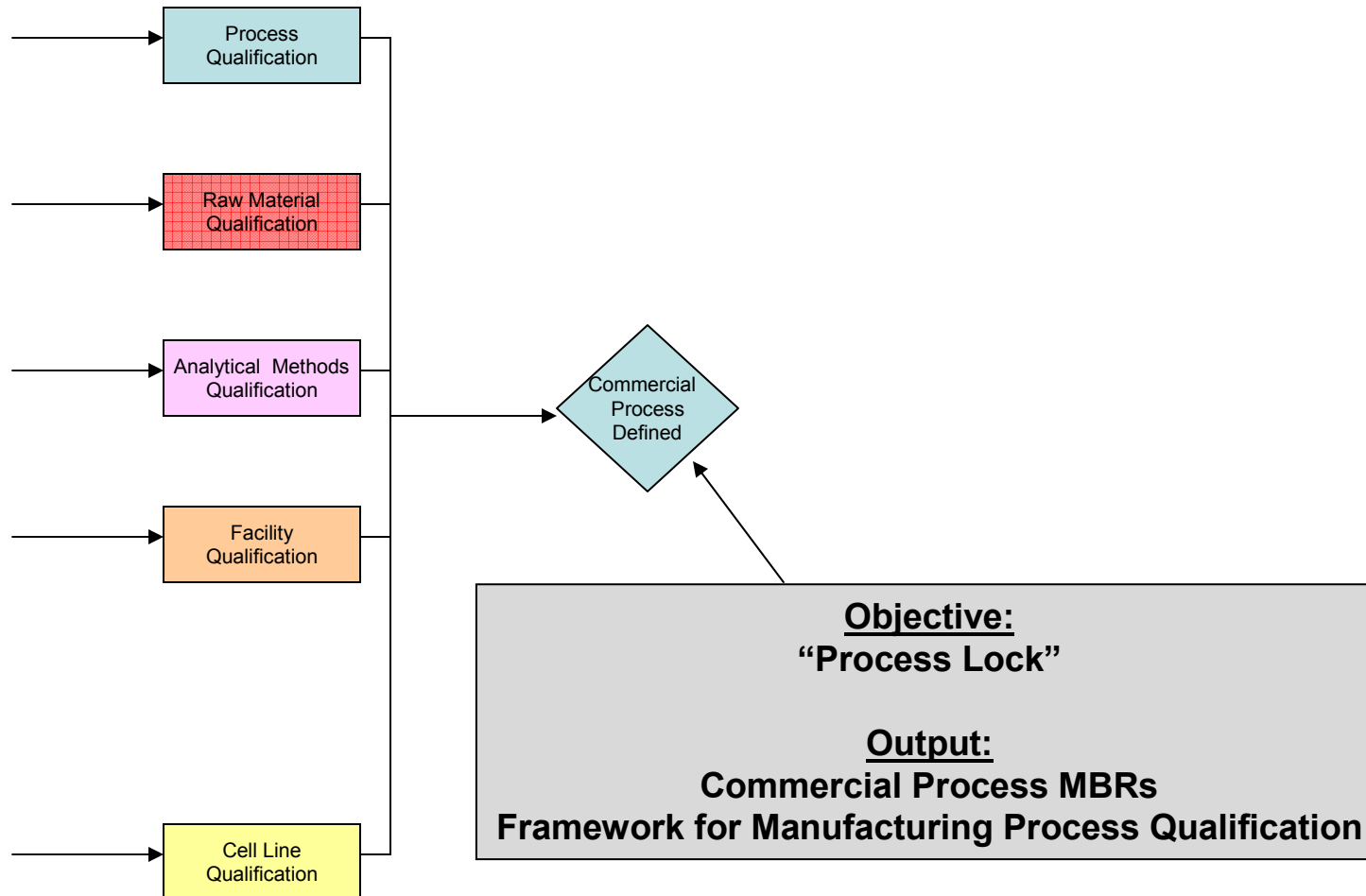
2008 PV Draft

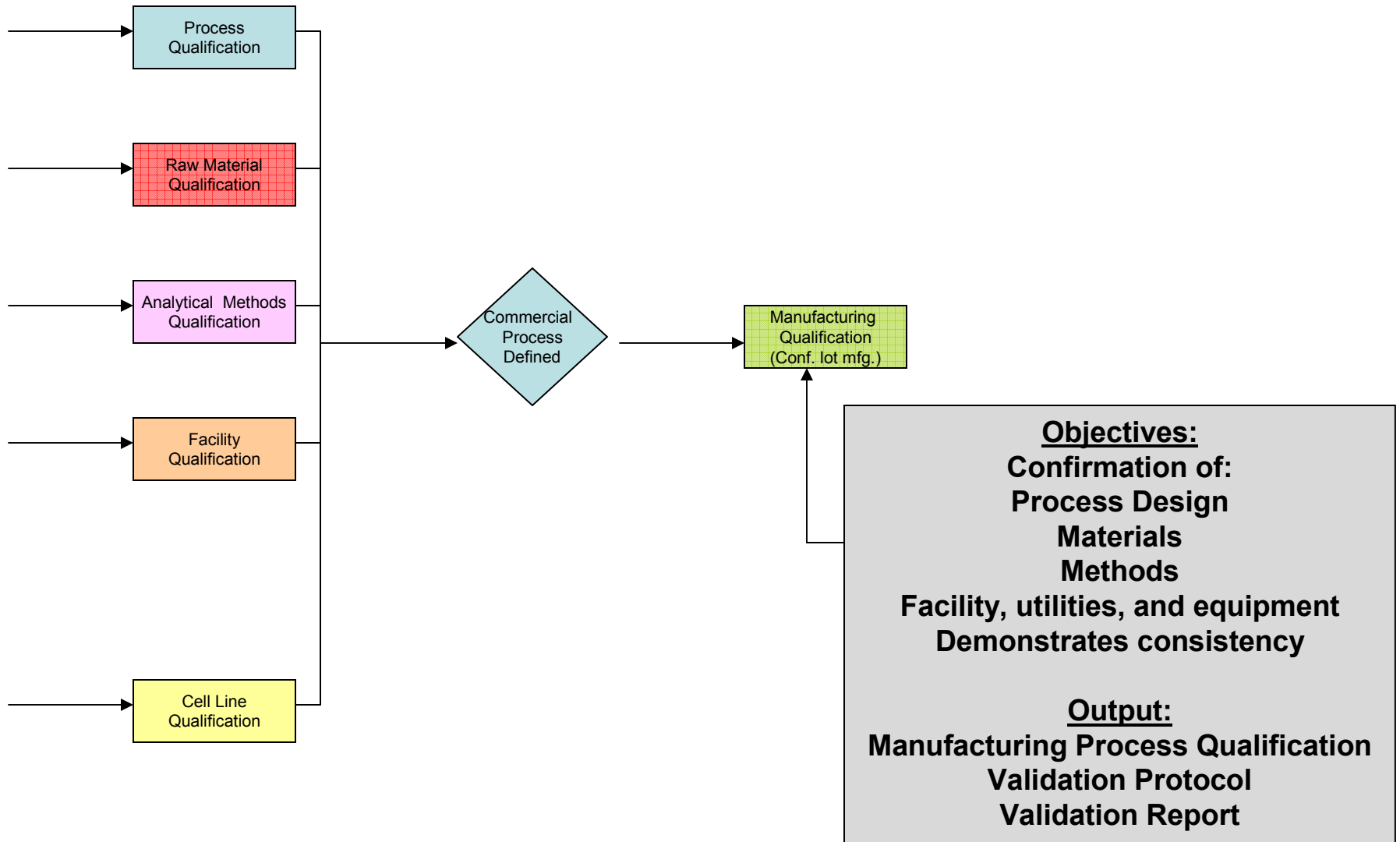
- » Scientific evidence
- » Significant
- » Full lifecycle approach
- » No fixed number for PQ lots
- » Large focus on use of statistical tools
- » Support innovation and continuous improvements

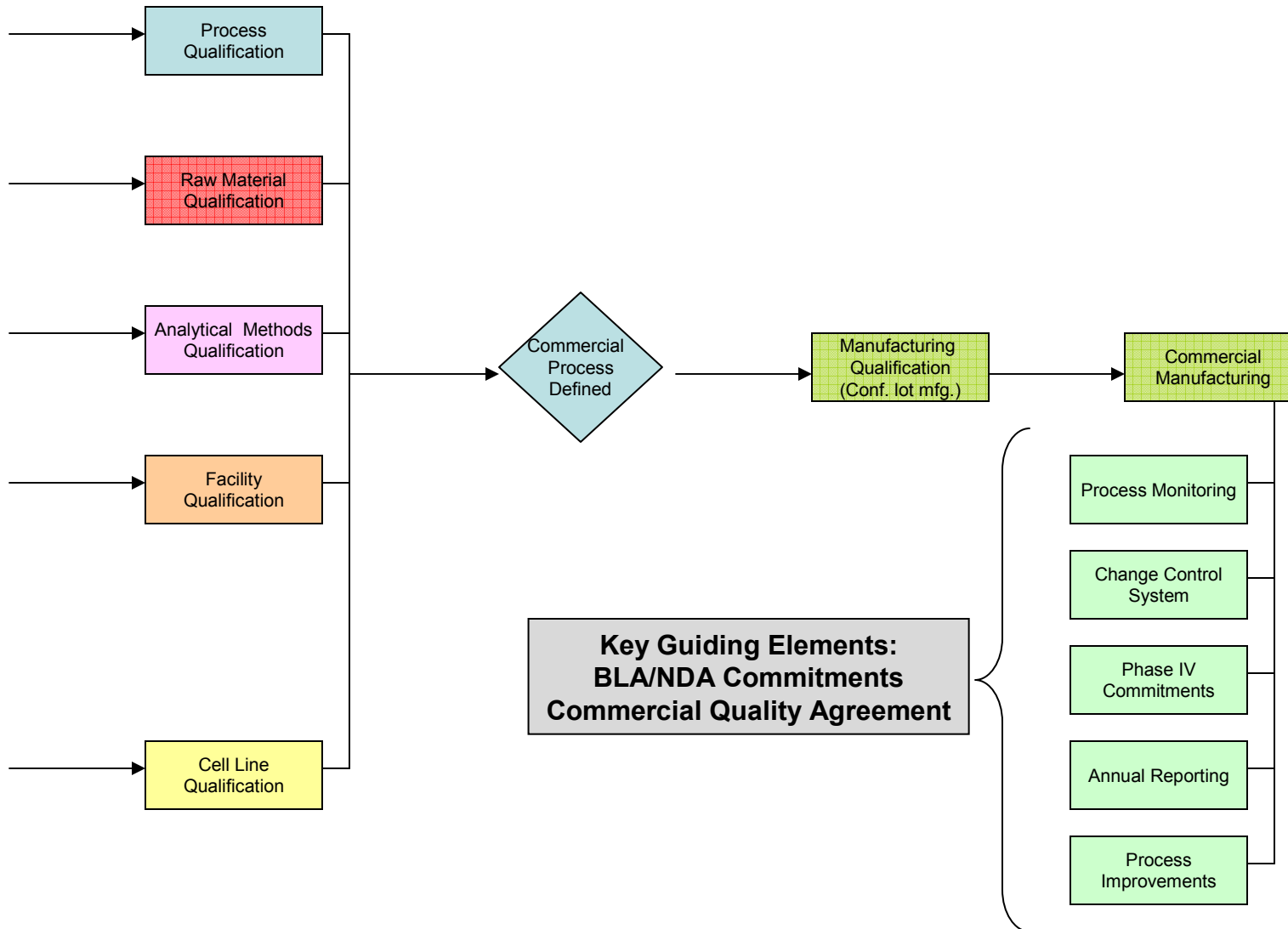
- » 'Continued Process Verification' (used by FDA),
 - » Ongoing collection of data to support that the process remains in a state of control to constantly increase the documented process understanding including sources of variability

VS

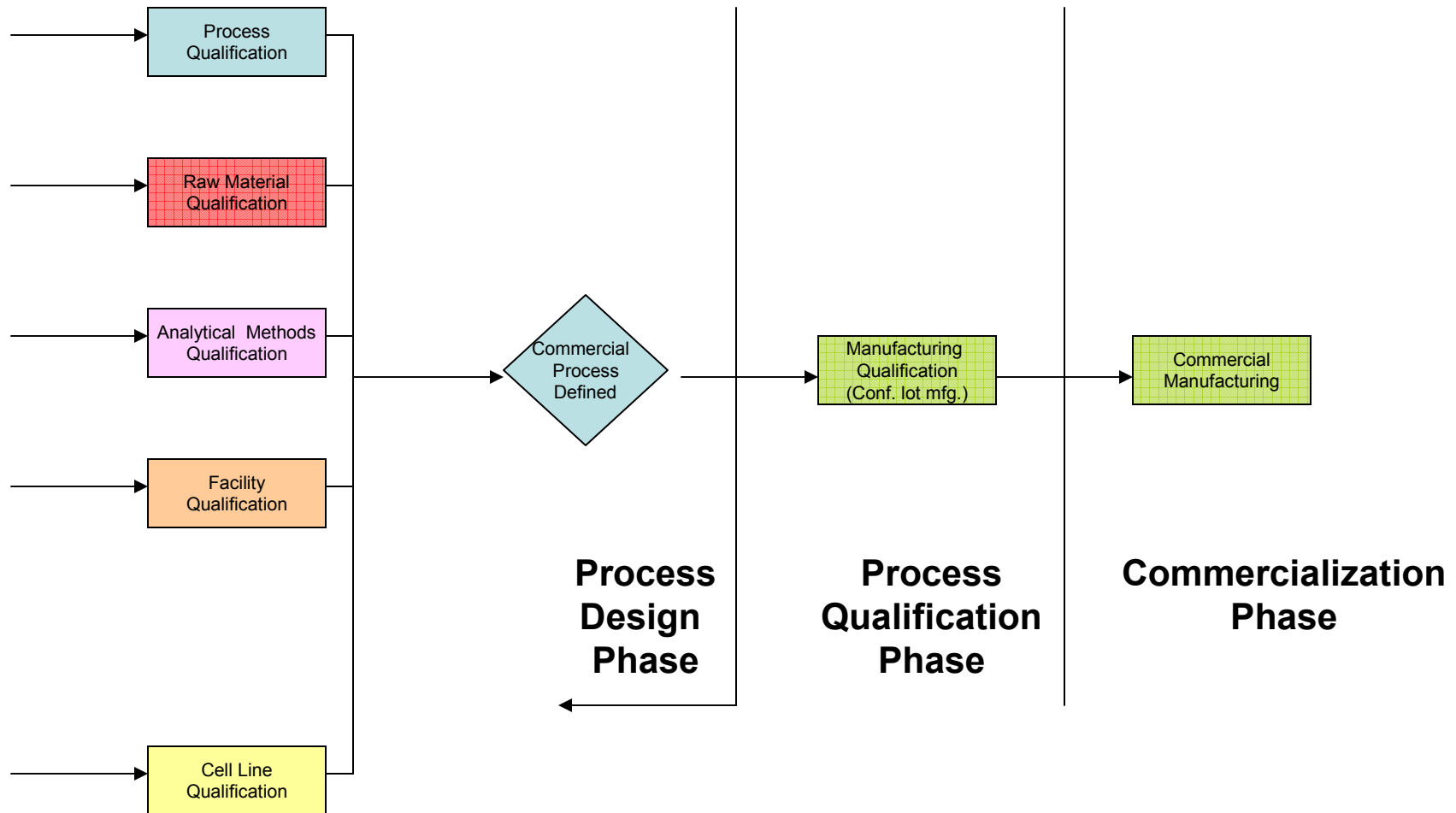
- » 'Continuous Process Verification' per ICH Q8
 - » Increasing use of In-process control data for product release and thus minimizing use of end-product release analysis - build in quality compared to tested in quality



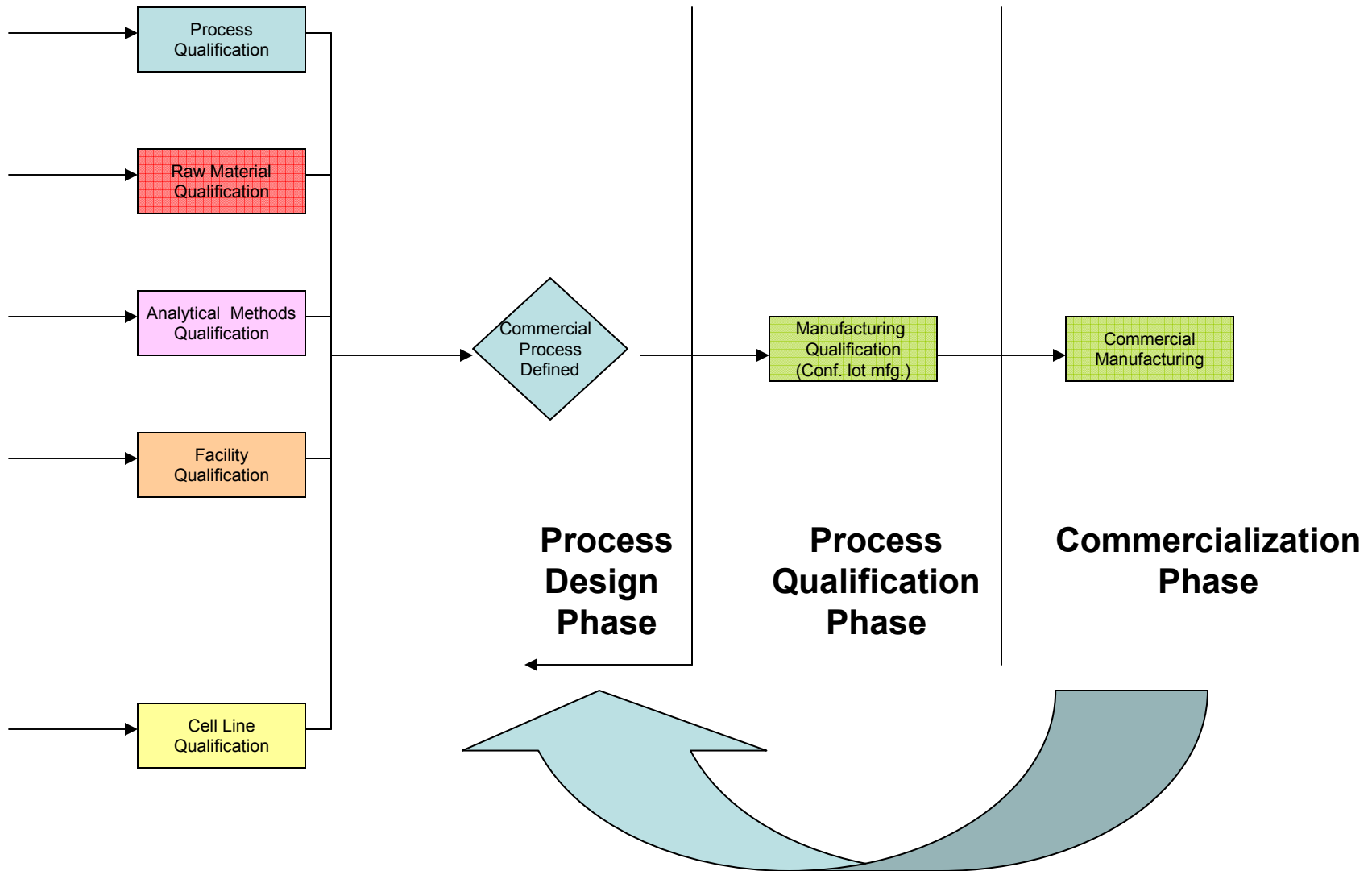




Idealized Process Validation



Idealized PV Lifecycle



Process characterization activities of Stage 1:

- » FMEA reports
- » Risk assessment output, ranking, references, justification
- » Small scale model qualification reports
 - » Engineering principles used, statistical comparison of data
- » Process characterization plan
 - » Study plan/protocol, no acceptance criteria
 - » Kept flexible to allow multiple rounds of DOE dependent on analysis results
- » Process characterization reports
 - » Results, statistical model, model diagnostics, design space, simulation to predict failure rate
- » Process characterization summary report
 - » Covers each unit operation in process
 - » NOR, acceptable range, criticality
 - » Description of design space
 - » Discussion of interacting parameters

Chris Smalley, Wyeth

- PAT Process Analytical Technology
- IPQ - International Pharmaceutical Quality - www.IPQpubs.com
- PDA TR 42 Process Validation Of Protein Manufacturing
- FDA Docket <http://www.regulations.gov/fdmspublic/component/main?main=DocketDetail&d=FDA-2008-D-0559>



» Process Analytical Technology

- » The scientific, risk-based framework outlined in this guidance, Process Analytical Technology or PAT, is intended to support innovation and efficiency in pharmaceutical development, manufacturing, and quality assurance. The framework is founded on process understanding to facilitate innovation and risk-based regulatory decisions by industry and the Agency

» Process Validation (Draft)

- » This guidance promotes modern manufacturing principles, process improvement, innovation, and sound science

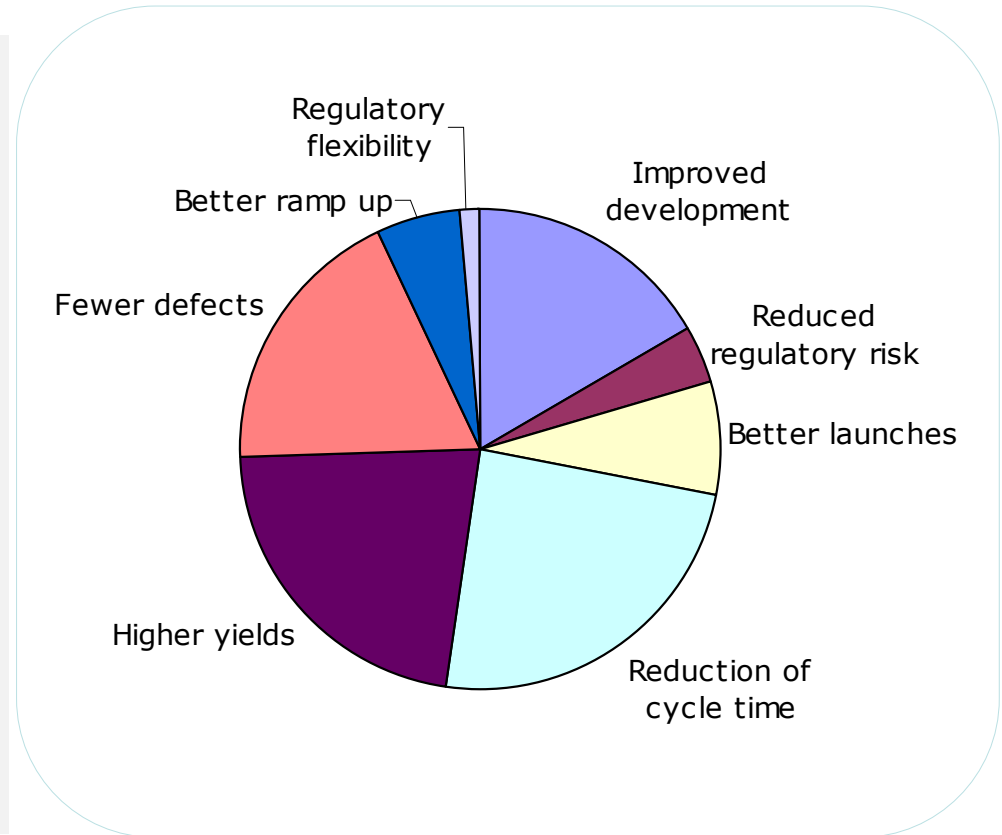
Ali Afnan, CDER

- » Quality by Design means
 - » Designing and developing formulations and manufacturing processes to ensure a predefined quality
- » Quality by Design requires
 - » Understanding how formulation and manufacturing process variables influence product quality
 - » Measuring in real-time material attributes critical to quality
 - » And controlling those attributes

Ali Afnan, CDER

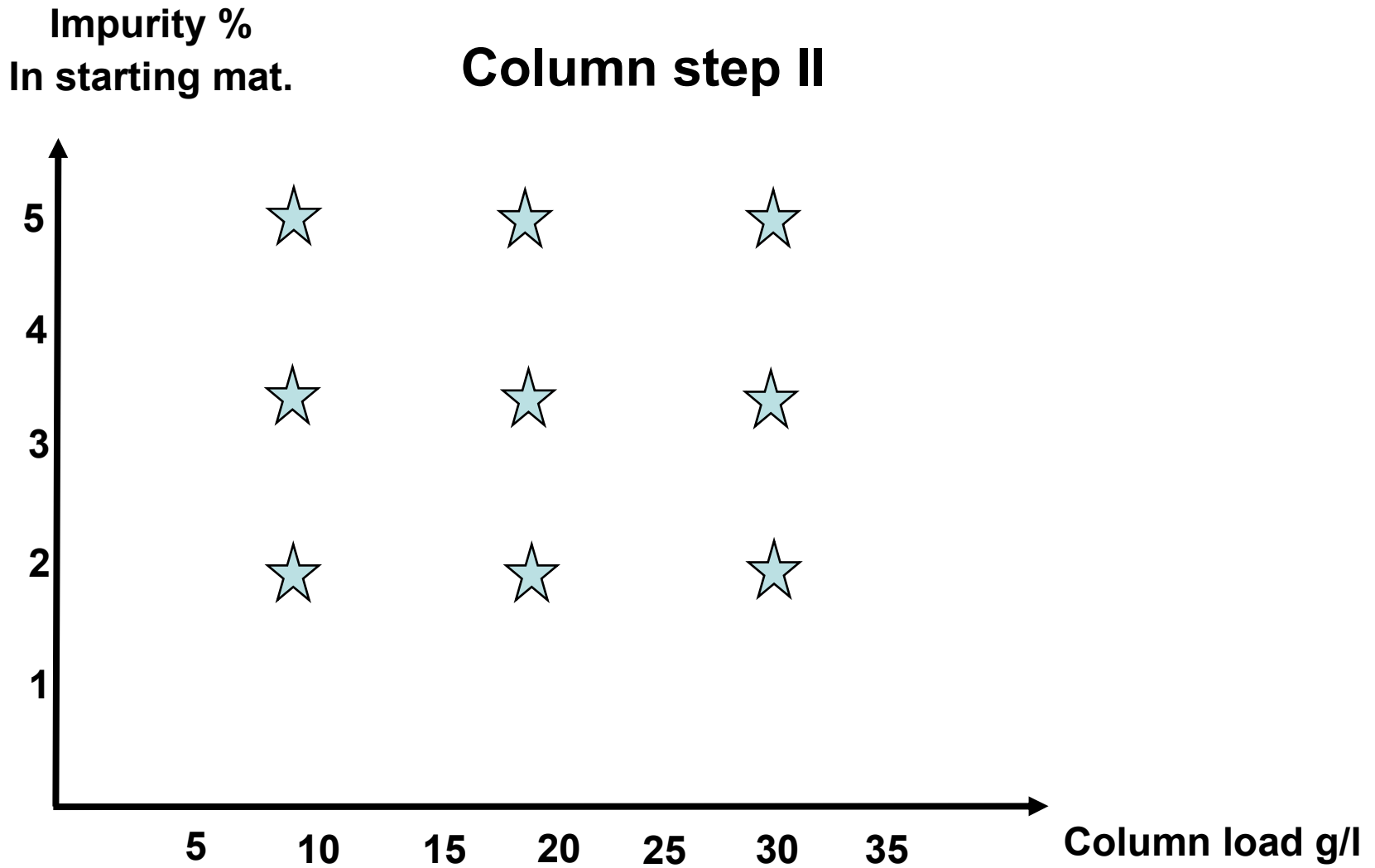
Direct benefits across industry from using QbD

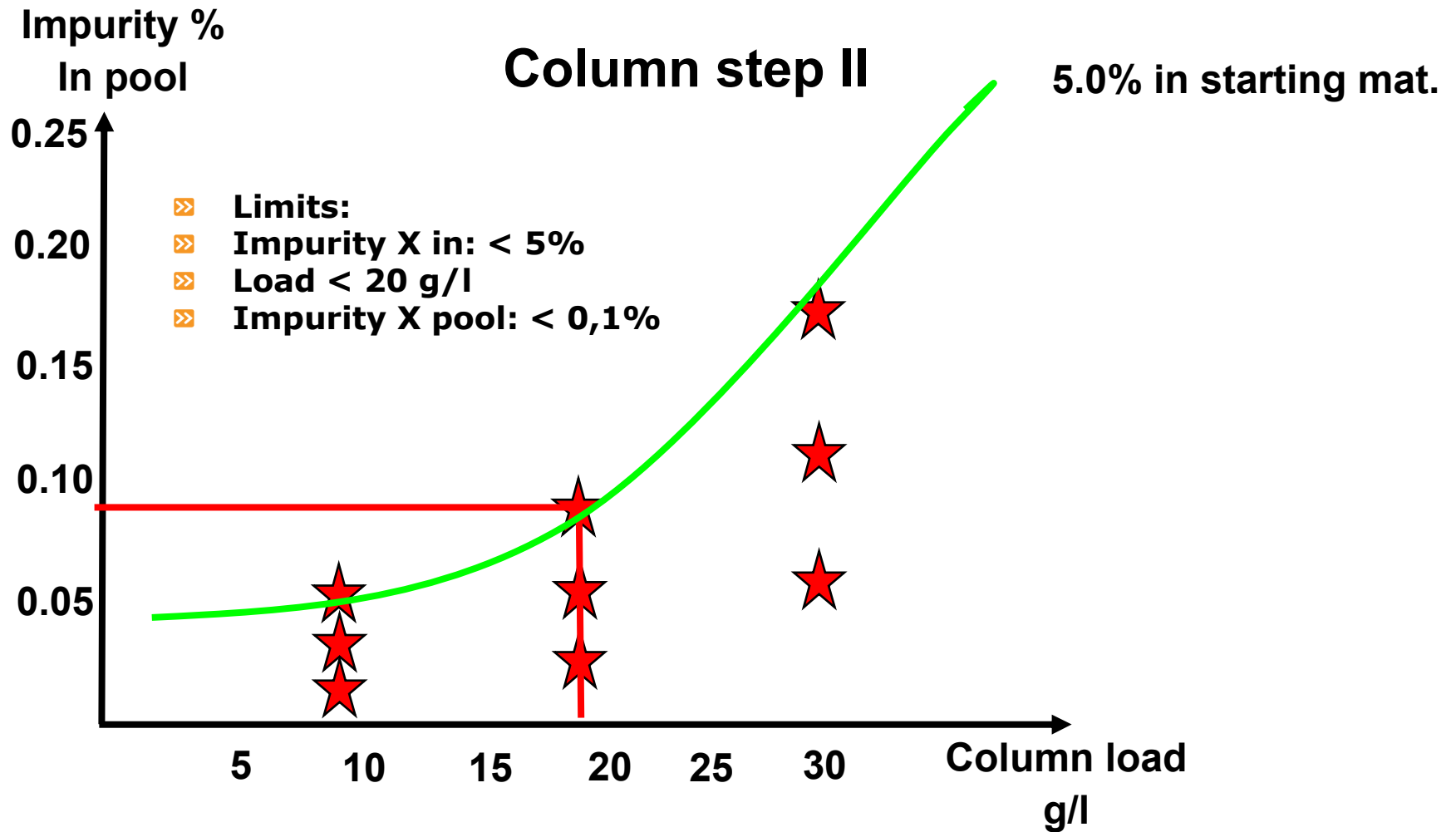
- » Reduction of cost of goods sold (\$15-25 billion)
 - » Reduction of cycle time (\$5-8 billion)
 - » Higher yields (\$5-7 billion)
 - » Fewer defects (\$4-6 billion)
 - » Better ramp up (\$1-2 billion)
 - » Use of design space to reduce regulatory burden (\$300 – 400 million)
- » Improved technology development (\$4-5 billion)
- » Reduced risk of regulatory citations (\$0-2 billion)
- » Increased sales through better launches (\$0-4 billion)

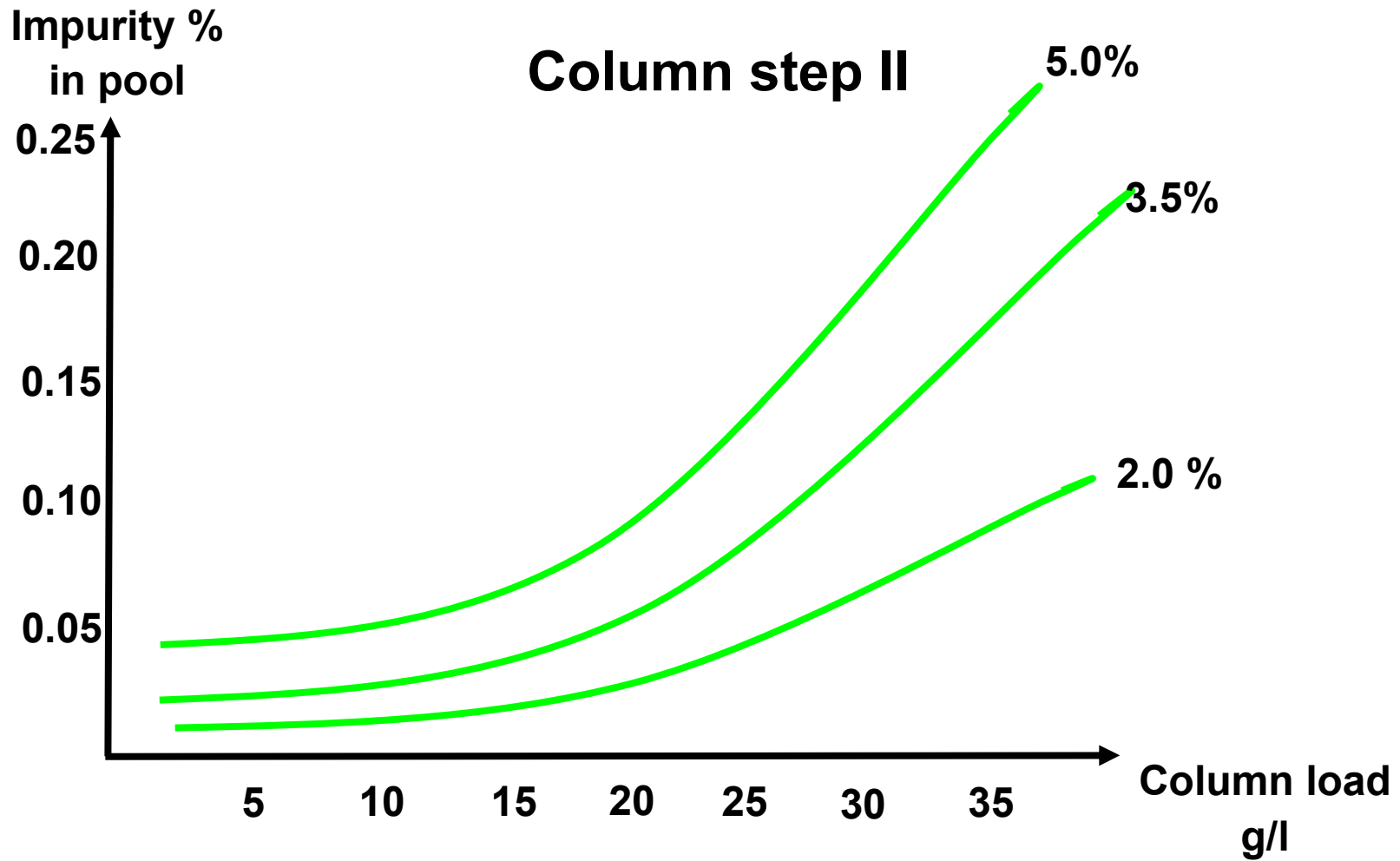


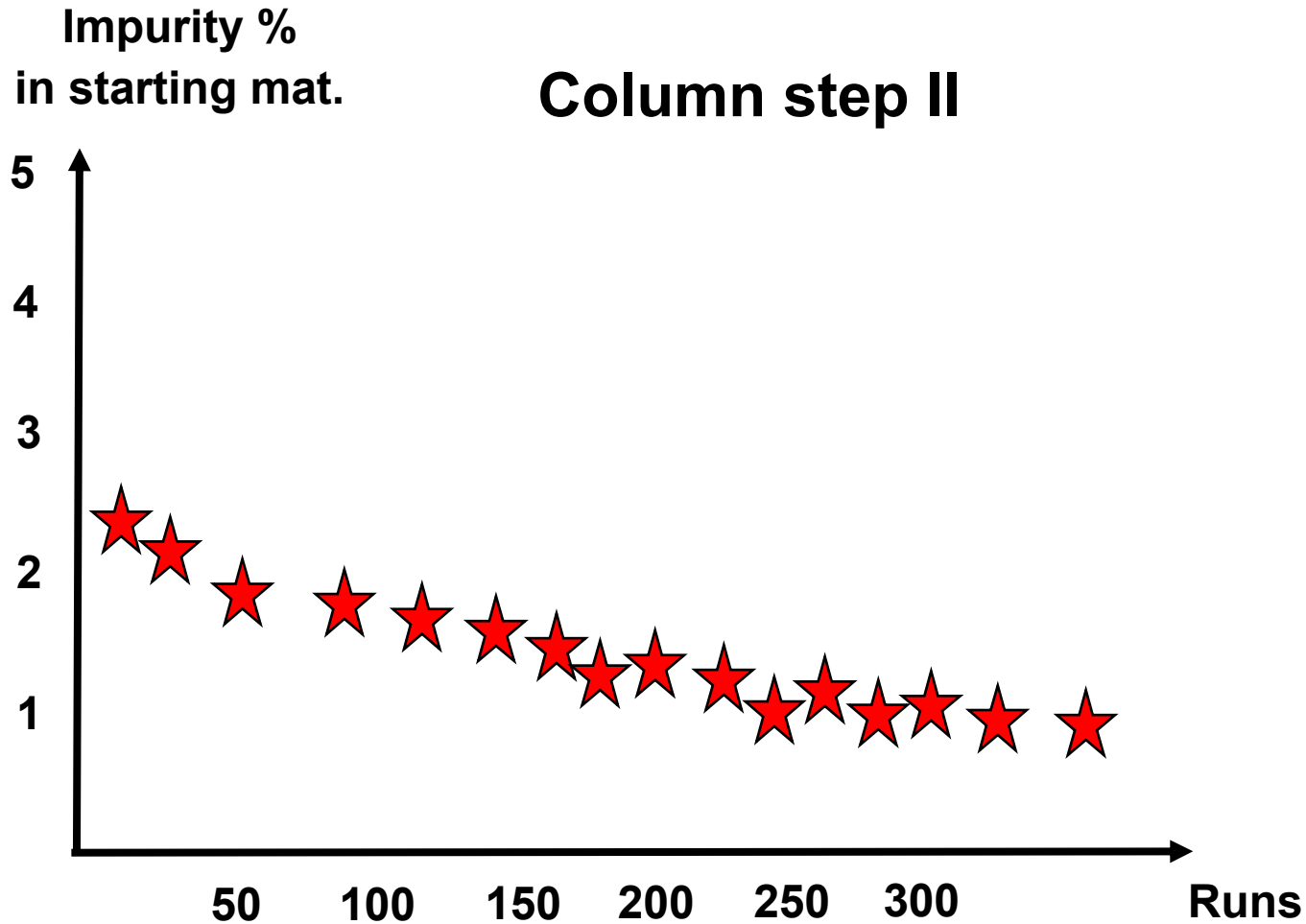
Source: McKinsey analysis quoted in "The Gold Sheet" January 2009.

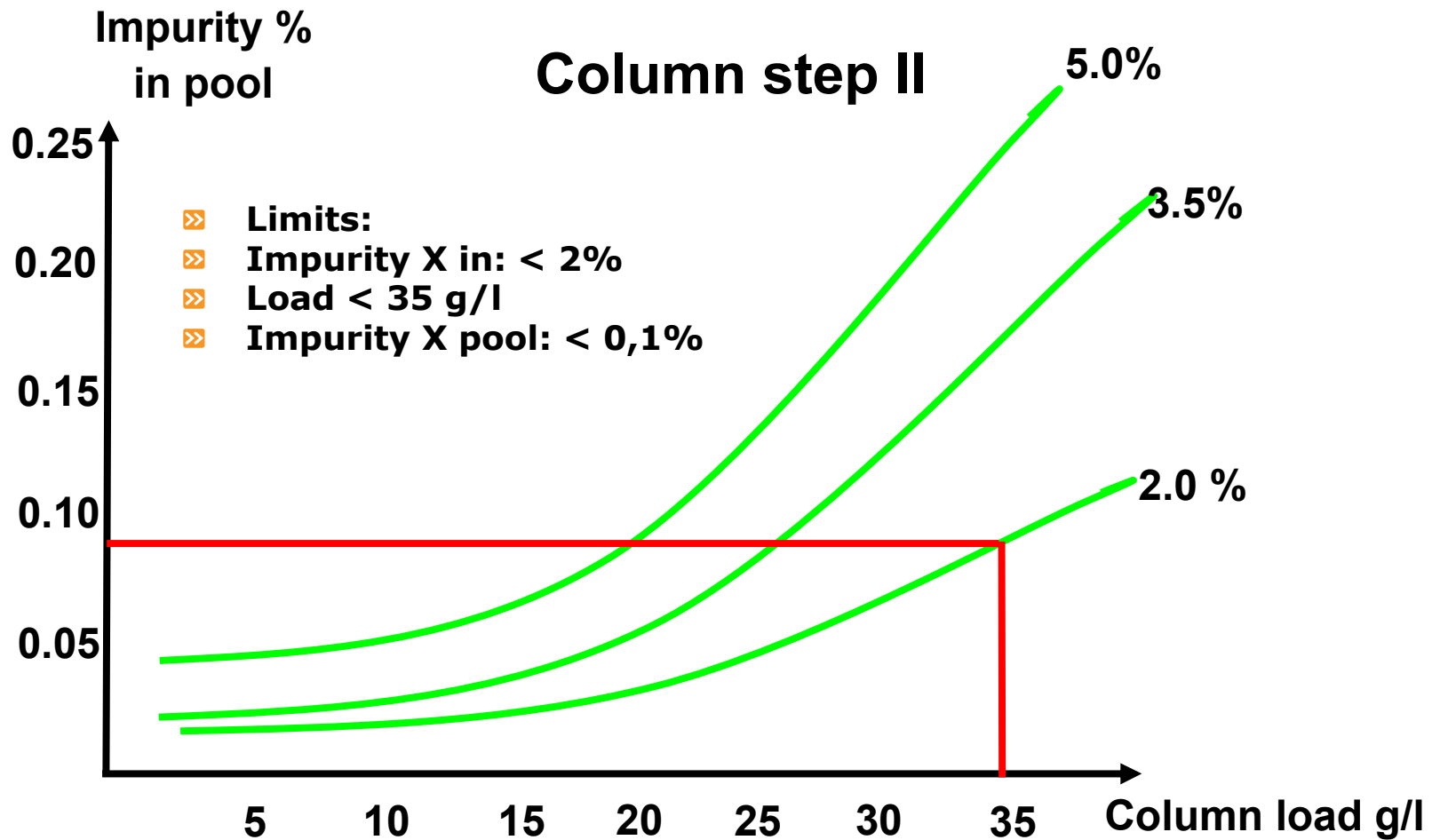
- » Column step II designed to remove impurity X
- » Impurity X in starting material 2 – 5%
- » Critical performance parameter
- » Column load
- » (Key) Operational parameter
- » Impurity in pool tested in clinical studies in ranges from 0,1% to 0,2%



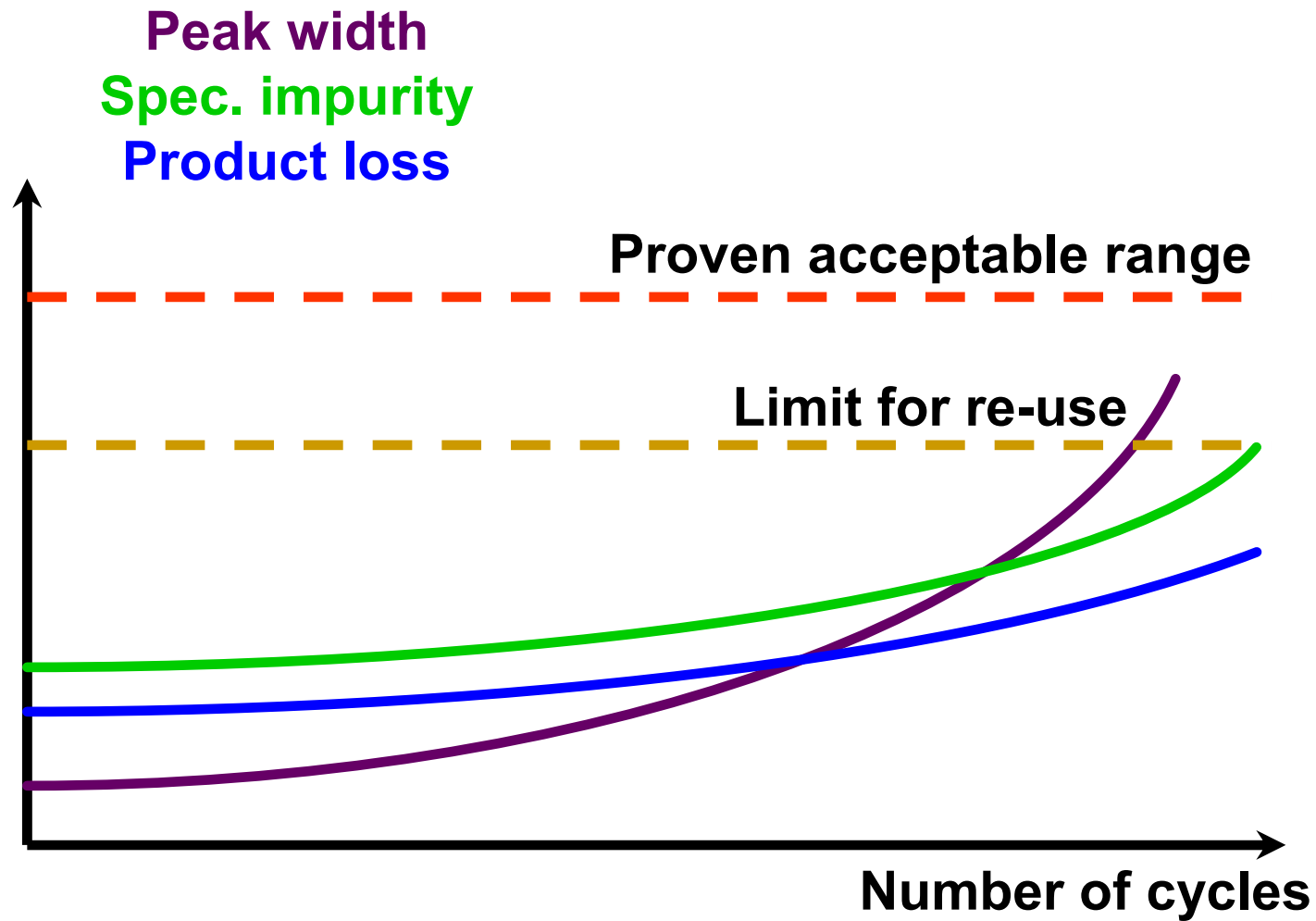




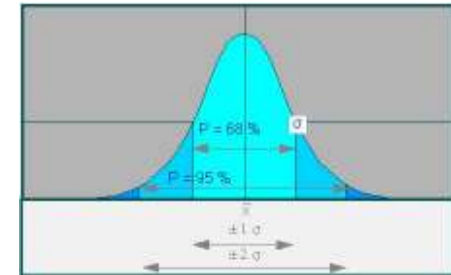




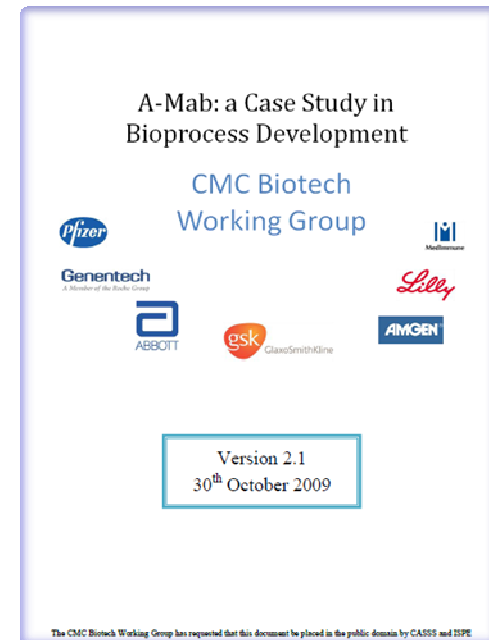
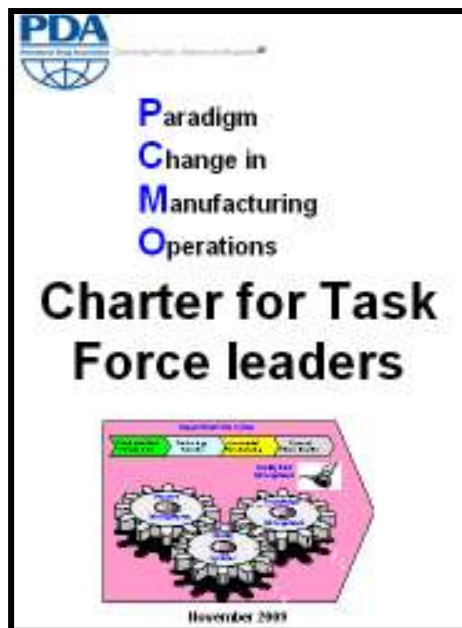
Determine resin re-use



- » A process is well understood when:
 - » All critical sources of variability are identified and explained
 - » Variability is managed by the process
 - » Product quality attributes can be accurately and reliably predicted
- » Accurate and Reliable predictions reflect process understanding
- » Process Understanding inversely proportional to risk
- » Option to implement process optimizations after commercialization



- » The authorities wants the industry to take lead in defining the future requirements
- » PDA initiative - PCMO (Paradigm Change in Manufacturing Operations)
- » ISPE initiative - PQLI (Product Quality Lifecycle Implementation)

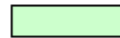


- » Utilizing PDA's membership expertise to drive the establishment of "best practice" documents and /or training events to aid the pharmaceutical manufacturers' (IMP and commercial products) to implement ICH Q8, Q9 and Q10

Dr. Lothar Hartmann, Roche

- » Enable an innovative environment for continual improvement of products and systems
- » Put science into practice
- » Enable increase of process robustness and knowledge
- » Foster relief from regulatory prescriptions

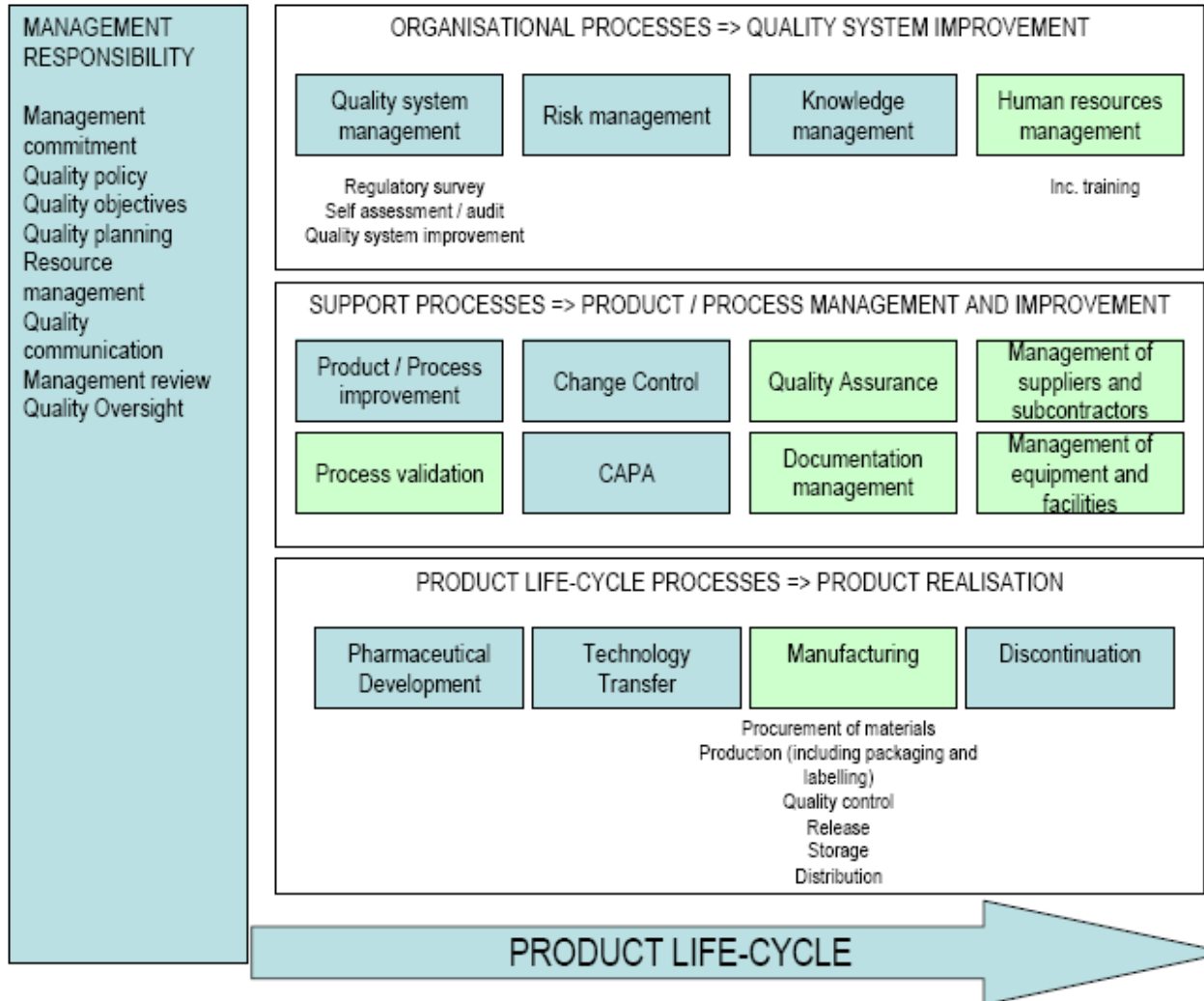
Dr. Lothar Hartmann, Roche

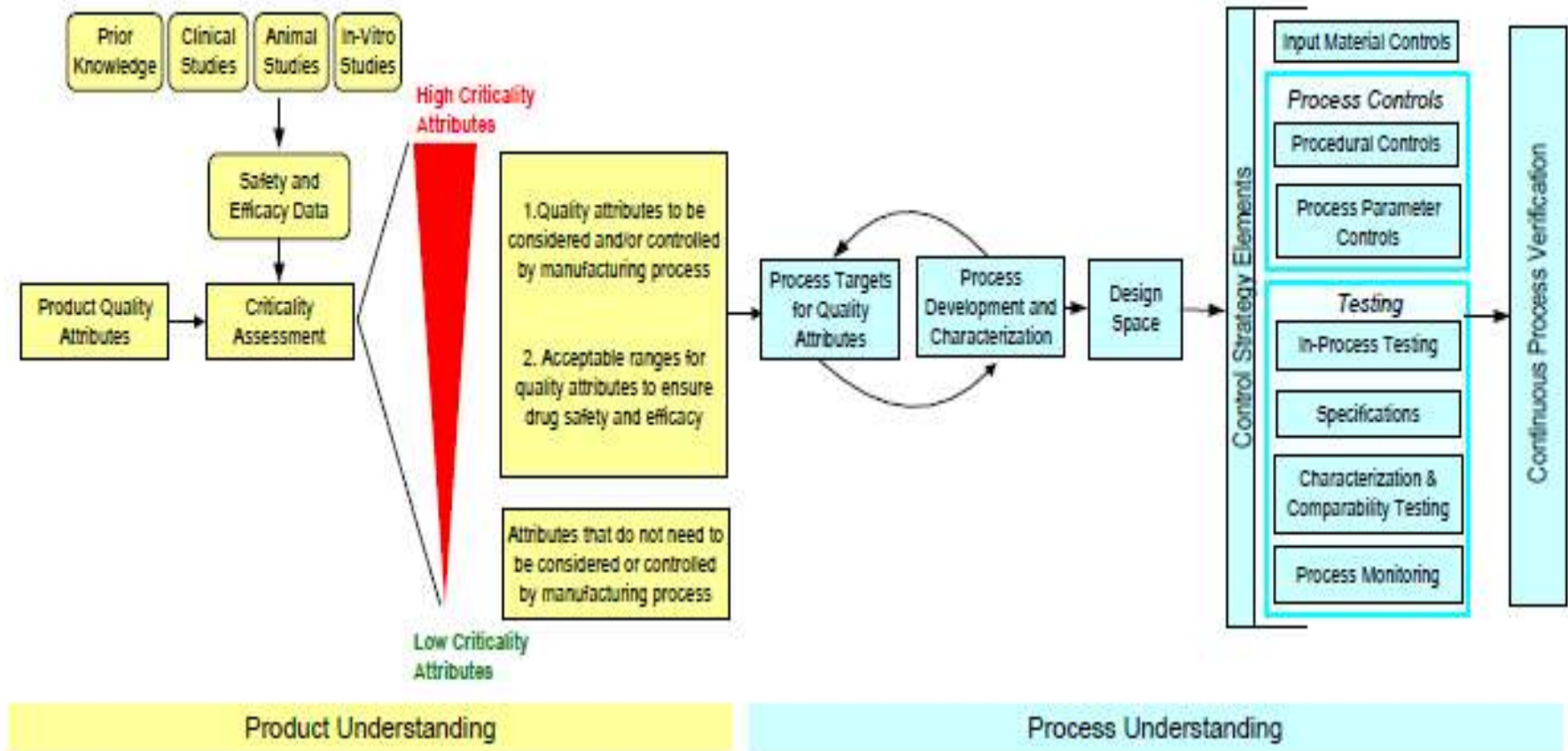


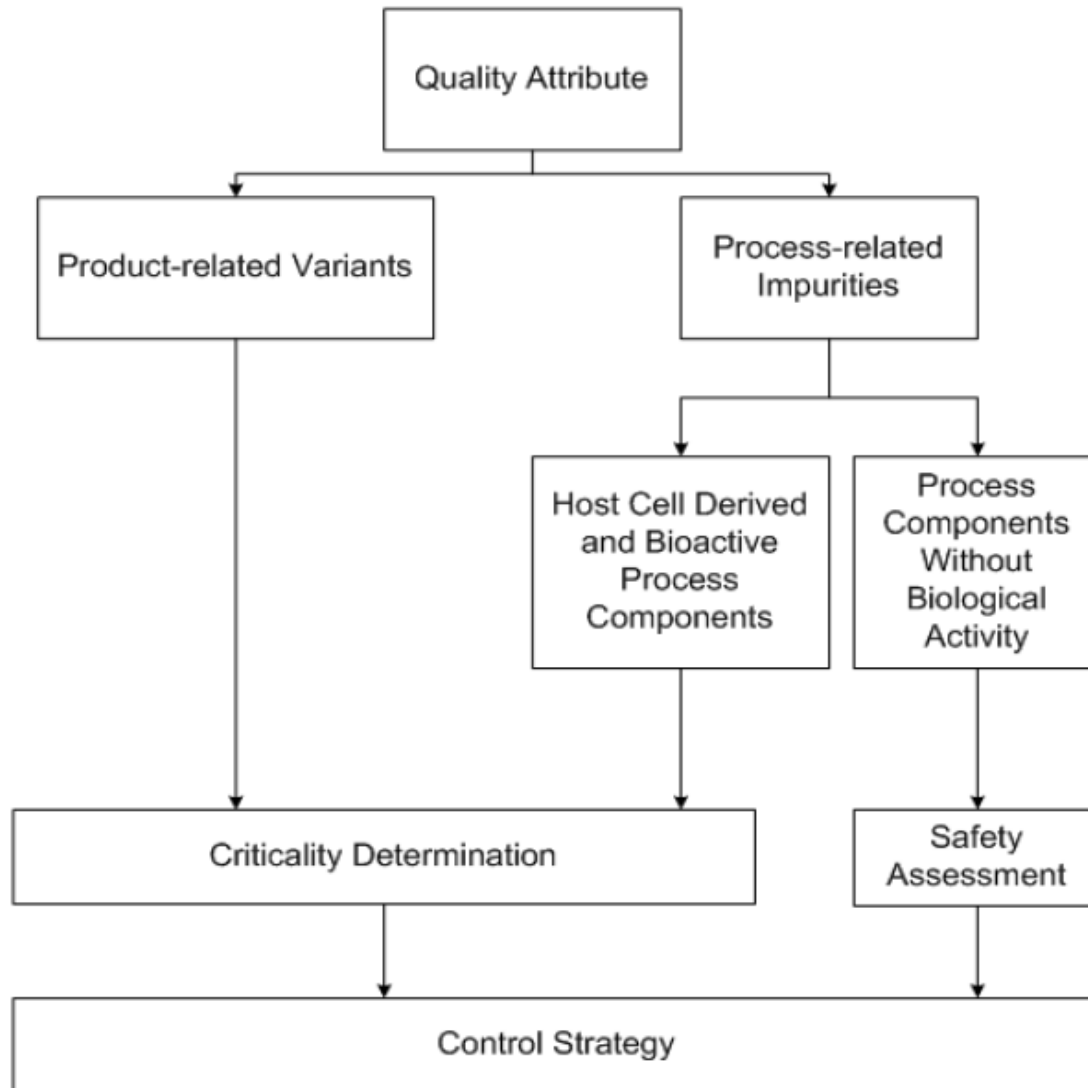
Covered by GMP



Covered by ICH Q10 draft







Terminology

CPP:	Critical Process Parameters
WC-CPP:	Well controlled - Critical Process Parameters
KPP:	Key Process Parameters
QA:	Quality Attributes
PA:	Process Attributes

CPP = Parameter impacts a Quality Attribute - Must be controlled tightly, limited robustness

WC-CPP = Parameter impacts a Quality Attribute - Well controlled, robust operation

KPP = Parameter impacts Process Attribute

Non-KPP = Parameter does not impact a QA or PA

Initial Risk Assessment

Process Parameter in Production Bioreactor	Quality Attributes						Process Attributes			Risk Mitigation
	Aggregate	aFucosylation	Galactosylation	Deamidation	HCP	DNA	Product Yield	Viability at Harvest	Turbidity at harvest	
Inoculum Viable Cell Concentr		Yellow					Green			DOE
Inoculum Viability							Green			Linkage Studies
Inoculum In Vitro Cell Age							Green			EOPC Study
N-1 Bioreactor pH							Green	Green	Green	Linkage Studies
N-1 Bioreactor Temperature							Green	Green	Green	Linkage Studies
Osmolality		Yellow					Green	Green		DOE
Antifoam Concentration									Green	Not Required
Nutrient Concentration in medium		Yellow								DOE
Medium storage temperature							Green			Medium Hold Studies
Medium hold time before filtration							Green			Medium Hold Studies
Medium Filtration							Green			Medium Hold Studies
Medium Age							Green			Medium Hold Studies
Timing of Feed addition							Green	Green	Green	Not Required
Volume of Feed addition		Yellow					Green		Green	DOE
Component Concentration in Feed		Yellow					Green			DOE
Timing of glucose feed addition							Green	Green		DOE-Indirect
Amount of Glucose fed							Green	Green		DOE-Indirect
Dissolved Oxygen		Yellow	Yellow				Green			DOE
Dissolved Carbon Dioxide		Red	Red	Yellow			Green	Green		DOE
Temperature		Yellow	Yellow	Yellow			Green	Green	Green	DOE
pH	Yellow	Red	Red	Red			Green	Green	Green	DOE
Culture Duration (days)		Red	Red	Red	Yellow		Green	Green	Green	DOE
Remnant Glucose Concentration	Yellow	Yellow	Yellow	Yellow	Yellow		Green	Green		DOE-Indirect

Final Risk Assessment

Process Parameter in Production Bioreactor	Quality Attributes						Process Attributes			Risk Mitigation
	Aggregate	aFucosylation	Galactosylation	Deamidation	HCP	DNA	Product Yield	Viability at Harvest	Turbidity at harvest	
Inoculum Viable Cell Concen.							█			DOE
Inoculum Viability							█			Linkage Studies
Inoculum In Vitro Cell Age							█			EOPC Study
N-1 Bioreactor pH							█	█		Linkage Studies
N-1 Bioreactor Temperature							█	█		Linkage Studies
Osmolality		█	█	█			█	█		DOE
Antifoam Concentration									█	Not Required
Nutrient Concentration in medium										DOE
Medium storage temperature										Medium Hold Studies
Medium hold time before filtration										Medium Hold Studies
Medium Filtration										Medium Hold Studies
Medium Age										Medium Hold Studies
Timing of Feed addition							█	█	█	Not Required
Volume of Feed addition							█	█	█	DOE
Component Conc. in Feed							█	█		DOE
Timing of glucose feed addition							█	█		DOE-Indirect
Amount of Glucose fed							█	█		DOE-Indirect
Dissolved Oxygen										DOE
Dissolved Carbon Dioxide		█	█	█			█	█		DOE
Temperature							█	█	█	DOE
pH	█						█	█	█	DOE
Culture Duration (days)	█						█	█	█	DOE

- » Process validation is not a “check list” GMP activity
- » Define your own company validation practices/strategy – keep it updated, challenge it, dare defend it and challenge the authorities
- » Process validation is a key element in establishing process understanding which will lead to higher quality processes
- » Quality = Money - Ask Toyota
- » Work with the authorities – on the company level and through industry organizations (ISPE, PDA, ASTM, PhRMA, ECA ect.

