

# Application of Parametric Tolerance Interval Tests (PTIT)

Session Moderators:

Dave Christopher (Schering-Plough)  
Walter Hauck (USP)

## PTIT allows increased sample size without penalty

- How does this fit with QbD?
  - QbD strives to reduce end-product testing
  - QbD may also lead to more of in-process testing to gain better information about true batch quality
  - Testing at the end confirms all the controls you had along the way; however, this presumes some end product testing, and PTIT could be an effective option for these tests

## One of QbD goals is to reduce end-product testing

- In DDU, several factors are involved
  - Formulation
  - Manufacturing
  - Container closer systems
- If adequate understanding and control of these factors can be demonstrated, may be able to achieve real-time release
  - Already in place for some products

## What PTIT can and cannot do

- PTIT characterizes a batch with respect to mean and variability
- This kind of testing cannot be used to reliably detect rare abnormalities
- Does this mean there are limitations because of no zero tolerance component?

## Zero Tolerance (ZT) Issues

- But a zero tolerance counting test can't reliably detect rare abnormalities either: if there is 1 defect in a 100,000 doses, no test can consistently detect it (short of 100% destructive testing of the entire 100,000 doses)
- An "outlier" (i.e., an extreme value) will always increase RSD (sample standard deviation) and will increase the chances of failing PTIT
- Sample should be representative of the batch so sample RSD should be reflective of batch RSD
- There could be a trigger (a qualitatively different outlier), for which a different mode of action is necessary.
  - (e.g., an empty can is not a simple "outlier" but specific kind of defect which could be an indicator of a gross problem)
- For ZT counting tests batch disposition may be determined from an Individual test result. With PTIT focus is on the mean and variability.

## Applicant choosing sample size is one of key QbD features

- Can producer choose a sample size of zero?
  - Yes. In QbD adequate development work to demonstrate good understanding of product and process may justify no release testing
  - E.g., may have an in-process PAT test, which tests 100% for spray weight for "real-time release"
- Does testing of 10 canisters adequately characterize a batch?
  - Depends; must be studied in development and justified

## Typical Assumptions for PTIT

- Normal distribution
  - Typically based on assumption of normality
  - However, PTIT can be designed to accommodate other than normal distributions
- Variability in test results are random
  - PTIT not designed to address non-random variability

## Why does US use LC not Batch Mean?

- EU focuses on batch mean
  - Different from FDA, challenging for global companies
- PTIT controls batch quality via both mean and variability (i.e., “trade-offs”)
  - An on-target batch is allowed higher variability than an off-target batch
  - If the mean is off-target, must have a tighter distribution
- PTIT based on LC addresses manufacturing process, not just individual batches
  - Patients rely on label claim
  - PTIT provides better control of batch quality to meet overall patient needs
  - Batches should not be looked at in isolation, but in relation to previous batches

## How do companies control variability?

- Many companies currently use ZT counting test to characterize/confirm variability (end product testing)
- In QbD, (and in some companies currently) in-process testing used to control variability by controlling:
  - » Valve
  - » Can
  - » Formulation
  - » Etc

## Areas where PTIT might be appropriate

- Where focus is on central tendency and variability
  - Dissolution testing
    - Certain percentage of tablets have to dissolve within certain time
  - For OINDP, only seen it proposed for DDU
- Where objective is to minimize producer risk without compromising consumer quality
  - Fix acceptable level for consumer quality standard, then select appropriate sample size to control producer risk (“Win-Win”)
  - Benefits to consumer and producer can justify larger sample sizes
- Generally not applicable to other OINDP tests
  - Sample sizes that may not be feasible for labor-intensive tests
  - Currently, PTIT is univariate and CI data is inherently multivariate
- Foreign particulates – not feasible
  - Data is not a well-behaved continuous response

## In what phase is it appropriate to start PTIT?

- If in-process testing is planned, when is it appropriate to start PTIT testing?
  - Start as early as possible in product/process development
- Increased sample size might be a consideration (e.g., 20/60 tier1/tier2 sampling)
  - Must balance resources and not overdo it
  - If PTIT approach is used early on, might develop and maintain a database for later use in decision-making and bridging
- Different approaches can be taken during stages of development
  - Early on: short-term estimate of variability
  - In later stages, more mature test method and product may provide better estimates

## Further considerations for “early stage” use of PTIT

- When making a decision to take product further
  - E.g., after phase 2a
  - Phase 1 might be too early because many things are still in flux (e.g., product), but may still provide benefit
  - DDU tests may not be a relatively large expense for big companies, but what about smaller companies?
    - Seems to be good statistics, good science even for a small company
    - Even with ZT counting test, you may require a sample size of 30, so using PTIT may not be much different in terms of sample sizes
  - How to balance the cost vs. benefit?
    - Might use different quality standard and confidence level for early stage testing compared to final product
    - But might be useful in understanding your product

## Practical considerations for application of PTIT

- For analytical chemists, what are the recommendations for data-base and other software to use?
  - There are “magic” (i.e., non-standard) tolerance interval coefficients required for PTIT
  - Once those *ks* are generated, MS Excel can be used for calculations
  - Cannot get *ks* from two-sided tolerance interval tables

## Considerations for developing a specific PTI test

- Essential to have right coefficients
- Calculating those includes specification of coverage, target interval, alpha, etc
- Recommendation to applicants: talk to agency beforehand to make sure have concordance about calculation algorithms, coefficients, etc

## What causes a batch to fail using PTIT?

- PTIT is predicated on an assumption that a certain percentage of defects is acceptable. How is that percentage determined?
  - This is the key question
  - The success of the recent process was in bringing attention to that main issue
  - Based on clinical relevance? (doesn't appear to be feasible currently)
  - Use data from batches used in clinical trials
  - This is not (directly) a statistical issue