Current Considerations for Manufacturing Processes in Prescription Drug Applications

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Discussion Points

- Introduction
- Understand what manufacturing information is expected in an application
- Recognize when the manufacturing information in an application is inadequate
- References
- Conclusion

How the customer explained it

How the project leader understood it

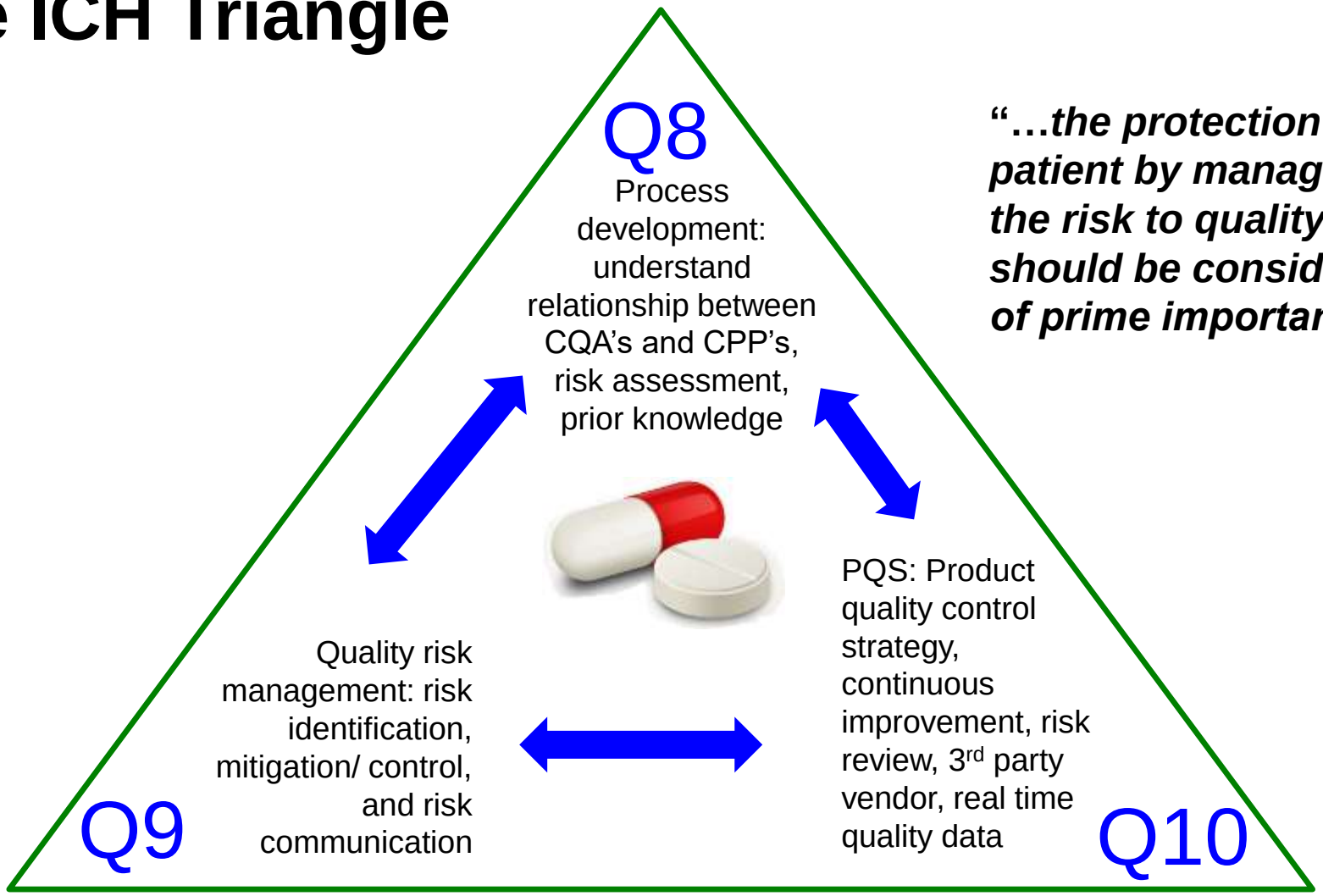
How the analyst designed it

How the business consultant described it

How the programmer wrote it

What exactly the customer wanted

The ICH Triangle



"…the protection of the patient by managing the risk to quality should be considered of prime importance."

3.2.P.2 Process Development

The process development (PD) section facilitates the evaluation of the commercial process for robust manufacture of quality drug product over the product life-cycle

Process and Equipment Selection

- Scientific rational for process selection
  - Initial risk assessment (RA) to identify high risk steps linked to product critical quality attributes (CQA)
- Developing an effective process control strategy
  - Process development studies, design of experiments
    - Identify process parameters and material attributes that impact quality attributes of intermediates and final product
  - Establish appropriate operating ranges/design space and process controls to obtain acceptable quality product
  - Update RA with risk mitigation approach and residual risk
  - Summarize critical studies, how the commercial process was arrived at, and how it is controlled to mitigate risk

Control of API and Raw Material Quality

- Summary of key material attributes that impact intermediate and/or final product quality. E.g.,
  - Particle size distribution, moisture level
  - Polymer mol. wt., viscosity, degree of substitution
  - API assay, polymorphism, physical properties, etc.
- Impact of raw materials and intermediate attributes/variability on subsequent steps
  - Examples: Bead assay and encapsulation, bead particle size distribution variability, segregation potential
- Establish appropriate controls

Scale-up Risk/Tech Transfer

- Brief summary of process scale up approach
  - Scale up factors - dimensionless numbers, models, etc.
  - Verification of the design space at commercial scale, if a design space is proposed
- Master batch record, is it different than executed batch record
- Summaries of (tables useful)
  - How the process parameters were adjusted across pilot/registration and commercial scale
  - Equipment differences, batch size, yield
  - Comparison with the executed batch

3.2.P.3: Process Description

Batch formula

- Batch formula should be consistent with clinical/registration batches (P1) and master batch record
- Clearly define the commercial batch size, including any,
  - Batch size variation, use of sub lots, etc.
  - Adjustment for API potency
  - Overages and manufacturing excess with rational
- Note any difference in the commercial batch formula from the clinical or registration batches

Manufacturing Process

- Comprehensive flow diagram
  - Complex processes may require multiple schematics for process sections
- Appropriate description of the process
- List of commercial equipment
- Include process parameters and ranges
- Justification - if there are significant changes to clinical/registration and commercial process
  - Discussion/supporting data on how changes are bridged
- Summary tables are useful

Manufacturing Process (contd.)

- In-Process Controls

  - List method, acceptance criteria, and rational
  - In-line/at line/online PAT tools, RTRT
  - Provide the sampling strategy
  - Note any difference in IPC between registration and commercial, including any deviations
  - Open discussion of proposed changes to IPCs after approval; also note the proposal in the IPC table
    - E.g., removing an IPC or widening the acceptance criteria
    - Avoid burying proposed changes in tiny footnotes
  - Information could be summarized in a table

Additional Considerations

- Process Validation (PV)
  - Sterility validation for sterile products
  - PV Protocol
- Lifecycle consideration
  - Comparability protocols (CP), if any
    - Clearly describe proposed change, and include all tests and acceptance criteria used to bridge changes
    - Insufficient detail or nonspecific CPs can hinder approval
  - Life cycle risk management
  - Post approval commitments (New Drug Applications)

Observations of Process Inadequacies

- Lack of or insufficient process development data
- Insufficient process controls or lack of information
- Proposed process parameter ranges are not supported by information/data
- Absence of the master batch record
- Process not scaled up or scale-up approach not provided
- Inadequate bridging data/information to support significant differences between clinical/registration and commercial processes

References

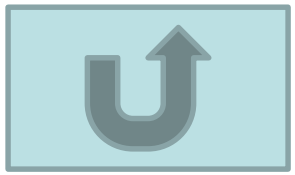
- CFR 21 Part 312.23 (7), 314.50
- CFR 21 Part 11, 210 & 211 - GMP
- eCTD Module, its structure and requirement
- ICH Q8, Q9 & Q10
- FDA Guidance for Industry

Conclusions

- Information submitted in the drug application serves as a knowledge bridge between the Agency and the Industry
- Processes are evaluated for their ability to manufacture quality drug products consistently
- Provide appropriate level of critical information with supporting data to demonstrate manufacturability and process robustness
- A comprehensive original application minimizes information requests and enhance first cycle approval

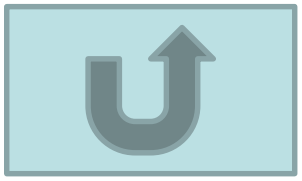
Example: Process Risk Assessment

	Unit operation -1	Unit operation -2	Unit operation -3	Unit operation -n
CQA-1	L	L	M	L
CQA-2	L	H	L	L
CQA-3	M	L	H	M
CQA-n	L	L	L	H



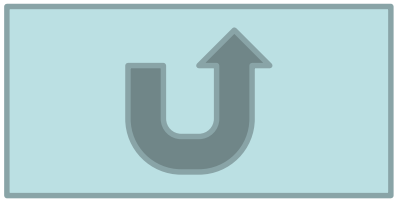
Summary Tables for Process

- Comparison between pilot, clinical, BE, stability, registration & commercial batches
- Equipment
- Process parameters: target and ranges
- Design space (if any)
- Use of PAT, RTRT
- Batch size, yield
- In-process tests



In Process Control

Step	Control	Acceptance Criterion	Summarize Registration Batch Results	IPC Differences between registration and commercial
Ex. Blending	BU	Xxx	Yyy	Zzz
Ex. Drying	LOD	Xxx	Yyy	Zzz



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Thank You

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