WHO Prequalification Programme: Priority Essential Medicines

Quality by Design (QbD) and Pharmaceutical Active Ingredient Manufacture

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In this presentation:

• An introduction to QbD and why regulators see it as important
• QbD in FPP development and production and its impact on the API and excipient manufacturer
• QbD in API development and production
ICH Q8
Pharmaceutical Development

• “Quality cannot be tested into products; quality should be built-in by design”

• Introduces a new (optional) development paradigm, Quality by Design (QbD), a systematic approach to pharmaceutical development.
Development of the drug product

Pharmaceutical Products are of good quality
   – End-product quality is not the issue?

• **But pharmaceutical development and manufacturing could be improved**
  • Batch failures and reworks
    • 5-10% of the pharm. batches have to be discarded or reworked
  • Long cycles times
  • Manufacturing processes often “frozen” following regulatory approval
  • Opportunities for improvement offered by new technologies are often missed
Current state

<table>
<thead>
<tr>
<th>Sigma</th>
<th>ppm Defects</th>
<th>Yield</th>
<th>Cost of Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>2σ</td>
<td>308,537</td>
<td>69.2%</td>
<td>25-35%</td>
</tr>
<tr>
<td>3σ</td>
<td>66,807</td>
<td>93.3%</td>
<td>20-25%</td>
</tr>
<tr>
<td>4σ</td>
<td>6,210</td>
<td>99.4%</td>
<td>12-18%</td>
</tr>
<tr>
<td>5σ</td>
<td>233</td>
<td>99.98%</td>
<td>4-8%</td>
</tr>
<tr>
<td>6σ</td>
<td>3.4</td>
<td>99.99966%</td>
<td>1-3%</td>
</tr>
</tbody>
</table>

6 σ - World class
5 σ - Superior
4 σ - Healthy
3 σ - Average
2 σ - Not capable
1 σ - Not competitive

Table from: PriceWaterHouseCoopers, 2001, Productivity and the Economics of Regulatory Compliance in Pharmaceutical Production
Uncontrolled variability in e.g. properties of the starting materials or the manufacturing process affects the quality of the medicinal product.
How can variability be reduced?

By obtaining increased process and product understanding in order to identify and appropriately manage critical sources of variability and hence achieve “right first time” performance.

Need for a shift in paradigm:

From compliance

To enhanced product and process understanding that will allow design of effective and efficient manufacturing processes and "real time" quality assurance
Process Analytical Technologies (PAT)

- A system for designing, analysing and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.

- PAT is a useful tool to achieve the desired state.

**PAT tools**
- Multivariate tools for design, data acquisition and analysis
- Process analyzers
- Process control tools
- Continuous improvement and knowledge management tools

**The focus is on Process/ Product Understanding**

**not on advanced online monitoring of the process**
Quality by Design (Q8 R2)

• “A more systematic approach to development (also defined as quality by design) can include, for example, incorporation of prior knowledge, results of studies using design of experiments, use of quality risk management, and use of knowledge management (see ICH Q10) throughout the lifecycle of the product.”

• “Such a systematic approach can enhance achieving the desired quality of the product and help the regulators to better understand a company’s strategy. Product and process understanding can be updated with the knowledge gained over the product lifecycle”.
How to deliver the desired state?

Invest in Pharmaceutical Development

- Identify critical material and process parameters affecting product quality (using prior knowledge, risk management tools, DOE, MVA)
- Understand and if possible express mathematically their relationship with the critical quality attributes
- Design a process measurement system to allow on-line or at-line monitoring of critical quality attributes
- Design a control system that will allow adjustment of critical quality attributes

Implement a quality system that allows continuous improvement
3rd step: Knowledge baseline

- Gather existing knowledge
  - Include all sources of knowledge (internal reports, historical production trends, scientific publications for similar processes/products)

- Identify product and process parameters that might affect product quality (Fish-bone diagram)

- The goals of this step are to:
  - Identify the Risk associated with the existing process
  - Identify the knowledge gaps
Identify CPPs
Fishbone diagram

CQAs

Drying
Temp
RH
Air Flow
Shock Cycle

Analytical
Sampling
Method

CQAs

Plant Factors
Operator
Temp/RH
Training

Compressing
Precompressing
Main Compressing
Feeder Speed
Press Speed
Punch Penetration
Depth
Tooling
Feed Frame

Granulation
Power Time

Raw Materials
Water
Binder
Spray Rate
Spray Pattern
P.S.
Scrape Down
Chopper Speed
Mixer Speed

Drug Substance
Age
Process
P.S. Conditions
LOD

Other
Disintegrant
Binder

P.S.
LOD

Endgame
Power Time
Develop process understanding - Experiments (DOE)

- Experimental strategy, where the parameters (factors) under study are varied together in a structured way instead of one at a time.
- The experimental data are used to create models that link the factors with the responses.
- Most commonly fitted models: linear or quadratic.
- Compared to one factor at a time:
  - Less number of experiments
  - Identification of interactions between variables
  - Less confounding (if the effects of variables are mixed up, cannot correlate product changes with product characteristics)
  - Identification of relative significance of variables
Example of DOE for the granulation step

Traditional method
Carry out the granulation in a rotor granulator using the following approved ranges
- Rotor speed: 1000-1100 rpm
- Amount of water: 1750 ml ±5%
- Spray pressure: 2.5-3 bar

DOE
Carry out the granulation to create granules at size <criterion> varying the amount of water, mixer speed and mixing time according to the relationship:
Size = f(mixer speed) + f(amount of water) + f(mixing time)
What is the purpose of ICH Q11?

• A new tripartite high level technical guidance harmonising the scientific and technical principles relevant to design, development and manufacture of drug substances as part of a total control strategy designed to ensure product quality and consistency.
  – Harmonisation
  – Facilitate innovative development over the product lifecycle in order to improve product and process understanding
  – No new regulatory requirements
  – Utility for regulators & industry
Why was a new guideline considered necessary?


• Region specific data packages and data presentation
• Differences in data requirement between regions present administrative burden to industry
• Inefficient use of industry & regulatory authority resources

• Application of concepts of the new quality paradigm (ICH Q8, Q9 & Q10) to drug substance
• Facilitate innovation in approaches to development and control of drug substance manufacturing processes, enabled by application of on-, at- and in-line analytical technologies coupled with robust risk management strategies
Scope of Q11

• **In scope:** 3.2.S.2.2 – 2.6 of CTD
  – New Chemical Entities – as defined in ICH Q6A
  – Biotechnological/Biological Products – as defined in ICH Q6B

• **Not in scope:**
  – Clinical trial materials
  – Regional post approval change requirements
What topics are covered in ICH Q11?

- Introduction & scope
- Manufacturing Process Development
- Description of the Manufacturing Process & Process Controls
- Selection of Starting Materials and Source Materials
- Control Strategy
- Process Validation/Evaluation
- Where to file information in CTD
- Lifecycle Management
- Illustrative Examples
- Glossary
Development of the manufacturing process

- Identifying CQA for drug substance in relation to drug product target product profile
- Defining a suitable manufacturing process
- Defining a robust control strategy to ensure process performance and drug substance quality
- Systematic evaluation, understanding and refining of the manufacturing process
  - Use of risk assessment tools, prior knowledge and experimentation to identify the material attributes and process parameters that can have an effect on drug substance CQA
  - Determining the functional relationships that link material attributes and process parameters to drug substance CQA
Information on the manufacturing process

- Summary overview
- Level of detail
  - pivotal v non-pivotal studies
- Relevance of development studies to the commercial process
- Effect of scale
- History of batches produced to date & linked to significant developments in the manufacturing process
- An applicant may adopt either a traditional or enhanced approach to development of the process or a combination of both
Starting / Source Materials

• Different perspectives for small molecule as compared to substances of biotechnology

• For biotech substances, advice concerning cell banks is given in Q5A, B & D

• For small molecules
  – Considerations for selection of a given molecule in the synthetic sequence as the regulatory starting material
  – Reassurance that the defined process and control strategy, operating within GMP will consistently provide drug substance of the required quality
  – Example provided to illustrate application of considerations
Development of the drug Substance

Example 1- Control of hydrolysis impurity in intermediate F

A → Step 1 → B → Step 2 → C → Step 3 → D → Step 4

Purification

Final Drug Substance

R₁ R₃ R₂ R₄

Crude Drug Substance

R₁ R₃ R₄

F → Step 5 → E

World Health Organization

QUALITY MEDICINES FOR EVERYONE
Control strategy for the drug substance

- Controls on material attributes (including raw materials, starting materials, intermediates, reagents, primary packaging materials for the drug substance, etc.);

- Controls implicit in the design of the manufacturing process (e.g., sequence of purification steps (Biotechnological/Biological Products), or order of addition of reagents (Chemical Products));

- In-process controls (including in-process tests and process parameters);

- Controls on drug substance (e.g., release testing).
Control strategy for the drug substance

• Control strategy applies irrespective of development approach adopted (traditional or enhanced)
• Point of application of control may differ depending on the nature of the attribute requiring control and process knowledge as a result of development studies
  – Sterility assurance
  – RTRT
Process validation for the drug substance

- High level overview of approaches to PV
- Includes optionality for ‘traditional 3 batch’ approach and continuous process verification approach described in Q8.
- All manufacturing processes to be validated prior to product commercialisation
- Differences in data requirements at time of MA submission/approval depending on molecular complexity/characterisation (NCE v biotech) and depending on nature of process (e.g. aseptic processing)
Process validation for the drug substance

- Quality risk management & process development
- Critical Quality Attributes
- Design Space
- Control Strategy
Development of the drug substance

Traditional approach uses this information to set target and maximum values (based on business needs & robustness) for time and water content to ensure hydrolysis impurity remains below 0.3%.

Enhanced approach uses 2nd order rate equation to determine relationship of time and water content.

Area below the line is the proposed design space.
Life cycle management

- Continual improvement of the drug substance manufacturing process is facilitated via quality systems elements & management responsibilities described in Q10
- Periodic re-evaluation of control strategy including any design space within the product quality review
- Knowledge management across the product lifecycle – incl supply chain
- Science and risk based approach to evaluation of impact of process changes
- Specific guidance for changes to biotech processes – link to Q5E
- Proposals for management of specific future changes can be included in the original pre-approval dossier – Example 2
- Regional requirements for post approval changes apply