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PDA Parenteral Drug Association

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PCMO[SM] (Paradigm Change to Manufacturing Operations) *Process Validation and Verification: A Life- cycle Approach*

Preview of New PDA Technical Report on Process Validation

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NE-PDA
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Process Validation and Verification: A Life-Cycle Approach

Presentation Contents

- Background and Technical Report Status
- Overview of Process Validation Lifecycle Concept
- Summary of PV Lifecycle Requirements by Stage
  - Stage 1: Process Design
  - Stage 2: Equipment and Process Qualification
  - Stage 3: Continued Process Verification
- Team Members

Background

- Paradigm Change in Manufacturing Operations (PCMO)
  - o PDA initiative; launched in 2008
  - o Implementation of scientific application of ICH Q8, Q9,Q10
  - o Emphasis on “Lifecycle” concept
  - o Establishment of “best practice” documents and training
  - o Teams currently addressing 16 different topics
- New FDA Guidance Document on Process Validation
  - o Draft Guidance in Nov 2008; Final Guidance in Jan 2011
  - o Emphasis on “Lifecycle”; “Scientific Justification”; “QRM”

Background

- Previous PDA Technical Reports Related to Process Validation
  - TR 14: Validation of Chromatographic Separations for Protein Purification (1992; updated in 2009)
  - TR 15: Validation of TFF for Biotechnology Applications (1992, updated in 2009)
  - TR 42: Process Validation of Protein Manufacturing (2005)

Technical Report Status

- Team Established in Fall 2009
  - 35 Contributors
  - Representing 24 Companies
- Co-Leaders
  - Scott Bozzone – Pfizer
  - Hal Baseman – Val Source
- General Approach
  - Sub-Teams develop report chapters
  - Teleconferences and Face-to-Face Meetings
  - Review at PDA Meetings & Peer Review
- Status
  - Peer Review completed (40 reviewers; 1100 comments)
  - Final Draft being compiled
  - Publication Target: end Q2 2012

Process Validation Lifecycle Stages

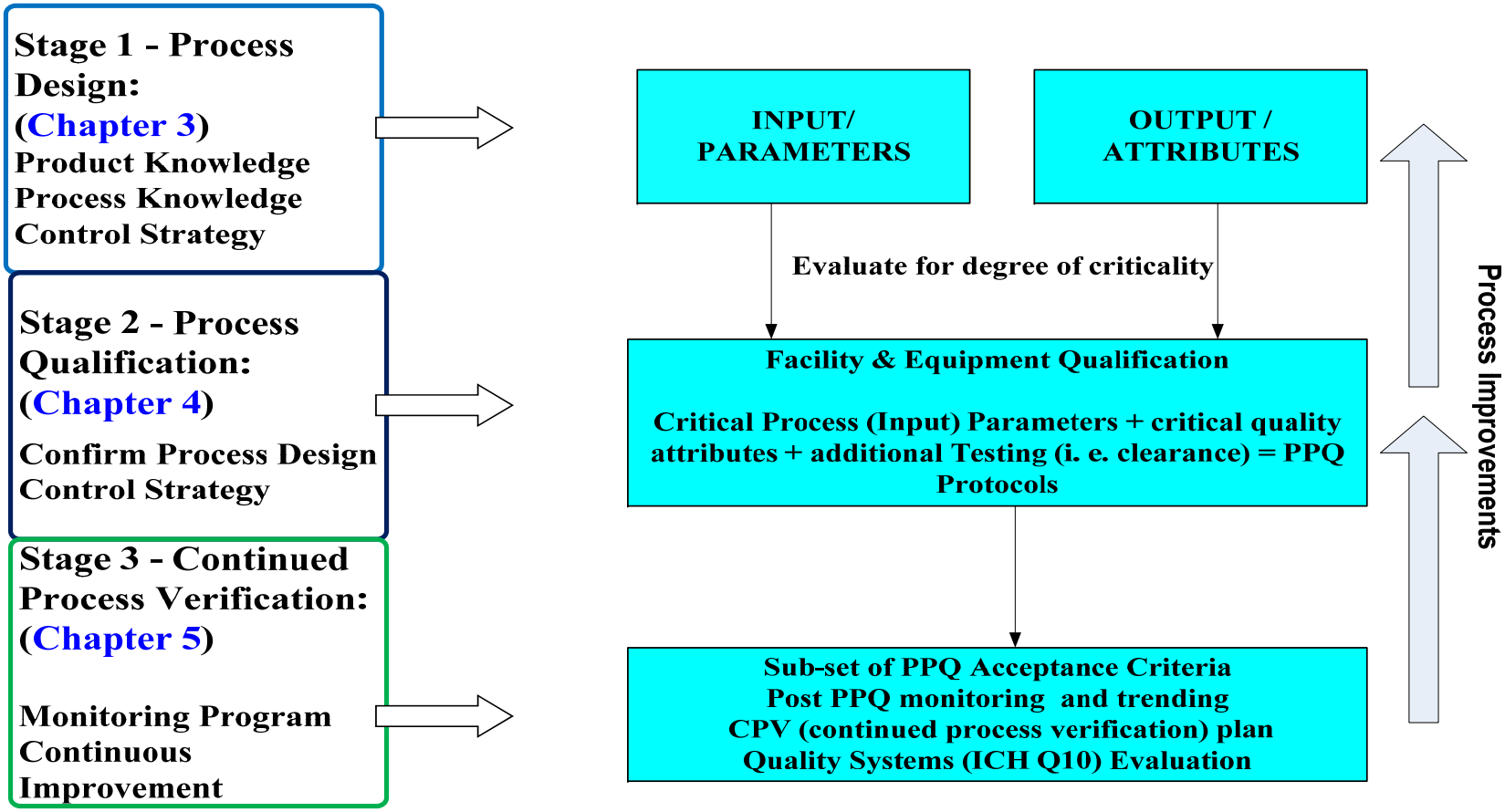

Figure from draft Technical Report

TR Organization

- Report organization reflects concepts introduced in FDA January 2011 Guidance
  - Introduction & Glossary
  - Stage 1 – Process Design
    - Building Product & Process Knowledge
    - Developing a Control Strategy
  - Stage 2 – Process Qualification
    - Equipment & Utilities Qualification
    - Process Performance Qualification
  - Stage 3 – Continued Process Verification
  - Tools (Risk Assessments, Statistics…)
  - Examples

Stage 1: Synopsis of Content

Deliverables at the end of Stage 1 listed and discussed

- Quality Target Product Profile (required at start of Stage 1)
- Critical Quality Attributes (with corresponding Risk Analyses)
- Process Descriptions; Flow Diagrams
- Analytical Methods
- Process Characterization Reports (Design Space; Parameter Ranges)
- Risk Assessments and Criticality Determination
- Control Strategy
- Characterization Test Plan
- Scale-up / Scale Down Approach (evaluation of lab models)
- Batch Records (Pilot, Clinical Manufacturing experience)

Stage 1: Development of a Control Strategy

- Elements of a Control Strategy
  - In-Process and Release Specifications
  - In-Process Controls
  - Process Parameter Acceptable Ranges (or Design Space)
  - Performance Parameter Acceptable Ranges
  - Stability (Intermediates, DS, DP, Process Solutions)
  - Raw Material Specifications and Impact of Variability
  - Process Analytical Technology (PAT)
  - Comprehensive Process Monitoring Plan

Stage 2 – Synopsis of Content

Activities included in Stage 2:

- Facilities / Utilities / Equipment Design and Qualification
- Equipment Capability Assessment
- Process Performance Qualification (PPQ)
  - Scale
  - Strategy & Approaches
  - Types of Studies
  - Setting Acceptance Criteria
  - Determining Number of PPQ Batches
  - Sampling, Testing, and Analysis
  - Documentation

Determining the Number of PPQ Batches

Three batches no longer the default number!!

Factors to consider include:

- Level of Risk for Process
  - Process Knowledge
  - Product Knowledge
  - Control Strategy
  - Novelty of Process / Unit Operations
  - Process Fit with Facility/Equipment
- Past experience / track record for organization
- What is being proven / demonstrated
- Statistical metrics being employed (intra-batch variability; inter-batch consistency)

Stage 3: Synopsis of Content

- Aspects of Continued Process Verification
  - Strategy
  - Developing the Process Monitoring Program
  - Data Analysis and Trending
  - Utilizing CPV Data
  - Documentation
  - Addressing Legacy Products
  - Change Control and CAPAs

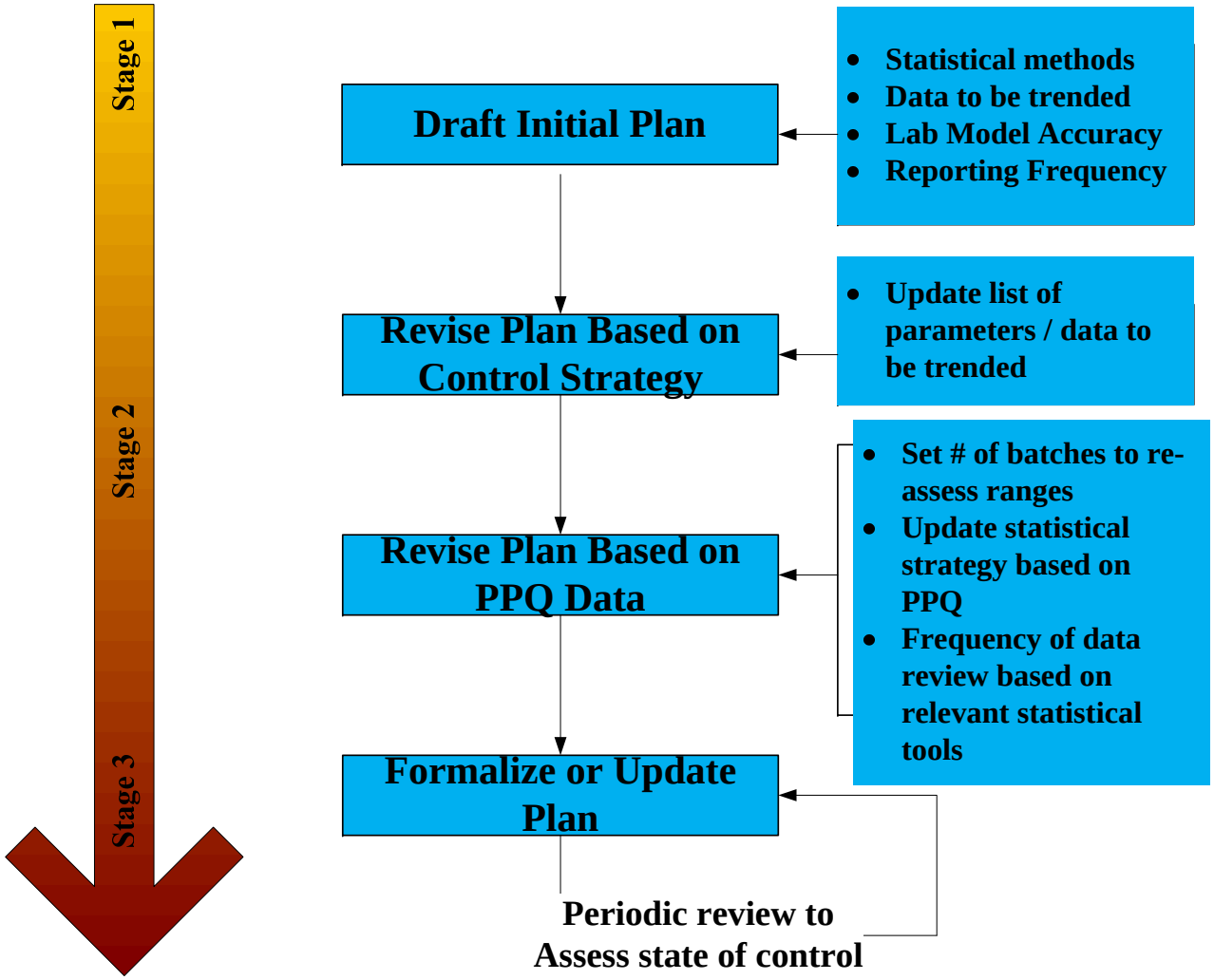

Figure from draft Technical Report

Tools for the Process Validation Lifecycle

- Quality Risk Management
  - Modeling Uncertainty
  - Risk Tools that can be applied to:
    - Process Understanding
    - Control Strategy
    - Facility Design & Verification
    - Raw Materials
    - Commercial Manufacturing and Monitoring (CPV)
- Statistical Analysis Tools
  - Design of Experiments (DOE)
  - Statistical Process Control (SPC) and Process Capability
  - Control Charts
  - Statistical Acceptance Sampling
  - Determining Number of Lots for Stage 2 PPQ

Tools for Analyzing Lot-to-Lot Variability

- Average run length to detect a lot failure
- Selecting range of inter-lot variation to be covered
- Normal tolerance intervals within and between lots
- Statistical Process Control Charts
- Process Capability Metrics
- Lot Conformance Rate at selected confidence level
- Wald sequential probability ratio
- Narrow limit gauging
- Comparison of between and within lot variation
- Demonstrating between lot std deviation at or below target
- Demonstrating lot-to-lot equivalence

Examples – Application of Concepts in the Guidance

- Biotechnology Product (monoclonal antibody)
- Radio-pharmaceutical
- Solid oral dosage form

Team Members

Name & Role		Company	Name & Role		Company
Scott Bozzone	Co-Lead	Pfizer	Igor Gorsky	Ch 6	Shire SP
Hal Baseman	Co-Lead	ValSource	Alpaslan Yaman	Ch 6	BPD Consulting, LLC
Julie Spyrison	Proj Mgr	BioTechLogic, Inc.	Mark Varney	Ch 6	Abbott
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Regina Pharis	Tech Writer	-------	Steve Duffy	Example	Covidien
Peter Levy*	Ch 3 co-lead	PL Consulting, LLC	John McShane	Co-Lead	Roche-Genentech
Praveen Prasanna	Ch 3 co-lead	Shire HGT	Jose Luis Ortega	Chap 3	Pharma Mar S.A.
Raj Jani	Ch 4 Lead	Baxter Healthcare	Norbert Hentschel	Reviewer	Boehringer Ingelheim
Panna Dutta	Ch 4	The Medicines Co.	Chris Ames	Reviewer	Genzyme
Rebecca Devine	Various	Consultant	John Bennan	Reviewer	Compliance Net
Wendy Lambert	Ch 1 + other	Abbott	Morten Munk	Reviewer	CMC Biologics
Vijay Chiruvolu	Various	Amgen	Laura Lei	Reviewer	Baxter Healthcare
Kurtis Epp*	Ch 5 Lead	BioTechLogic, Inc.	Iolanda Teodor	Reviewer	Baxter Healthcare
Michael Blackton	Ch 5	ImClone Systems	Kris Barnthouse	Reviewer	Centocor (J&J)
Elizabeth Plaza	Ch 6 Lead	Pharma-Bio Serv	Markus Schneider	Reviewer	Novartis Pharma AG
Pedro Hernandez	Ch 6	PHPD Consultants	Victor Maqueda	Reviewer	Consultant
Irwin Hirsh	Ch 6 QRM	NovoNordisk	Joanne Barrick	Reviewer	Eli Lilly
EJ Brandreth	Ch 6	Althea Technologies			

*ISPE Liaisons

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Thanks for your attention

Questions?

Comments?

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