# Patient-Centric Considerations for PTIT

## Addressing unintended consequences in the draft 2018 guidance

## Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products--Quality Considerations

**"Digital Poster" Prepared for the IPAC-RS/RDD 2020 Joint Symposium**

**by the Product Quality Demonstration Strategy Working Group**

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**April 2020**

# Main Messages

- After decades of use to manage product quality, the counting test continues to serve the patient well
- The parametric tolerance interval test (PTIT) as currently configured in the draft guidance has the potential consequence of limiting availability of acceptable product to the patient
- Options are available for better aligning PTIT performance with patient needs

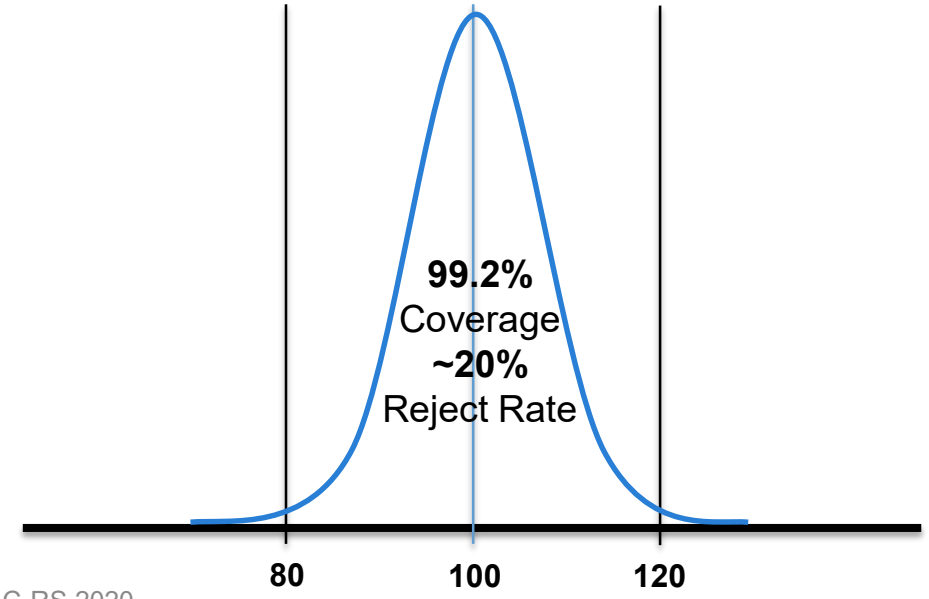
# Counting Test

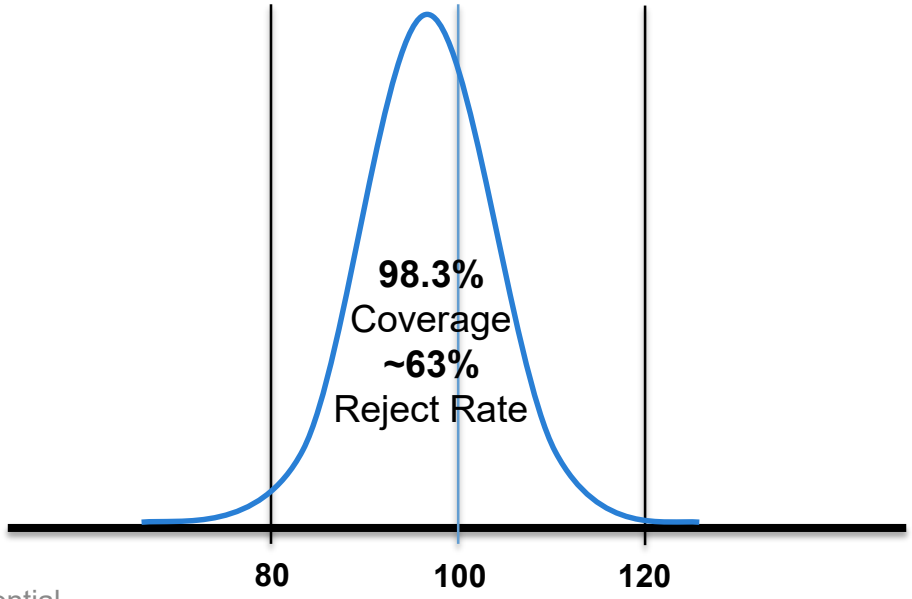
- The counting test has been used successfully for decades to provide safe and effective products to patients
  - No indication of allowing ineffective or unsafe product to reach the patient (i.e., manages to appropriate quality standard).
  - IPAC-RS PBE WG Database*[1]*
    - Provides delivered dose characteristics for contemporary MDI products
    - Total RSD for all MDI products, across life stages and accounting for between- and within-batch variations, ranged from 2 to 14%
    - 10% at 4% RSD or less; 50% at 7% RSD or greater; and 10% at 10% RSD or greater
- Counting test continues to serve the patient well by appropriately managing product quality

***[1]* Performance of the Population Bioequivalence (PBE) Statistical Test Using an IPAC-RS Database of Delivered Dose from Metered Dose Inhalers.** Beth Morgan, Stephanie Chen, David Christopher, Göran Långström, Christopher Wiggenhorn, Elise Burmeister Getz, Hayden Beresford, Thomas Hoffelder, Daniela Acerbi, Steven Andrews, Mark Berry, Monisha Dey, Joshi Keyur, Mary McKenry, Marisa Pertile, Helen Strickland, David Wilcox, Svetlana Lyapustina AAPS PharmSciTech. 2018 Apr;19(3):1410-1425. doi: 10.1208/s12249-017-0941-8. Epub 2018 Feb 12. https://www.ncbi.nlm.nih.gov/pubmed/29435904.

# PTIT Decision Making Consequences

- Batch acceptance under current PTIT proposal is dramatically more stringent than counting test with no evidence of benefit to the patient
  - A batch with **more than 99% coverage** at target *(<0.40% in either tail)* would be **rejected more than 20% of the time** *[the same batch would pass 99% of the time with the counting test]*
  - A batch with **more than 98% coverage** at 4% off target *(<2% in either tail)* would be **rejected more than 60% of the time** *[the same batch would pass 97% of the time with the counting test]*
  - Would vastly reduce the availability of product deemed suitable for use by patients under the counting test



# Options for aligning PTIT performance to patient needs

- Provide scientific justification for adjusting PTIT parameters (e.g., sample size (tiers), confidence level, coverage or tail proportions, goalposts) to reduce rejection of acceptable product
- Examples:
  - Changing confidence level from 95% to 90% would decrease the probability of rejecting a batch with 99% coverage at target from more than 20% to ~5%
  - Changing the coverage from 90% to 87.5% would further reduce rejection of product with quality deemed suitable by counting test

# Ability to use PTIT in lifecycle approach

- The current proposal does not allow PTIT to be used in a lifecycle approach that incorporates commercial production data from previous batches to be used to make better decisions about a current batch.
- It is not aligned with FDA's risk-based approach for product quality and process lifecycle management. Mature product and process knowledge is not used to make better decisions for the patient.
- The guidance could be modified to allow PTIT to be used as a transactional test (i.e., only single batch information used), with the potential for justified transition to non-transactional use incorporating data from previous batches.
- The current PTIT proposal is not in alignment with consensus standards
  - Doesn't allow for lifecycle approach
  - PTIT Terminology inconsistent across industry and standards with the potential for incorrect interpretation
    - Need to clarify and/or align with consensus standard definitions
    - Develop glossary with sufficient description (e.g., 90% coverage is not equal to NMT 5% in either tail)

# Conclusions

- After decades of use to manage product quality, the counting test continues to serve the patient well
- The parametric tolerance interval test (PTIT) as currently configured in the draft guidance has the potential consequence of limiting availability of acceptable product to the patient
- Options are available for better aligning PTIT performance with patient needs

# Summary

| Key Issue | Consequence | Recommendation | Details / Considerations |
|---|---|---|---|
| The recommended PTIT test parameters and acceptance criteria result in decisions inconsistent with the time-tested quality standard represented by the counting test for which there is no indication of allowing ineffective or unsafe product to reach the patient. | Safe and effective drug product batches may not reach the patient with the potential for drug shortages. | Allow justified modification of PTIT test parameters and acceptance criteria to mitigate those consequences. | Sample size (Tiers)<br>Confidence level<br>Coverage or tail proportions<br>Goalposts |
| Current proposal does not allow PTIT to be used in a lifecycle approach that incorporates commercial production data from previous batches to be used to make better decisions about a current batch. | Not aligned with FDA's risk-based approach for product quality and process lifecycle management. Mature product and process knowledge is not used to make better decisions for the patient. | Allow PTIT to be used as a transactional test (i.e., only single batch information used), with the potential for justified transition to non-transactional use incorporating data from previous batches. | Follow lifecycle approach consistent with consensus standards . |
| PTIT Terminology<br>(Variety of definitions exist across industry and standards.) | Potential for incorrect interpretation across industry. | Clarify and/or align with consensus standard definitions | Glossary with sufficient description (Example: 90% coverage is not equal to NMT 5% in either tail) |