Get Ready for Biopharmaceutical Process Characterization

CMC Biologics
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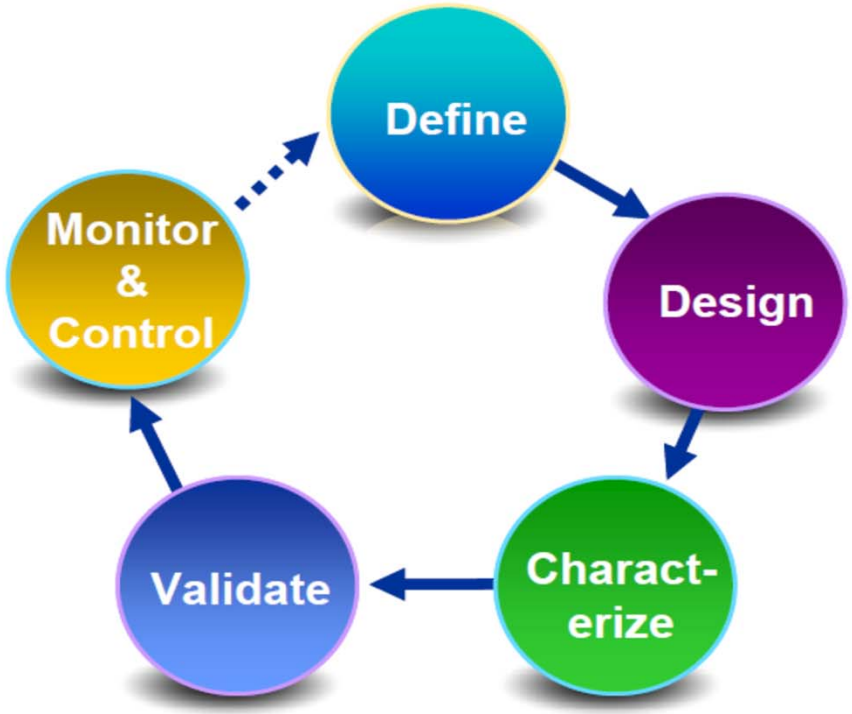
BioProcess Technology Consultants
www.bptc.com

Overview

- Getting Ready for a Process Characterization Study…
  - Apply QbD principles
  - Perform risk assessment, (i.e., how to prioritize parameters to study in PC work)
  - Define the "goal" of PC studies
  - Design the Process Characterization Study

Quality by Design



"Quality by design means designing and developing manufacturing processes *during the product development* stage to **consistently ensure a predefined quality** at the end of the manufacturing process…"

- FDA Draft Guidance, Sept. 2004

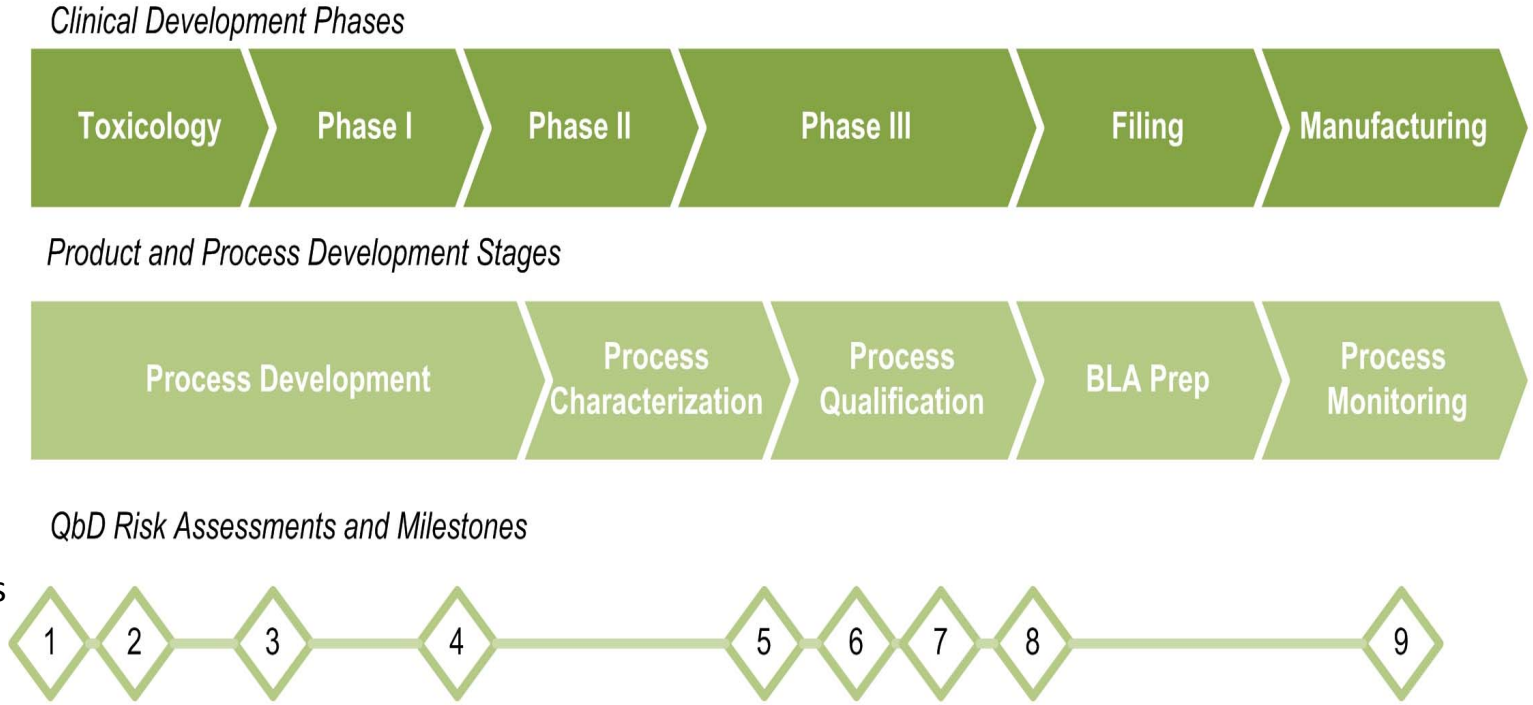
QbD is a risk & science based approach for development & commercialization

- Clinical Aspects
  - Efficacy
    - Clinical indication
    - Mechanism of action
  - PK/PD
    - Criticality of half-life
  - Safety
    - e.g., Immunogenicity
- Drug Product Format
  - Concentration (strength)
  - Desired shelf life
  - Desired mode of delivery

*A. S. Rathore and H. Winkle, Quality by Design for Pharmaceuticals: Regulatory Perspective and Approach, *Nature Biotechnology*.

Quality by Design – An (Imperfect) Lifecycle Approach

- Systematic lifecycle approach to development
  - Iterative process building on knowledge gained
- Emphasizes product and process understanding and process control
- Quality risk management
  - Use risk assessment tools consistently
  - Revise risk assessments as knowledge is gained



1. Target Product Profile Identified
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3. Critical Quality Attribute Risk Assessment
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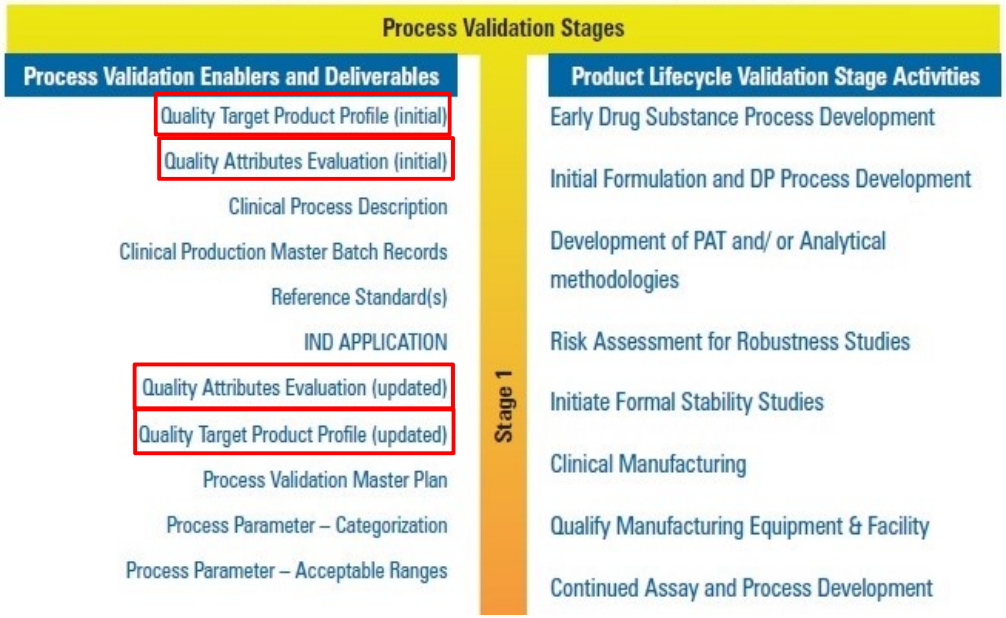
Reference: *Richter S. Recovery of Biological Products XVI (2014)*

Validations Stages: A Life Cycle Approach (PDA TR60)

- Stage 1: Process Design
  - Defining the commercial process
  - Based on development & scale-up experience
- Stage 2: Process Qualification
  - Confirming that the process design is capable of reproducible commercial manufacturing
- Stage 3: Continued Process Verification
  - Gaining ongoing assurance during routine production that the process remains in control

Validations Stages: A Life Cycle Approach (PDA TR60) – STAGE 1

Figure 1.2-2 Common Timing of Process Validation Enablers and Deliverables to Validation Stage Activities



- Notes:
  - Clinical manufacturing, formal stability studies precede IND submission
  - PVMP initiated at beginning of stage 2 after process design or after all modifications to process made

Quality Target Product Profile (QTPP)
A prospective summary of the quality characteristics that ideally will be achieved to ensure the desired safety and efficacy of the drug product (dosage form & strength, purity, quality attributes affecting PK, activity etc.)

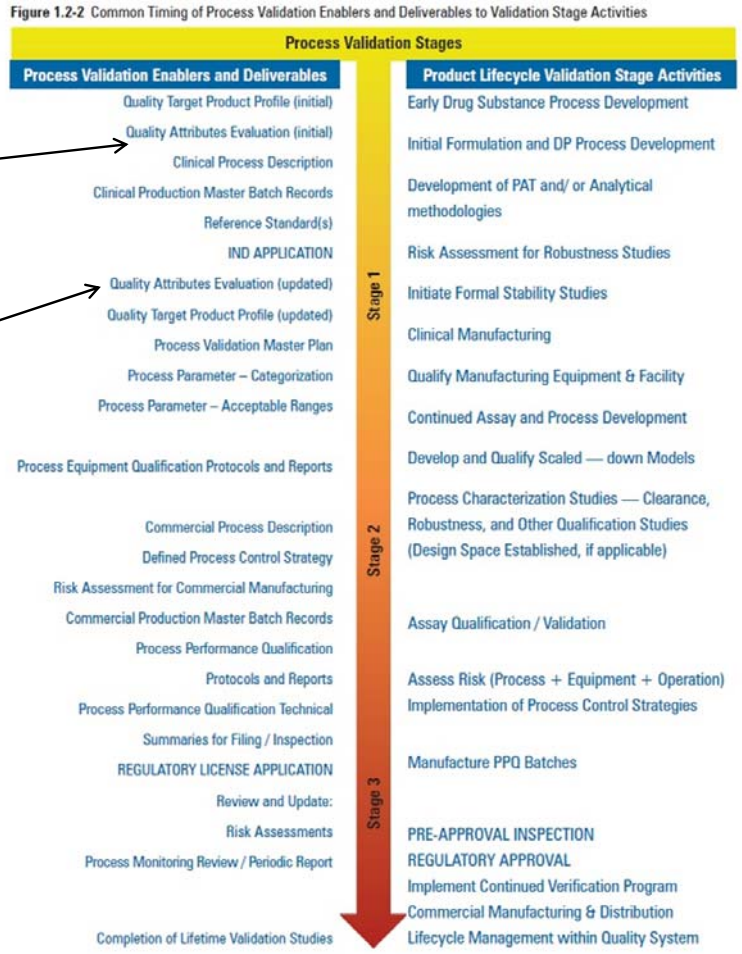
Critical Quality Attribute (CQA)
A physical, chemical, biological or microbiological property or characteristic of the product whose variability might have potential impact on the safety and efficacy of the product. At early stages of development some of these are likely to be "potential CQAs"

Timing for Determining CQAs

From TR-60: Process Validation: A Life Cycle Approach, PDA, 2013

Quality Attributes Evaluation: Initial

Quality Attributes Evaluation: Updated



- TR-60 shows this as the last time the CQAs are update
- Pure fantasy for a biopharmaceutical

- Often don't get final CQA until right before filing BLA

Timing For Determining Risk Assessments

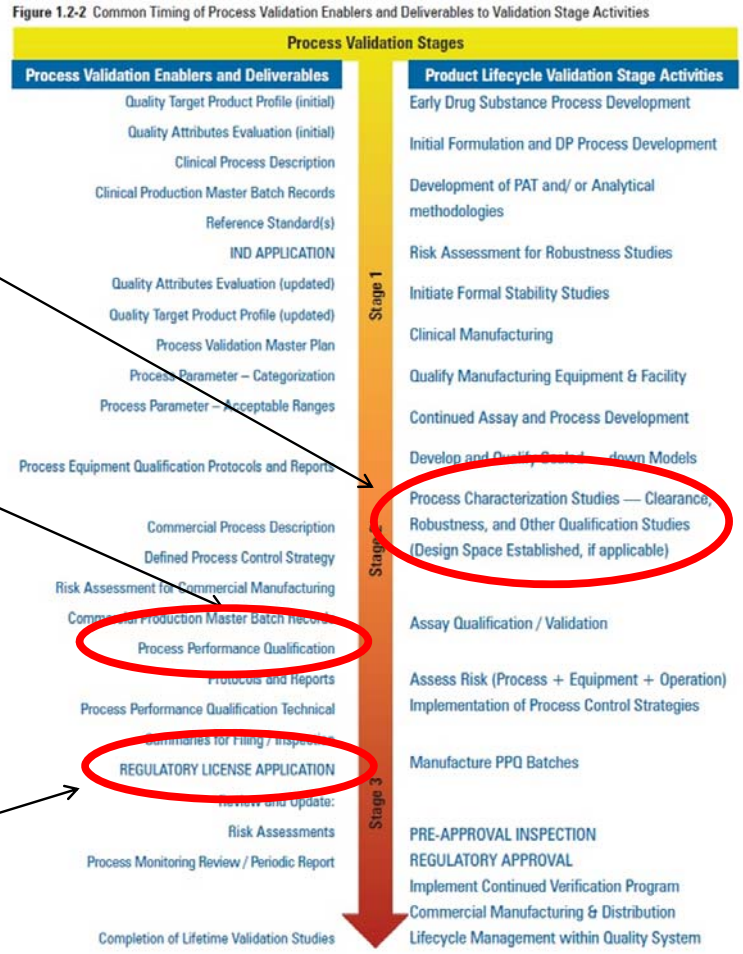
- NOTE: For biopharmaceuticals, do not agree with many of the relative timings presented in TR-60

From TR-60: Process Validation: A Life Cycle Approach, PDA, 2013

Do first risk assessment well before start of PC program

Do another risk assessment prior to drafting PPQ protocols

Do one more risk assessment prior to filing BLA



Why Do Risk Assessments?

- Risk analyses are the single most important validation activity
  - **First**: It's the logical organizing principle that guides process characterization strategy & process control strategy.
  - **Second**: It creates pauses at various points in development so we can spend time discerning between what we really know about the process and what we only think we know about the process.
  - **Third**: Gets us thinking where all the possible variances in the process exist.
  - **Fourth**: The number of permutations of process parameters is infinite. We can't study everything.
    - Question: What do we then choose to study?
    - Answer: The parameters we believe pose the greatest risk to the process
  - **Fifth**: Gives confidence to regulatory agencies that you are an organization that routinely evaluates risks to the process and takes action
    - Real (Multiple) Examples: FDA asks, "Have you studied the impact of parameter X". Sponsor answers, "No, because our risk assessment indicated it was not a significant risk to the process." Although the FDA did ask the sponsor to perform post-approval studies looking into the parameter, the FDA was very satisfied with the answer because it showed the sponsor was evaluating risks

FMEA Scoring

- What do we rank
  - Process Parameters (PP, inputs)
  - Examples: temperature, pH, conductivity, media & buffer compositions, pressure, raw material quality, hold times, processing times, protein loads to chromatography (mg/mL) and TTF (g/m^2)
  - Consider the (O)ccurance that PP will venture outside the "norm" and if it does can we (D)etect it
- What are the impacts for which we will determine the (S)everity
- What are the CQAs for each step

Scores

Occurrence	1	< 0.5%
	3	< 2.0%
	5	5%
	6	10%
	8	20%
	10	30%
Severity	1	no impact on CQAs expected
	3	marginal impact on CQAs expected
	5	low impact on CQAs expected
	6	noticable on CQAs expected
	8	strong impact on CQAs expected
	10	unaceptable deviation of CQA
Detectability	1	100% will be detected in all cases
	3	75%
	5	>50%
	6	<50%
	8	25%
	10	0% not detectable

A parameter is regarded as **potentially critical** if:

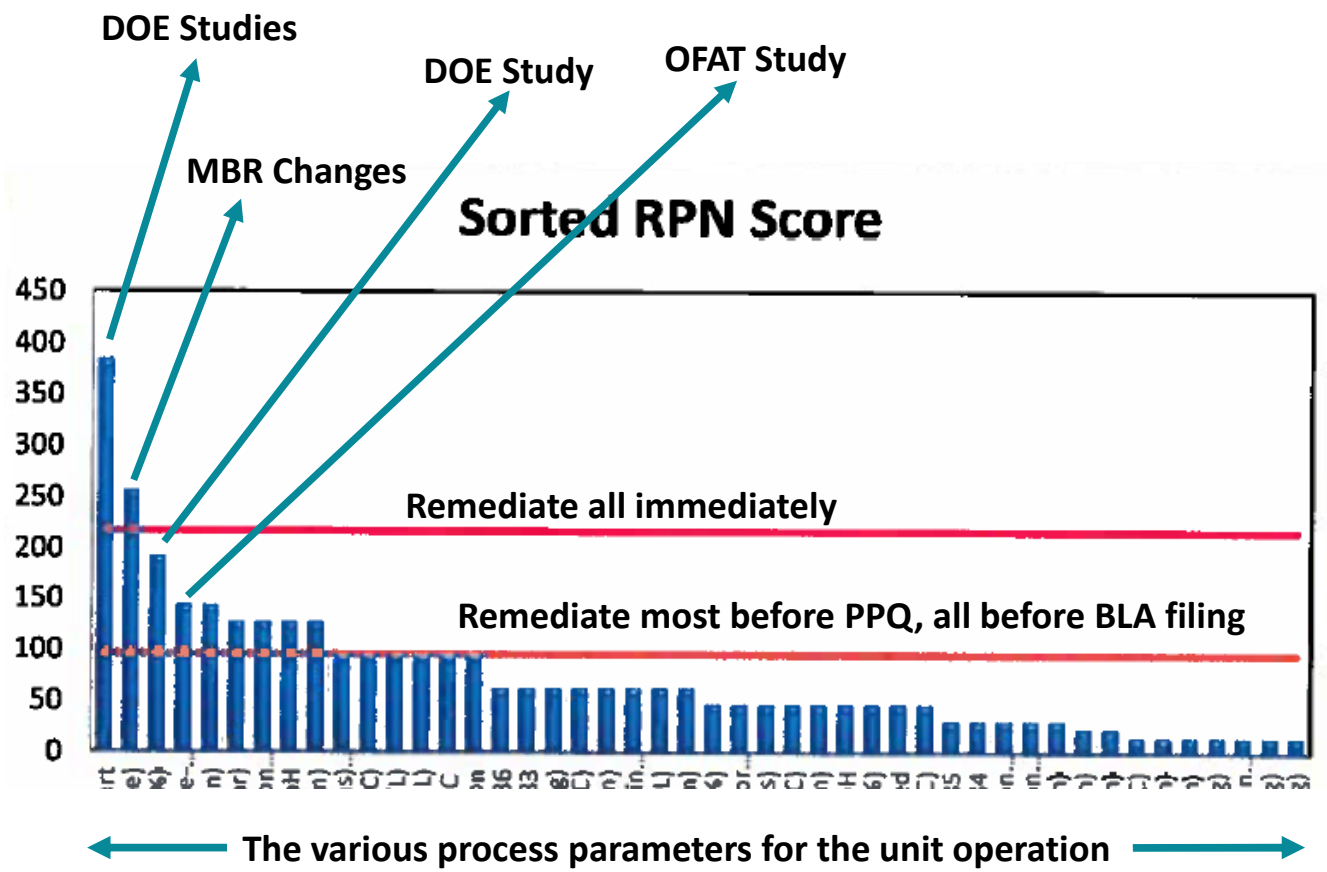
risk priority number (rpn) = **O * S * D > 125** or **S = 10**

FMEA Report – Absolutely Vital!!!

- FMEA will be a road map to guide many decisions on the road to commercialization – SO DOCUMENT IT ASAP after FMEA meeting
- Impacts **process characterization** strategy (what to study)
- Impacts changes to MBRs
- Will help decide what additional data may be required from upcoming full scale runs
- May impact analytical validation strategy (what test methods need to be qualified/validated for what process streams)

FMEA Is Done: What Do We Do With It? Remediate the Risks

- First, rank all the RPNs for a given step
- Next, decide what RPN values require action
  - Immediately
  - Before PPQs
  - Before filing
- For the parameters that require action, decide what action is required for each
- Capture proposed action in FMEA report or separate report



With Goal Now Defined, How Do We Design PC Program?

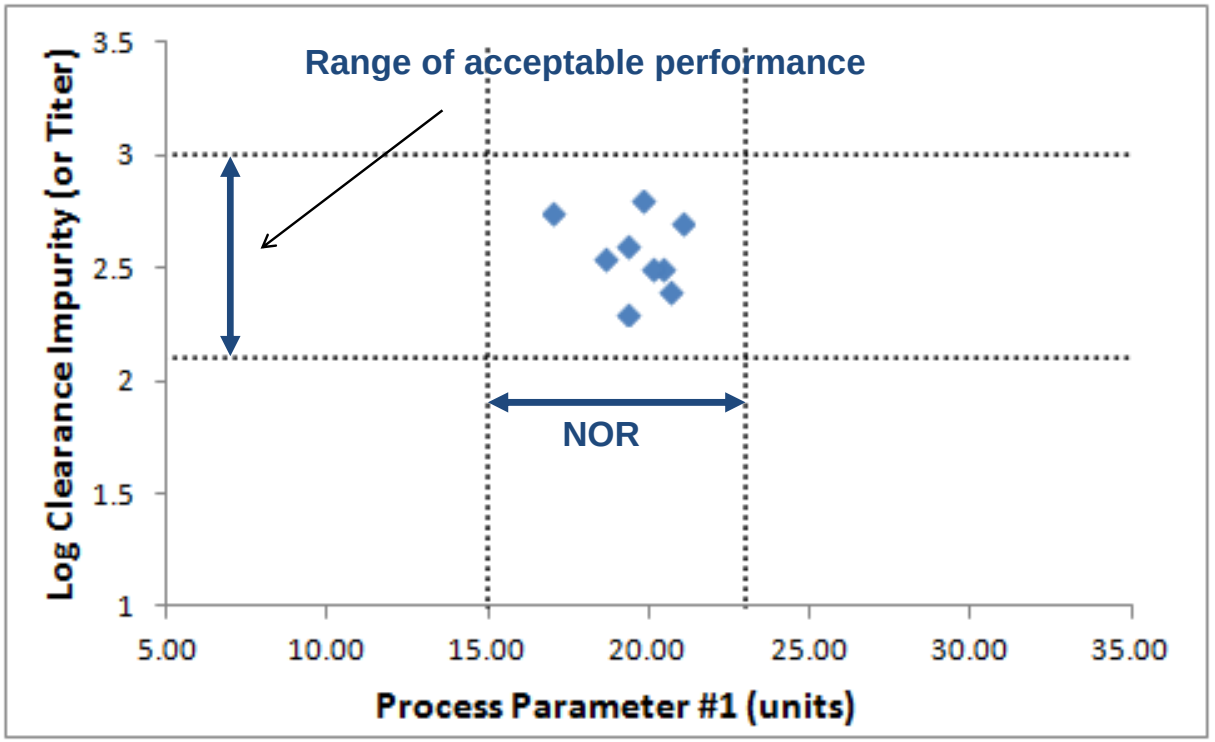
- What variables do we study?
  - Those that are at the greatest risk of screwing up your PPQ campaign
- What variables would those be?
  - Those that were ranked the highest during the risk assessment (e.g., the RPN score from an FMEA)
- OK, we have the variables we want to study, what ranges do we study for each variable
  - Study values a little bit outside of the Normal Operating Ranges (NORs) to account for measurement error and deviations
- How do we determine what the NORs are?
  - …….

What is an NOR and How Do We Establish Them?

- One definition of NOR
  - From TR60: "a defined range, within (or equal to) the Proven Acceptable Range, specified in the manufacturing instructions as the target and range at which a process parameter is controlled, *while producing unit operation material or final product material meeting release criteria and CQAs"*
    - NOR ≤ PAR (That's the only guidance TR60 gives)
- Not a helpful definition. For example …..
  - Suppose we have data to know that a temperature between 34 and 39 ^{o}C has no impact on product quality or process performance (i.e., the PAR is 34 to 39). How does this help us define NOR?
    - Is it 34 – 39? 35 – 38? 36.5 – 37.5????????
    - Key term in NOR is "normal". Where does the process normally run? What is a reasonable range within which to control a process parameter regardless of PAR?

What is a PAR and How Do We Establish Them?

- One definition of PAR
  - From TR60: "A characterized range of a process parameter for which the operation within this range, while keeping other parameters constant, will result in producing a material meeting relevant quality criteria."
- "…. producing material meeting relevant quality criteria".
- What is relevant quality criteria?
- Again, can rely on historical performance of clinical batches
- Graph shows historical clinical batches



Establishing Critical Process Parameters

- One definition of CPP
  - From TR60: "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".
  - Not a helpful definition.
    - A temperature of 60 ^{o}C would probably have an impact on almost all biopharmaceutical products, but does that fact alone make temperature a CPP?
      - If temperature will never come anywhere close to 60 ^{o}C, then why should temperature be a CPP?
      - Implies some aspect of the likelihood that process may venture beyond the PAR

Tying It All Together: Quality by Design (QbD) – Lifecycle Approach

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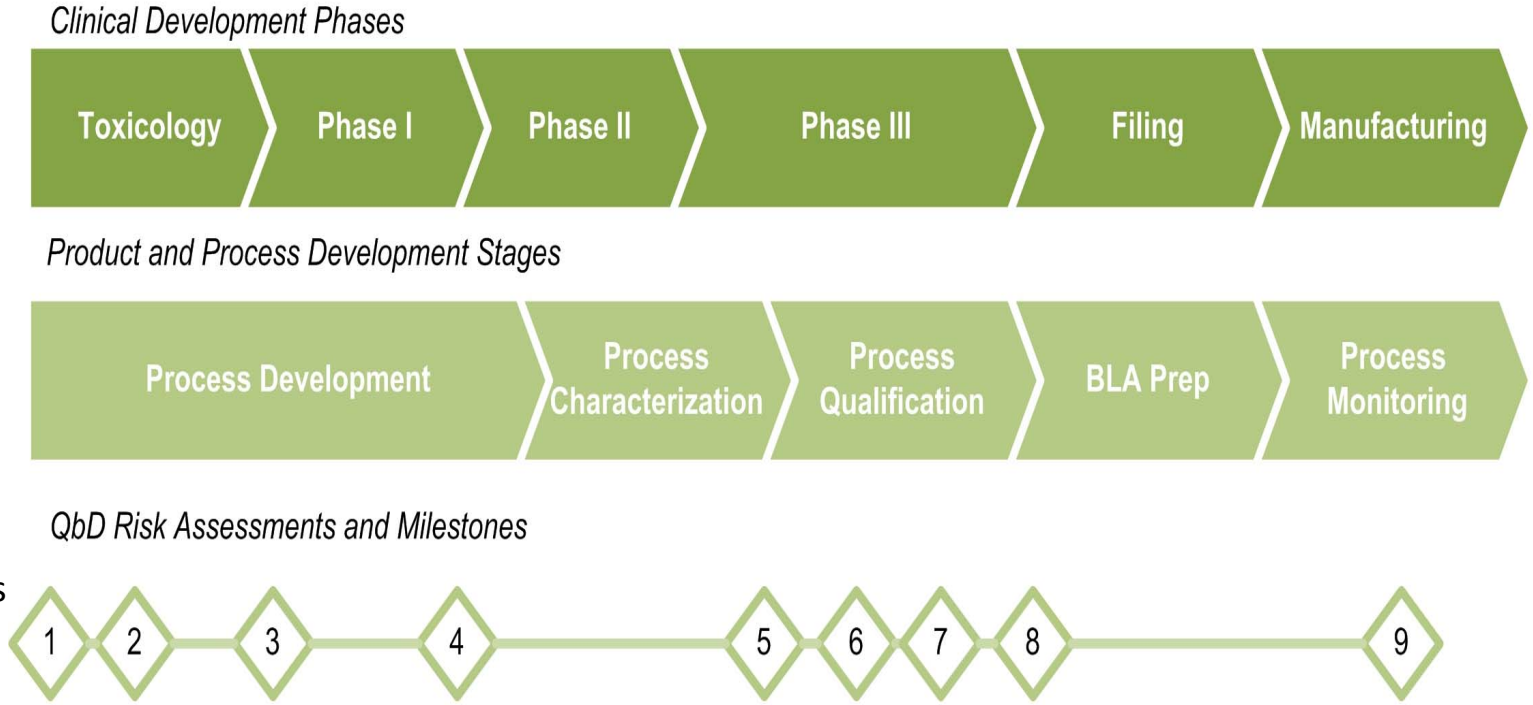

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Thank You!

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