Current Industry Practices in Manufacturing Process Validation

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- **The objectives for validation are:**
  - ***Demonstrate control over the process and finished product.***
  - ***Demonstrate that the process will consistently produce product which meets all specifications and quality attributes.***
  - ***Generate a knowledge base for the product as well as accommodate any further business needs.***

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FDA instructs investigators to look for a series of product information during PAIs. The source of these data may vary but the information needed may be listed as:

- **Drug substance characterization**
- **Process procedures**
- **In-process tests**
- **Finished product specifications**
- **Dissolution profiles**
- **Stability**

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Manage Process Validation as a Continuum

1. **Utilize a DOE mentality for development batches to identify parameters and interactions for all process steps.**
2. **Early stages for formulation and process steps are established as the basis for refinements.**
3. **Subsequent pilot scale batches further add to the knowledge base for process steps and parameters used.**
4. **Product introduction at or near commercial scale at the launch site to further enhance the data base (Bio Batch).**
5. **Accumulated process knowledge forms a sound strategy to carry out the validation campaign.**

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The continuum may be thought of as several components:

1. Conventional Aspects
   - Development Reports, Stability Reports
   - Validation Protocol, Validation and Scale-Up Reports
2. Enhancements
   - Proven Acceptable Ranges
   - Quality Risk Analysis
   - Process Comparability

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Process development should be used as a platform to establish proven acceptable ranges starting early in the development cycle.

- ***Proven acceptable ranges:***
  - **Provide a historical database for the product.**
  - **May start at a broad range during the early stages which are subsequently tightened.**
  - **Require a systematic reporting method which is referenced during pilot scale, scale-up and validation.**
  - **Become a part of the knowledge store for the product and basis for statistical process control.**

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Proven acceptable ranges (continued):

- **Establish a chart for all process steps and controllable parameters.**
- **Brief description of the process step and controlled parameter.**
- **The engineering units which are recorded.**
- **The anticipated result for exceeding the proven acceptable range.**
- **Risk evaluation of exceeding the range is it major or minor.**

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Proven acceptable ranges (continued):

- **Establish the operating range to be utilized in the plant for process control.**
- **The proven acceptable range is documented. It may be referenced in the development report, batch records, validation reports and protocols.**
- **Acceptable ranges which are dependent on scale changes may be listed as to be determined (number of spray guns, FBD air volumes).**

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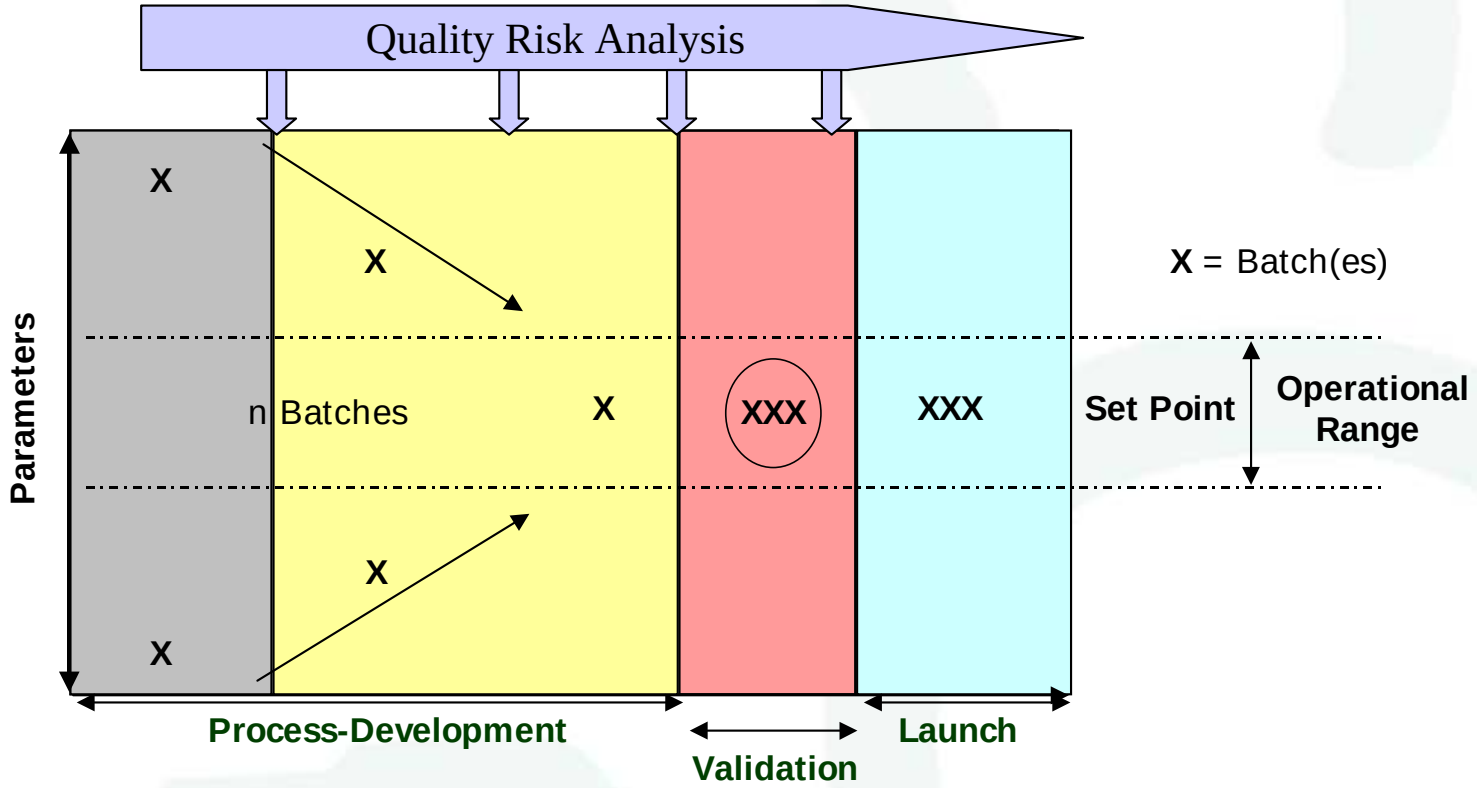

Validation: specified parameters at operational range if required (by operations).

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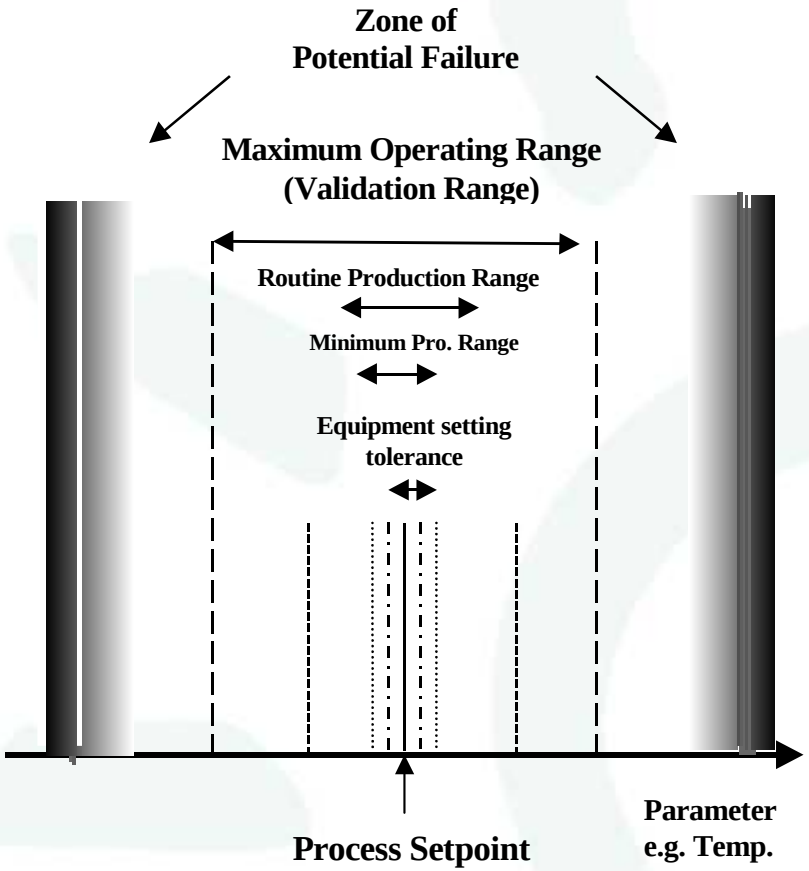

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Establish both a *good scientific* and *common sense* approach to rate each process step as having high, low or no impact on product quality.

This will aid in minimizing the subsequent validation effort (SUPAC equipment terms add clarity).

Critical area checklist:

- **Weighing / addition of raw materials (vendors, personnel)**
- **Pre-blending of materials (volume, bulk density)**
- **Granulation (speed, rate of addition, time)**
- **Drying (LOD, time, temperature)**

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Critical area checklist (continued):

- **Particle size reduction (screen, feed rate, speed)**
- **Blending / lubrication (time, bulk density, assay)**
- **Compression (speed, feed rate, force)**
- **Coating (suspension prep., endpoint, air flow, temperature, spray rate)**

This provides for subsequent data review for traits and atypical behavior. Data may be shown graphically to identify process variability within established specifications (process comparability).

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While it is not required, the completion of validation prior to filing would appear as the most expedient means to assure rapid market entry.

- **This view may not be acceptable to all the players but it seems a logical strategy.**
- **The hypothesis is that validation is just one step in the journey to 100% business efficiency (Peak Sales!)**

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Establishing a technology strategy which will qualify change in the context of scale-up / transfer as well as possible post approval changes expedites product development and shortens approval time.

Effort spent in creating an IVIVC relationship early in the development cycle is well placed.

- **While not always possible it will yield benefits for formulation and process optimization and the creation of meaningful specifications.**
- **The data will be specific to the formulation in question which may be considered a downside.**

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An IVIVC strategy makes it part of the methods used to guide formulation development.

IVIVC Strategy:

- **At the product concept phase use a target in vivo profile and base in vitro specifications on an assumed IVIVC. The prototype is tested using various dissolution methods.**
- **The result will be a comparison of dissolution methodology with biodata allowing an IVIVC to be established.**

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IVIVC Strategy (continued):

- **During optimization of the formulation / process the IVIVC is defined and predictions from the IVIVC validated.**
- **During scale-up the dissolution data are used to judge the impact of process changes as well establishing final specifications for dissolution.**
- **The database may be utilized during further scale-up and site transfer as well as supporting post approval changes.**

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How do we look for the 21st Century?

- **Working continually to fully understand our processes and making them efficient.**
- **The development procedure used provides a guide to potential sources for process variability and risk assessment.**
- **The process incorporates the latest technology and provides innovative quality driven product results with a continuous improvement dimension.**

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How do we look for the 21st Century?

- **Establish product specifications based upon our understanding of the formulation and process (IVIVC).**
- **Product knowledge as a process control such as SPC applications during encapsulation and compression.**

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Where are we going?

- **Technologies with future PAT application have been put in place.**
- **Theses include**
  - **Vision systems**
  - **Endpoint control (fluid bed drying)**
  - **Compression control (feedback systems)**
  - **Process Chromatography control**
  - **NIR for drug substance, excepients and in process materials**

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References

R. Kieffer, L. Torbeck, Pharmaceutical Technology, 6, 66 (1998)

J. Butler, The Pharmaceutical Journal, 1, 31 (1999)

Guide to Inspection of Solid Dosage Forms Pre/Post Approval Issues for Development and Validation, Issued January, 1994

P. J. von Dochren, R. St. John Forbes and C. D. Shively, Pharm Tech, 6, 139 (1982)

K. D. Popp, Drug Dev. And Ind. Pharm., 13, 2339 (1987)

K. Chapman, R&D to Manufacturing, ERIPT Meeting, 1983

R. Somma, Technology Transfer, The International Experience, EPTM Meeting, 1990

R. Somma, The Research-Production Interface, AAPS Annual Meeting, 1995

D. Ellsworth, Pharmaceutical cGMP's for the 21st Century: A Risk Based Approach May,2003

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References

G.Migliaccio, Manufacturing Science, June, 2002

A.H.Kibbe, Process and Analytical Validation Working Group, June, 2002

A.S. Hussain, The Subcommittee on Process Analytical Technologies (PAT): Opening Remarks, June, 2002

G.K.Raju, Laying The Foundation for a “CAMP” Response, March, 2003

F.Erni, PAT Meeting, Novartis US, April, 2003

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