

Quality Tolerance Limits



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Risk Based Quality Management

Project Scope

- Define role of QTLs in QbD, in particular the relationship to CTQs (Critical to Quality Factors), Estimands and continuous quality improvement (CQI)
- Discuss the use of QTLs in Early Development/small studies, bio equivalence and complex designs
- Discuss examples of how to define QTLs, different methodologies and different parameters in use across the industry
- Discuss difficulties and challenges of implementation of QTLs
- Examine role of QTLs as part of the of the lessons learned (RCA) feedback loop

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Objectives & Deliverables

Release of draft White Paper

Timelines

Q3 2022

Publish White Paper

Q3 2023

Deliverables

[Assessing the Use of Quality Tolerance Limits in the Pharmaceutical Industry.](#)

CURRENT STATUS Q4 2023

- Continuing to work on their White Paper

Problem Statement

QTLs - the role they play in defining quality within the QbD framework, their relationship to Critical to Quality factors, associated methodologies and the interpretation of them have not been fully defined in clinical development, in particular where early development/small studies, bio equivalence studies and complex designs are concerned.

Problem Impact

This will impact the whole clinical development process and allow the move away from perfection to a defined and achievable quality, from which continuous quality improvement can begin.

QbD Terminology and development

TPP

Target Product Profile, is the driver

- ▶ From the TPP can define the QTPP - Quality Target Product Profile
- ▶ This will typically define the desired characteristics of the product itself
- ▶ Many related only to production

CQA

Critical to Quality Attributes

- ▶ Once a (Q)TPP has been established, the "Critical Quality Attributes (CQAs)" for the product can be defined
- ▶ Not all attributes are critical to the quality of the product, and so some work will need to be done in order to establish what is critical and what is not
- ▶ Can rank order of importance of the various attributes, focus on the most critical parameters and consequently de-risk the product LTFU (Lost to Follow-Up)

CTQ

Critical to Quality factors

- ▶ Introduced in GCP Renovation document (Jan '17) and in ICH E8 R1 (draft May '19)
- ▶ CTQs are the internal critical quality parameters that relate to the wants and needs of the customer.
- ▶ The (internal and external) customer requirements get translated into Critical-To-Quality (CTQ) features.
- ▶ These CTQs define the criteria to evaluate what good looks like i.e., how well the project scope and deliverables meet requirements

QTL

Quality Tolerance Limits (ICH E6 R2)

- ▶ Ability to move away from "perfection" to defined quality
- ▶ Most CTQ should have a paired QTL to measure
- ▶ Forms an essential part of Plan-Do-Study-Act cycle

Terminology Example:

- Target Product Profile (TPP)
 - Patient wants extended dosing from current BD product on market
- Critical Quality Attribute (CQA)
 - Once a day dosing
- Critical to Quality Factor (CTQ)
 - In early stage trials drug levels shown at 24 hours
 - In Phase 2-3 demonstrate efficacy
- Quality Tolerance Limit
 - Pre-define what will be acceptable limits for acceptance
 - These QTL's will change at different stages