Industry Insight: Clarity and Consistency for Complex Generics

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The views expressed in this presentation are based on broad industry commentary and should not be interpreted as unique or specific to Viatris Inc. or its subsidiaries unless specified.

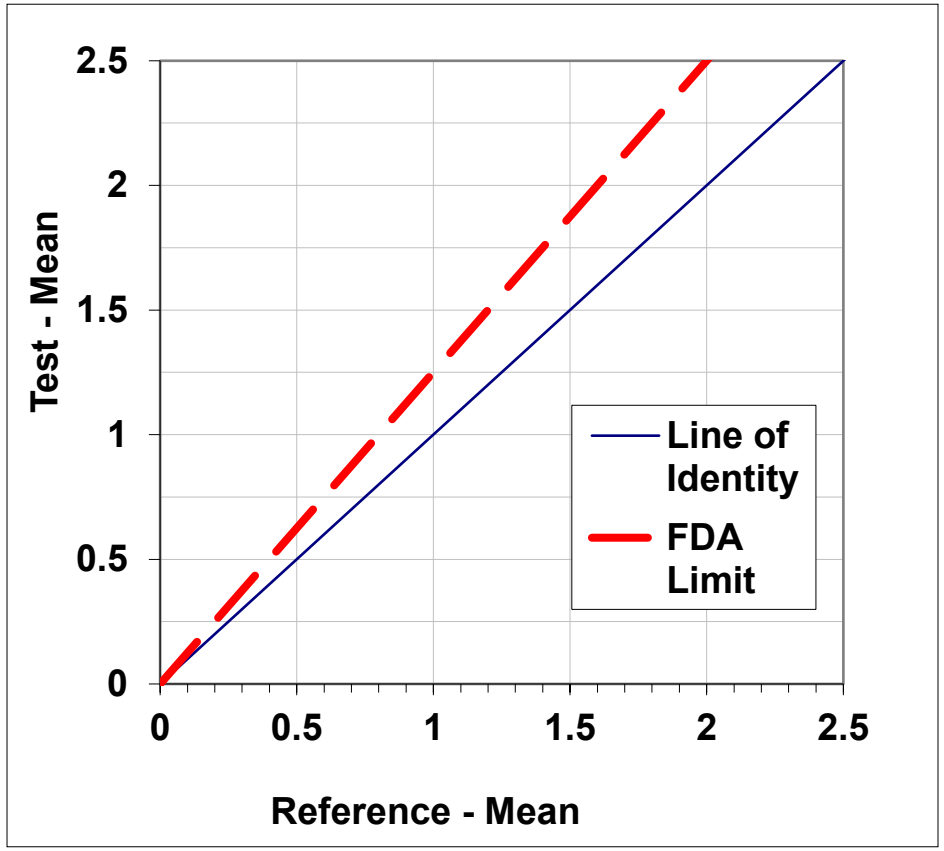
Current state: what are some of the challenges for complex generic drug development today?

Today's presentation will focus on challenges surrounding:

Irritation or Adhesion | Hypersensitivity of the Original FDA Criteria

- In situations of low or minimal irritation response or very good adhesion, the margins allowed are far lower than would be permitted relative to products with worse performance (i.e., scores >1).
- Originally, stat criteria based on an upper non-inferiority margin of 25% of Ref.

$$95\%\ UCL\ (Mean\ Test \leq 0.25\text{*Mean RLD}$$



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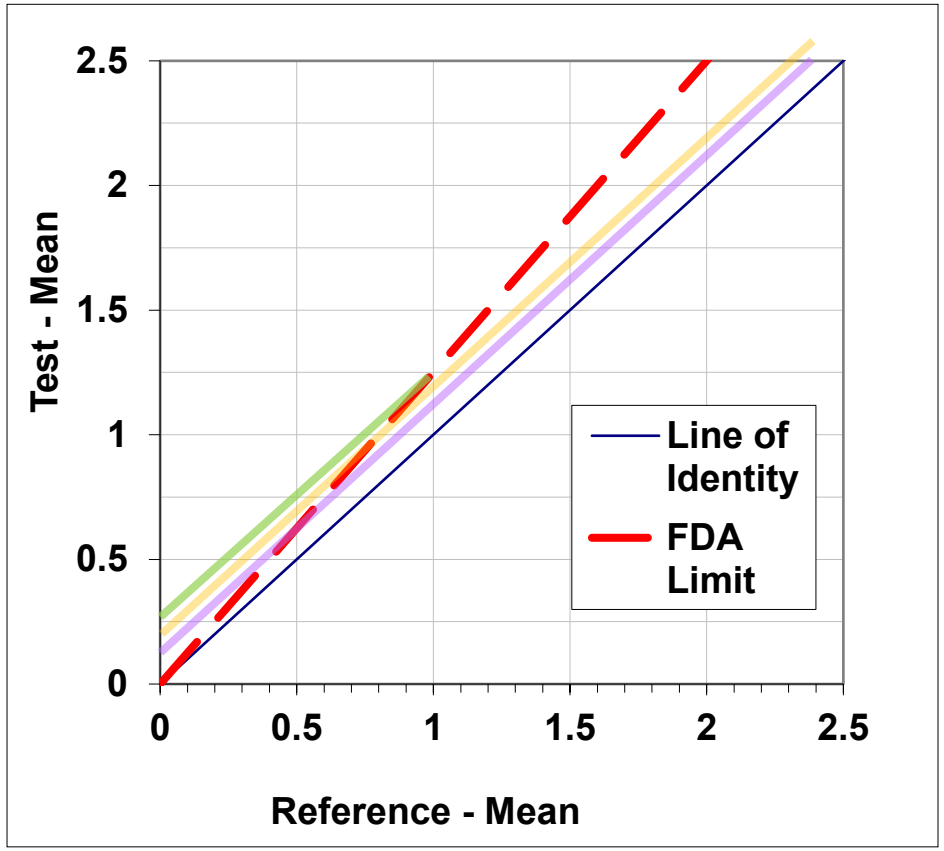
Agency Adopted Criteria for *Adhesion or Irritation Relative to Original FDA Limit*

The issue has been resolved at lower levels of irritation but there is now an exacerbated challenge at higher levels.

- **Original** suggestion – absolute margin of 0.25 (green) up to Ref Mean of 1; then resume relative scale (+25%)
- FDA Adopted Irritation – absolute margin of 0.20 adopted. (orange)
- FDA Adopted Adhesion – absolute margin of 0.15 adopted. (light purple)
- Both cases accommodate low scores, but penalized higher scoring comparisons, particularly above Ref score of 1.
- Thus, we now see potential challenge for meeting non-inferiority for products with Reference Means that exceed 1 for Irritation or Adhesion.

$$95\%\ UCL\left(\frac{Mean\ Test - MeanRLD}{1}\right) \leq 0.20 \text{ (or } 0.15\text{)}$$



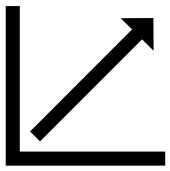
Patient BE Challenges

- **PK sampling in patients** → Issues with recruitment, variability within multicentric studies
- **Patient compliance** → Protocol compliance, missing samples, drop-outs, anomalous data.

Biostatistics | Some Challenges

- Complex injectables sometimes have pAUC requirement that can occasionally be overly sensitive. Slight shifts in profile may not be clinically relevant, particularly in chronic administration with accumulation.
- For Highly Variable Drug products, that are **very-highly variable**, meeting a ratio requirement appears to be more subject to chance. In theory, these criteria should be relaxed.
  - Possible considerations, for point estimate criteria (PEC) relaxation:
    - Partial coverage of 80-125 by CIs.
    - Widening PEC for very-highly variable products: e.g.
      For ISCVs 60-90%, move ratio to 75-133
      For ISCVs >90, move ratio to 70-143

Recommendations



- **Suggestion for addressing irritation and adhesion scoring acceptance criteria:** a fixed absolute margin when Reference mean ≤ 1 but then switch to a relative margin when Reference mean > 1.

- **For very highly variable drug products,** we suggest reconsidering the criteria around point estimate constraint.