DEFINING AND ENSURING THE QUALITY OF PHARMACEUTICALS

Terrence Tougas
Boehringer Ingelheim, Ridgefield, CT

Dennis Sandell
S5 Consulting, Lund, Sweden
Part A: Defining Quality

Transforming the general concept of Quality into objective, well defined and actionable criteria
“Quality means those features of products which meet customer needs and thereby provide customer satisfaction” †

“Quality means freedom from deficiencies” †

Joseph M. Juran†
Quality = the extent to which a product meets customer expectations.

- For a pharmaceutical product, this should translate primarily into its effectiveness and safety
- Need surrogate end-point(s) to confirm these
- In practice, pharmaceutical quality = the degree with which a product sample comply with requirements
- A more fundamental statement of the expectations on the product/population with respect to the particular quality attribute is missing
- Focus is on the sample rather than the population
Consumers:
- Patient
- Health care provider
- Insurer
- Regulator

Quality Expectations:
- For individual dosage unit
- For the dose
- For the unit (bottle, inhaler, ...)
- For the batch/population
- Something else?

Often a disconnect between meeting QC specification requirements and any direct statement of what this implies for individual units/doses
Defining the Quality of a Pharmaceutical Product

What is our Quality goal?

- Assure all tablets within 45.0-55.0 mg?
- Most tables? On average?

What is meant by labeling? What is the patient/customer expectation?
“Thus, any official article is expected to meet the compendial standards if tested, and any official article actually tested as directed in the relevant monograph must meet such standards to demonstrate compliance.” USP General Notices 3. Conformance to Standards

- Does this provide an unambiguous definition of the expected Quality of a product?
- Is it possible to guarantee adherence to this standard?
- To have some level of confidence of meeting this requirement, release or internal requirements need to be (much) more conservative than the stated USP monograph
Pharmaceutical world in general views Quality with a “Goal Post” mentality.
Quality for most products is better described by the concept of Loss Functions.
There is usually no point where quality abruptly changes from good to bad.

Two discrete levels of Quality: Product work as intended or not at all.

The Quality of a product is optimal at the target value and is gradually reduced when moving away from the target.
The value of reducing the variability of a product/process and the impact on Quality must necessarily consider economic factors.

Follows a “Law of diminishing returns”; i.e., there is not typically a direct relationship between reducing variability and the benefit to patient.

Consider two hypothetical scenarios:

<table>
<thead>
<tr>
<th>NSAID Product A</th>
<th>NSAID Product B</th>
</tr>
</thead>
<tbody>
<tr>
<td>220±5 mg</td>
<td>220.0±0.5 mg</td>
</tr>
<tr>
<td>Cost: $1.00/tablet</td>
<td>Cost: $10.00/tablet</td>
</tr>
</tbody>
</table>

Which product is of better Quality?
Specifications as an Agreement

- All specifications can be viewed as a Quality Agreement between producer and customer(s)
  - Many types of internal and external customers and producers
- Must strike balance between the customer’s need(s) and producer’s ability to make
  - May require negotiations between parties
- Agreement/Specification must be unambiguous
  - Common understanding by both “producer” and “customer”
  - Objective and well defined agreements that are testable
Alternative Definition of Quality based on Population not Sample

- Make Quality statement for the batch/population, e.g.,:
  - Limits/goal posts
  - Required minimum proportion of units within limits
  - Required confidence level (Type 2 error)
- Manufacturer then develops a statistical plan to verify Quality statement
  - Type 2 error (consumer risk) fixed by above Quality statement (and regulatory agreement).
  - Type 1 error (producer risk) driven by the manufacturer’s tolerance of risk for rejecting an acceptable batch
  - Sampling plan, evaluation parameters, critical region
Defining Limiting Quality: Quality Standard expressed as ‘Coverage’

- Lower Limit (LL) < P% < Upper Limit (UL)
- 100-P% outside LL and UL (shaded gray)
Benefits of Coverage Concept

- Quality defined in terms of population rather than sample
- Easily translatable into “consumer” expectations of Quality
- Removes ambiguity arising out of different sampling plans or instances of testing
- Fixed type II error (consumer risk) while allowing the producer to optimize extent of testing versus producer risk
Illustrations of Coverage Concept

A- Batch that is close to limiting quality, but acceptable

B- Batch that is unacceptable due to a shift in mean

C- Batch that is unacceptable due to shift in variability

D- Limitation of end product QC testing
Example: Assume a Quality Agreement of 95% of units with H$_2$O < 4%; <1% risk of type II error @ limit
Example: Assume a Quality Agreement of 95% of units with H₂O < 4%; <1% risk of type II error @ limit
Probability of passing a batch where less than 95% of all units have $\text{H}_2\text{O} < 4\%$ is $<1\%$ for all decision procedures regardless of sample size.

Manufacturer free to balance risk of failing acceptable batch against amount of testing.

Manufacturer not penalized for more testing (vs. zero tolerance scenario).

Manufacturer rewarded for improving Quality (i.e. lower water content) with less testing.

More transparent and testable statement of Quality for all.
The sponsor proposes an appropriate “quality statement” for regulatory consideration.

This quality statement specifies, for each parameter judged important to the quality of a product (CQAs), a coverage statement that unambiguously defines the expected quality and Type II error for the associated statistical test.

Once the quality statement is accepted by regulatory authorities, the sponsor is responsible for designing test procedures with associated limits such that the claims of the quality statement are fulfilled with high likelihood.

Sponsor free to adjust testing plan as additional experience gained or process improved as long as it confirms approved “quality statement”
Part B: Ensuring Quality

Quality Systems, Robust Processes and Control Strategies

… and good understanding
Pillars of Quality

- Quality Systems (ICH Q10)
  - Quality infrastructure that assures adherence to Quality practices/procedures
  - *Relates to the Quality of the entire Enterprise*

- Quality by Design (ICH Q8)
  - Robust process and product designed to inherently deliver Quality
  - *Relates to the Quality of a Product*

- Control Strategy (ICH Q8 Annex)
  - A set of controls and monitors that assure or verify the Quality of a particular batch/lot
  - *Relates to the Quality of Individual Batches/Lots*
Pharmaceutical Quality System. Management system to direct and control a pharmaceutical company with regard to quality. ICH Q10 based upon ISO 9000: 2005
"The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product." ICH Q8(R2)

"Quality by Design (QbD): A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management." ICH Q8(R2)
A control strategy can include, but is not limited to, the following:

- **Control of input material attributes** (e.g., drug substance, excipients, primary packaging materials) based on an understanding of their impact on processability or product quality;
- **Product specification(s);**
- **Controls for unit operations** that have an impact on downstream processing or product quality (e.g., the impact of drying on degradation, particle size distribution of the granulate on dissolution);
- **In-process or real-time release testing** in lieu of end-product testing (e.g., measurement and control of CQAs during processing);
- **A monitoring program** (e.g., full product testing at regular intervals) for verifying multivariate prediction models.”
Key Elements of a Control Strategy

- A range of requirements applied at various stages of product manufacture
- Process control through automated in-line measurements and feedback/forward control loops (PAT)
- Alignment of these requirements and controls with Quality statements
- Monitoring of process performance over time
  - Maintain state of control
  - Signal need for action prior to reaching OOS situation
  - Learn about, adapt and improve process performance
  - Statistical Process Control (SPC), Process Capability and Performance Analysis (PCA, PPA)
CQA: Critical Quality Attribute

The physical, chemical, and microbiological properties of the final drug product that are essential to safety and efficacy, stability and manufacturability of the drug product.

CPP: Critical Process Parameter

A critical attribute of the manufacturing system that impacts the quality of final drug product.
Aligning CQAs with Control Strategy

\[ CQA = f(CPP_i, PAT, IQA_i, PP_\varepsilon, IQA_\varepsilon) \]

<table>
<thead>
<tr>
<th>IQA</th>
<th>Intermediate Quality Attribute</th>
</tr>
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<tbody>
<tr>
<td>PAT</td>
<td>Process Analytical Technology Attribute</td>
</tr>
<tr>
<td>PP</td>
<td>Process Parameter</td>
</tr>
<tr>
<td>i</td>
<td>known and monitored</td>
</tr>
<tr>
<td>(\varepsilon)</td>
<td>unknown or unmonitored</td>
</tr>
</tbody>
</table>
Parametric Release??

- If $\varepsilon$ absent or insignificant, then CQA can be assured through CPP, PAT and IQA (why is this advantageous?)

- If significant $\varepsilon$ present, then end product testing for CQA required
NOTE: Also when not routinely monitoring CQA directly, test and limits for the actual CQA are needed

- Need test for CQA to establish
  \[ CQA = f(CPP, PAT, IQA) \]
- Need test and limits to investigate – OOS, complaints
- Regulator requirement of “If tested will comply”
Need to balance limits on CPPs, PATs, IQAs to be consistent with limits on CQAs

- If CPP, PAT, IQA limits much more stringent than CQA limit(s), unwarranted cost with little Quality benefit
- If CPP, PAT, IQA limits much less stringent than CQA limit(s), can’t assure meeting CQA limits and will need to directly monitor CQA to assure Quality
Test/Attribute Selection

- Have we selected the right set of tests that characterizes the overall quality?
  - Risk Assessment
  - Prior Knowledge
  - Regulatory Expectations and Standards
- Are acceptance criteria consistent with safety thresholds? Clinical efficacy?
  - Toxicology and OCCs
  - Clinical experience, “IVIVC & Rs” and OCCs
- When/How should the Critical Quality Attribute be monitored/controlled?
  - Risk Assessment
  - Prior Knowledge
- Are the analytical methods capable of measuring quality attributes?
  - Method Validation, Gauge R&R Studies
Process Capability & Performance Analysis (PCA, PPA)
- Statistical evaluation of process variability with respect to limits
- Typically includes both process and measurement variability

Operating Characteristic Curves (OCC)
- Statistical evaluation of decision making process related to an individual test
- Considers influence of different test structures: numbers of samples, average vs. individuals, tiered testing...
- Allows assessment of test performance relative to Requirements (Quality Standard)

Statistical Process Control (SPC) & Control Charts
- Intended to detect unexpected trend and allow correction before a process goes out of control
- Gain insights/knowledge that can be applied to process improvement
When specifications are linked to process capability...

- One consequence is a disincentive to process improvement
  - Reducing variability in the manufacturing process leads to more restrictive acceptance criteria rather than greater confidence in meeting requirements
  - Since the ultimate purpose is efficacy and safety, why should requirements change when the process is optimized?
Final Thoughts

- Authors propose adoption of an alternate approach to defining quality by specifying what proportion of product produced falls within specified limits.
- Consequence is an unambiguous definition of quality that assures an easily understood level of quality while affording testing flexibility for the producer while keeping consumer risk under control.
- Appropriate Control Strategies for pharmaceutical products should reflect:
  - In-depth understanding of required performance characteristics of the product
  - Thoughtful selection of critical tests and controls
  - Statistical design and evaluation of tests and acceptance criteria.
The End