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Applied QbD Hybrid Approach: Process Characterization, Roadmap & Validation

Fast Track (Orphan) Biological Therapeutic in a Virtual Company

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Problem Statement

- Fast Track Virtual Bio-Therapeutic Company's late Phase II Product
- How do we deliver a Process Validation in most expeditious manner that gets us approved?
  - Where, when and how?
  - How much will process validation cost?

Approach to Fast Track 1/2

- QbD Hybrid Approach
  - Requires establishing active effective relationship with Project Team
  - Define the Desired State
  - Establish and Assess "As Is" Process & Product Characterization ("The Assessment")
  - Identify and Remediate QbD Gaps
  - Identify and Establish QbD Product/Process Development and Validation Roadmap

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Approach to Fast Track 2/2

- Identify key risk factors (based on Gap Assessment)
  - Additional studies/data to support attaining the Desired State
  - Risks related to using the CMO model for initial scaled development, process validation & commercial launch
- Refine and develop process flow to include Critical Quality Attributes, Critical Process Parameters and Critical Material Attributes
- Update the CMC section for the final BLA based on the outcomes of the assessment and aligned with the Desired State

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"As Is"
Process & Product Characterization 1/5

- Application of the Science and Risk Based QbD Principles:
  - Requires Project Team Active and Iterative Interaction
  - Established the boundaries for conducting GAP Assessment
  - Applied to Process Characterization Data and CMC Submissions Rationale and Justifications

"As Is"
Process & Product Characterization 2/5

- QbD Principles provided foundation for
  - Studies
  - Documentation
  - Submission Sections
  - Personnel and team interviews
  - and Raw Data
- Over 600 pages of information were reviewed in the Process Characterization GAP Assessment
- Several "walk-throughs" of Process elements and flows were done to develop the final flows that identified the Critical Process elements.

"As Is"
Process & Product Characterization 3/5

- Results of QbD and Risk Based Process Characterization GAP Assessment provided:
  - Baseline reference of Process Characterization
  - Clear ranked view of each Process Step
  - A detailed, multi-page Process Flow chart depicting all key process steps and the respective CQAs, CMAs and CPPs.
  - Raw Data Integrity and documentation of resolved and unresolved Process Characterization Issues
  - Risk Ranking of the unresolved Process Characterization and Data Integrity issues
  - Prioritized Project Plan to effectively remediate the ~25 High Risk items of the >350 unresolved Characterization Issues

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"As Is"
Process & Product Characterization 4/5

- The Science and Risk Based QbD GAP Assessment illuminated:
  - Project Team's vertical and horizontal knowledge
  - The Key/Critical Product and Process elements
    - CQAs
    - CMAs
    - CPPs
    - Control Strategies

"As Is"
Process & Product Characterization 5/5

- Identification of CQAs, CMAs, CPPs, and Control Strategies streamlined and focused the following needs:
  - Basis of Process Validation
  - CMC Submission Content
  - Raw Data Integrity and Compliance

"As Is" P&P Characterization EXAMPLE

COMPANY X DPXXX Product/Process
Companion Document t
- Traceability of Changes
Work in Pro
As of 22Mar

Note: The table below covers more than 7 years of DPXXX deve
Given that fact, a practical and reasonable "can do" path forward to address all the

COMPANY X DropBox Document	Assessment Observation & Recommended Remediation	Risk Rank	COMPANY X' Selected Remediation(s)	Raw Data Record Located & Where Archived
CMC Summary PPT	Was this PPT Slide Deck shared with any Regulatory Body or Agency? List to whom and when, as must then be able to defend what each Body/Agency has received.	Low Needed before BLA		Confidential discussion
	Culture Medium Initial Bx Charge DOCUMENT NAME pg 2 of 105	Medium		
	Slide #1: Need Protocols, Reports, and Raw Data that justify content.	High		
	Slide #3: Need Protocols, Reports, Raw Data, and Change Management Documents for Dev Work of xL - xxL Bx @ COMPANY X.	High		
	Slide #3: Need Protocols, Reports, Raw Data, and Change Management Documents for Dev Work of XXXL & XXXL in XXXXL SUBs @ CMO.	High		
	Slide #3: Need Visual TimeLine displaying Changes by Segments and 3-5 word phrase of purpose: 1) Pre Nov 2006 2) Nov2006 - Aug2008 3) Aug2008 - Feb2010 4) Feb2010 - Dec2010	High		
	Slide #3: There are XXXL SUB Batches E01 & G01, what happened to F01?	Low Needed before BLA		
	Slide #3: What are the CQAs/CMAs for the XXXL & XXXL in XXXXL SUBs.	High		
	Slide #3: Need to confirm and provide better traceability to MCB & WCB claims to the Mfg Records and Controlled Freeze, Storage, and Storage Integrity.	High		
	Slide #3 & Slide #5: Need copy of the Immunogenicity Investigation Change Management as well as the stated Claims confirmed traceability to Raw Data and alignment with DPXXX Dev Pharm Effect 1 File in DropBox. (Root Cause, Remediation(s), Implementation Effectiveness Documented Confirmation, Impact to Ref Std and P1/P2 Effectivity & Safety Results).	High		
	Pre-Culture (Seed) DOCUMENT NAME pg 2 of 120 1 Vial Expansion xx mlL SF xx mL SF xx mL SF X L BioRx xxL WB xxL WB	High		

QbD Development & Validation Roadmap 1/3

- Science and Risk Based QbD Roadmap is Driven and Justified by:
  - CQAs
  - CMAs
  - CPPs
  - and resulting Control Strategies
- Requires Incorporating Project Team Iterative Interactions

QbD Development & Validation Roadmap 2/3

- Establishes clear Science and Risk Based Rationale for:
  - Streamlined Process Validation and Compliance Traceability
  - Content and Justification of each Commissioning, Verification or Validation activity
  - What Raw Data must be collected;
    - How, Why, and ROI
    - Clear traceability to each respective Roadmap element

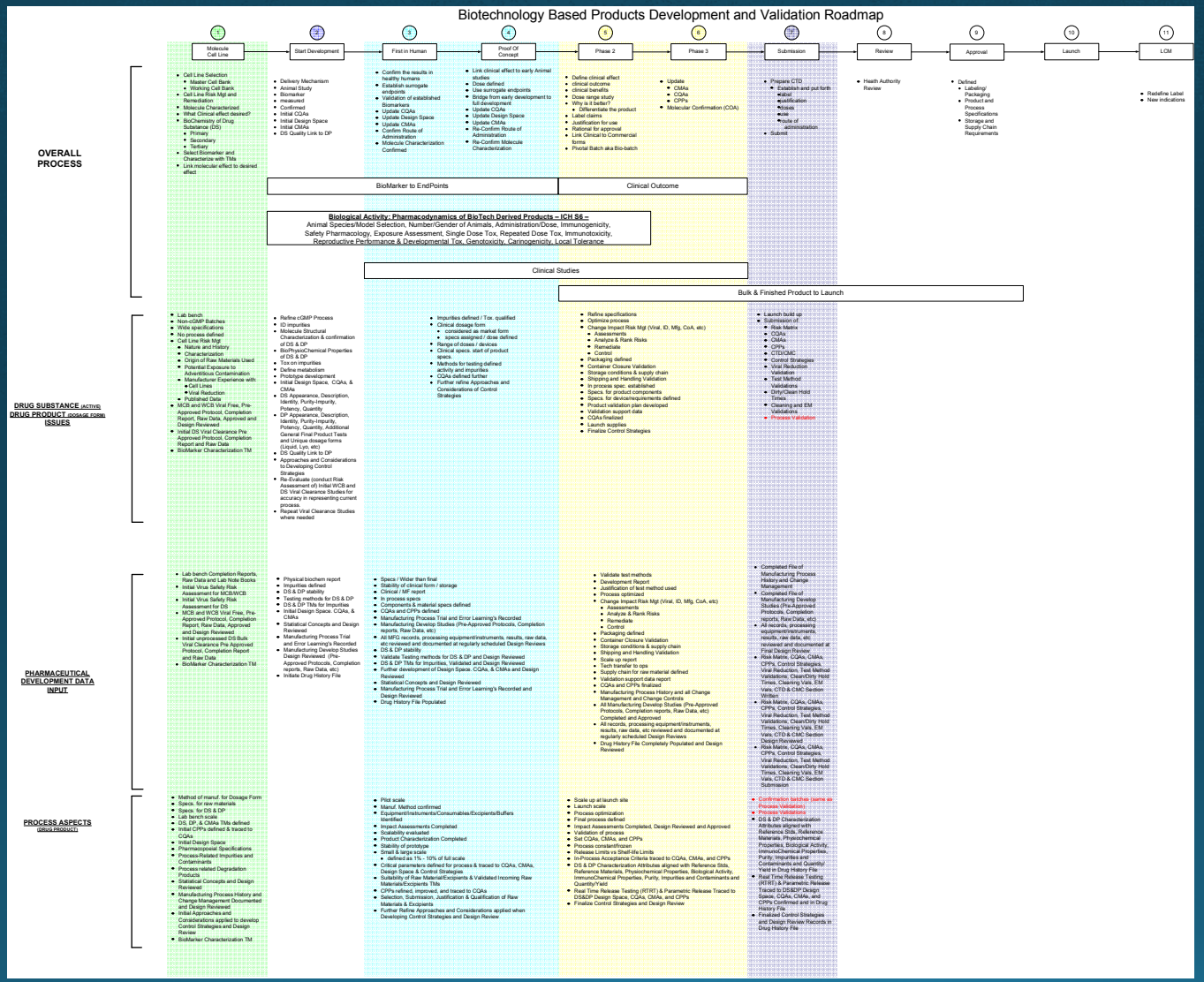
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QbD Development & Validation Roadmap 3/3

- Essential Re-Use
  - Results in Consistent, Streamlined and Compliant Development of:
    - Current Product/Process
    - Future Product/Process
    - Pre-Launch Process/Product Improvements
    - Post Launch Problem Root Cause Identification, Remediation and Effectiveness Justification

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Roadmap Example



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Key Risk factors for Virtual Company with CMO Validation 1/4

- Expected verses Actual GAPs Identified
  - Actual CMO Process Validations were compared with Expected Process Validation CQAs, CMAs, CPPs, and Control Strategies
  - Expected CQAs, CMAs, CPPs, and Control Strategies vetted with Project Team

Key Risk factors for Virtual Company - CMO Validation – 2/4

- Provides Common Ground for alignment with CMO
  - GAPs Readily justified per CQAs, CMAs, CPPS and Control Strategies

Key Risk factors for Virtual Company - CMO Validation – 3/4

- CMO Process Validation Revised and Streamlined:
  - Science and Risk Based
  - Driven by CQAs, CMAs, CPPs, and Control Strategies
  - Incorporates Project Team Iterative Interactions

Key Risk factors for Virtual Company - CMO Validation – 4/4

- Revised and Streamlined CMO Process Validation also provides:
  - Raw Data for Virtual Company QbD CMC and Drug History File
  - Reusable approach as it is now included as an element within the Roadmap and future CMO Contracts

Refined Process Flow includes: CQAs, CPPs, & CMAs 1/2

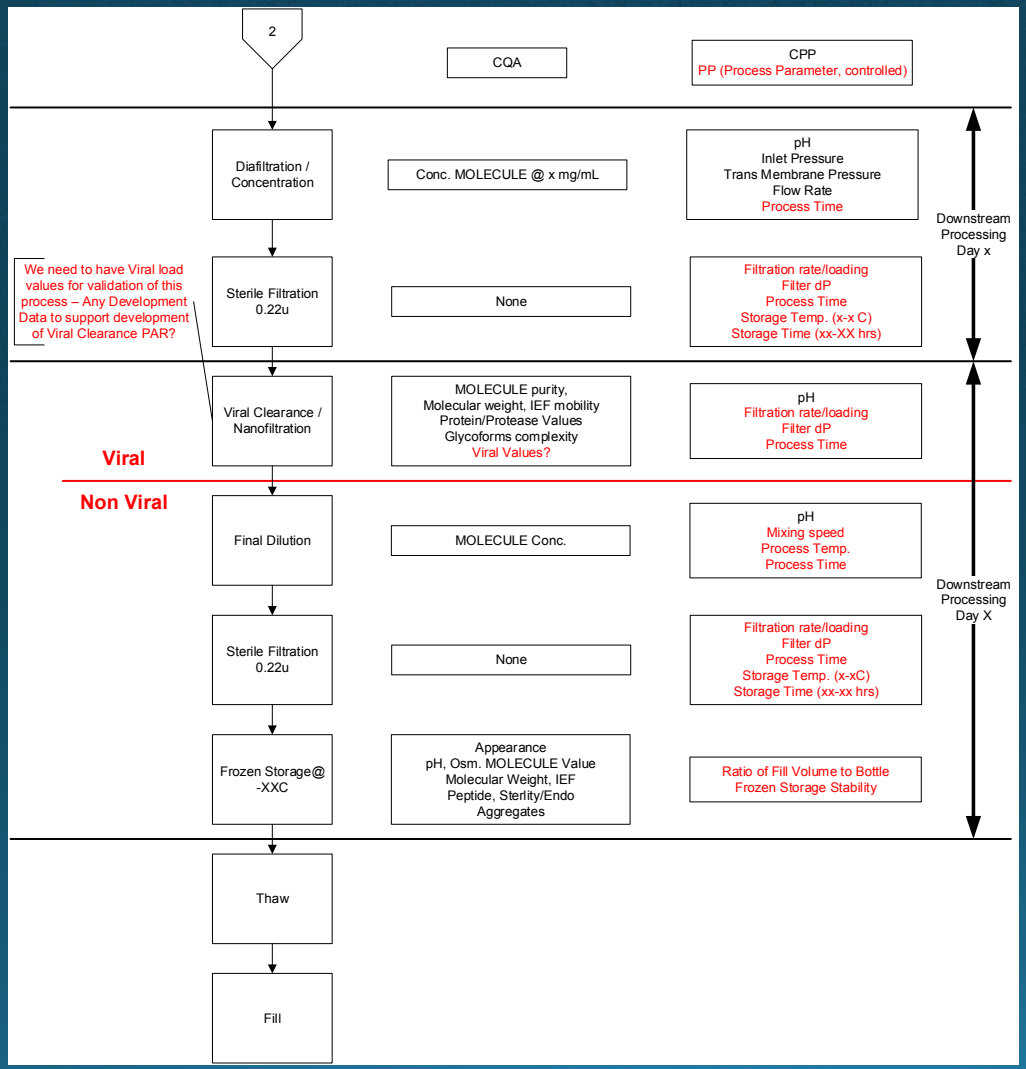
- Process Flow Diagram(s) focused on the "significant few" steps
  - Ease of Use
  - Ease of Readability
  - One-third the size and only CQA, CMA, CPP, Control Strategy Steps

How ?

Refined Process Flow includes: CQAs, CPPs, & CMAs 2/2

- By including ONLY Process Steps associated with CQAs, CMAs, CPPs and Control Strategies
- Includes Project Team Iterative Interactions

Refined Process Flow EXAMPLE



CMC Updated for Final BLA 1/3

- CMC Submission:
  - Refined and streamlined to only one-half the original size
  - Incorporates Project Team Iterative Interactions
  - Includes refined Process Flow Diagram
  - Content follows refined Process Flow Diagram

CMC Updated for Final BLA 2/3

- Raw Data and need for Raw Data Integrity directly traced to and justification for content of refined Process Diagram

CMC Updated for Final BLA 3/3

- All Product and Process Changes Streamlined and Compliant per:
  - Institutionalized Knowledge within Project Team and Company Stakeholders
  - Process Diagram and Roadmap
  - CQAs, CMAs, CPPs, and Control Strategies
  - Science and Risk Based QbD Process Characterization
  - Linked examples\DPXXX Process and Product Characterization Assessment Report Final.doc

Questions?

Thank You !

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