Impact of the Statistical Approach in the United States Food and Drug Administration (US FDA)'s 2016 Draft Guidance on Assessing Adhesion with Transdermal Delivery Systems (TDS) for Abbreviated New Drug Applications (ANDAs)

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Abstract

Background: The US FDA's product-specific guidances (PSGs) for TDS historically recommended a ratio of means (ROM)-based non-inferiority (NI) approach for evaluating TDS adhesion, based upon the mean adhesion score throughout the product wear. The main drawback of this statistical approach was a low power for well-adhering TDS (i.e., TDS with a mean adhesion score close to 0; = 90-100% adhesion), which impacted the approvability of high-quality generic TDS products. Mathematical proof and simulations revealed that the low power of the historical statistical approach for well-adhering TDS was caused by the use of a ROM NI test coupled with the direction of the adhesion scale (a smaller score for better adhesion).

Method: In June of 2016, the US FDA's Center for Drug Evaluation and Research published a draft guidance entitled "Assessing Adhesion with Transdermal Delivery Systems and Topical Patches for ANDAs". An improved statistical approach was recommended, replacing the historical ROM NI test with a difference-of-means (DOM) NI test, still based upon the primary endpoint of (weighted) mean adhesion score across a series of assessments throughout the duration of wear for a TDS, with an acceptable margin of 0.15. Initially, simulations had demonstrated that the new statistical approach significantly improved the low power of the historical approach for well-adhering products. After more than one year following publication of the draft guidance, a meta-analysis was conducted to systematically evaluate whether the new statistical approach improved the low power of the historical approach as intended.

Result: A review of thirty-five (35) TDS adhesion studies submitted in ANDA after the publication of the 2016 adhesion draft guidance demonstrated that: out of the 35 adhesion studies, 13 (37%) involve moderately- to well-adhering proposed generic TDS that fail the NI test by the historical approach despite having comparable adhesion scores to the reference product, but that now appropriately pass the NI test using the new approach; Conversely, one of the 35 studies involves a poorly-adhering proposed generic TDS with a higher (inferior) mean adhesion score than the RLD, which passes NI by the historical approach, but which appropriately fails by the new approach; The other 21 studies either consistently fail both or pass both the historical and the new approaches. In addition, while up to thousands of subjects would typically have been needed for well-adhering TDS with close to perfect adhesion to pass the historical NI test, among the 29 TDS adhesion studies that pass the NI test based on the new approach, 27 have a sample size of ≤ 100 subjects.

Conclusion: These ANDA results, as well as results from previous simulations, indicate that the new statistical approach greatly improves the low power for well-adhering TDS of the historical statistical approach, corrects the excess power for poorly-adhering TDS of the historical statistical approach, and uses an NI margin of 0.15 that is reasonable, efficient, and does not create a burden of an unreasonably large sample size. In conclusion, the statistical approach recommended in the 2016 guidance corrects the lower power of the historical approach for well-adhering TDS, thereby enhances the approvability of well-adhering generic TDS products, and promotes the availability of high quality, affordable generic drug products to patients.

Introduction and Motivation

Introduction: An adhesion study (cross over or matched parallel) needs to demonstrate that the adhesion performance of the generic (TEST) TDS is non-inferior to the reference listed drug (RLD) TDS. Recent advances in adhesives technology and TDS design have increased the prevalence of well-adhering TDS drug products.

Problem: The *Low Power (i.e., Passing Rate)* of the historical statistical approach recommended in old PSGs for well-adhering TDS products made it challenging for well-adhering TEST TDS to demonstrate non-inferior adhesion compared to the RLD.

Solution: In June of 2016, the US FDA published a draft guidance recommending a new statistical approach, intended to *correct the low power* of the historical statistical method in the old PSGs.

Objectives

After more than one year following publication of the new draft guidance, our objective was to systematically evaluate the following statistical considerations:

1. Was the low power of the historical approach for well-adhering products appropriately corrected by the new statistical approach?
2. Is the NI Margin of 0.15 appropriate?
3. Is the resulting sample size needed for adhesion studies unreasonably large?
4. What is the impact of the new statistical approach on the power for poorly – adhering products?

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Methods

Historical Statistical Approach in Old Product-Specific Guidances

- Primary endpoint: mean adhesion scores across all time points for a TDS based on FDA's widely-used, established 5-point scale.

  0 (90-100% adhesion), 1 (75-<90%), 2 (50-<75%), 3 (>0-<50%), 4 (0%)

- The recommended statistical approach was a ratio of means NI test:

$$H_0: \frac{\mu_T}{\mu_R} > 1.25;\ H_1: \frac{\mu_T}{\mu_R} \leq 1.25$$

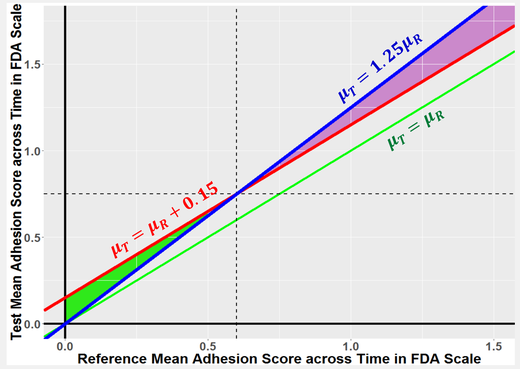
New Statistical Approach Recommended in the 2016 Draft Guidance

- In the new draft guidance, a new statistical hypothesis was recommended, replacing the traditional *ratio of means* NI test with a *difference of means* NI test, still using (weighted) mean adhesion scores across all time points for a TDS based on FDA's 5-point scale

$$H_0: \mu_T - \mu_R > 0.15;\ H_1: \mu_T - \mu_R \leq 0.15$$

- The NI margin of 0.15 for the difference of means was determined to be appropriate based upon collaborative research by clinicians, statisticians and other scientists. We reviewed the study results of a set of numerous TDS products with a range of adhesion quality submitted to FDA in ANDAs, as well as results from numerous simulated scenarios encompassing different potential data distributions.

Figure 1. Schematic Comparison of Statistical Hypotheses between FDA's Historical Product-Specific Guidances for TDS and FDA's 2016 New Draft Adhesion Guidance Assuming No Data Variation



- In Figure 1, the area below the *blue* line establishes NI according to the *old* PSGs: $\frac{\mu_T}{\mu_R} \leq 1.25$, and the area below the *red* line establishes NI according to the *current* draft guidance: $\mu_T - \mu_R \leq 0.15$.
- The *green* line is the symmetric line when TEST and RLD have *identical means*: $\mu_T = \mu_R$, which is *parallel* to the *red* line - the *current* non-inferiority criteria . The *same* criteria (0.15 of absolute mean difference) is applied for *all* products, whether well-adhering or poorly-adhering.
- The *green* shaded area is the *additional* power *gained* under the *new* draft guidance for well- to moderately-well adhering products (RLD mean < 0.6) compared to the old PSGs.
- The *purple* shaded area is the *excess* power that existed under the *old* guidance for poorly-adhering products (RLD mean > 0.6), that has been remediated now.

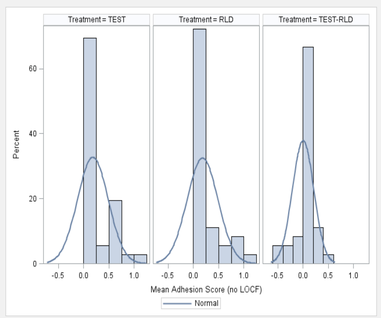
- The current two-group DOM NI hypothesis

$$H_0: \mu_T - \mu_R > 0.15;\ H_1: \mu_T - \mu_R \leq 0.15$$

corresponds to a one-group NI hypothesis:

$$H_0: \mu_D > 0.15;\ H_1: \mu_D \leq 0.15$$

Where μ_D is mean of the paired difference between TEST and RLD for individual subjects and $\mu_D = \mu_T - \mu_R$. This releases the distribution requirement for the marginal distributions of TEST and RLD mean adhesion score for individual subjects, which are usually highly skewed.



Meta-Analysis Results

Review of 35 Adhesion Studies After Publication of 2016 Draft Guidance

Figure 2. Comparison of NI Test Result Using FDA's Historical vs. New Statistical Approach

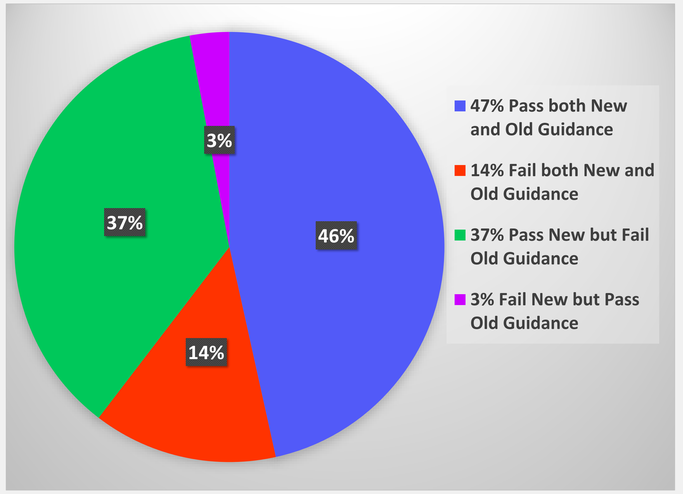
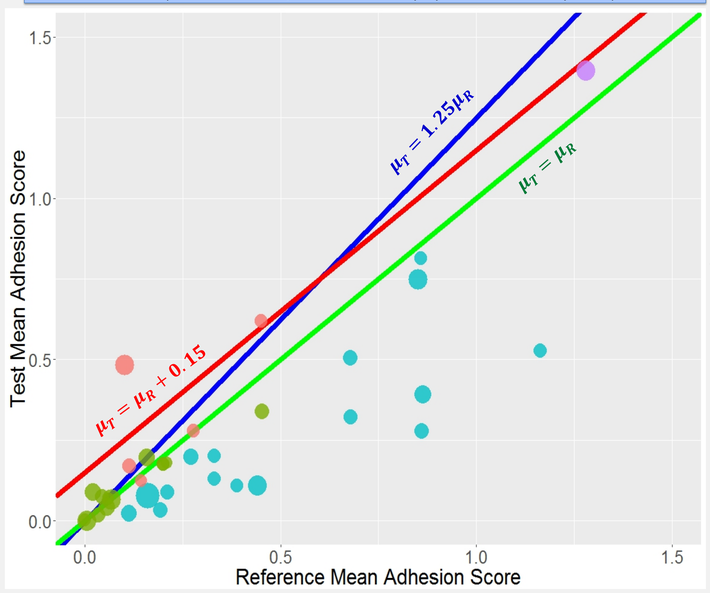


Figure 3. Comparison of NI Test Result Using FDA's Historical vs. New Statistical Approach: Individual ANDAs (with data variation; size of each dot is proportional to the sample size)



Among these 35 adhesion studies representing 28 ANDAs submitted after the publication of the 2016 draft guidance,

1) Green Dots: 13 (*37%*) involve well or moderately-well adhering TEST TDS with *comparable* adhesion scores to the RLD (around the symmetric line) that *failed* NI by the *historical* approach, but now *passed* NI by the *new* approach
2) Blue Dots: 16 (*46%*) involve well-, moderately- or poorly- adhering TEST TDS with *NI* adhesion scores to RLD (below the symmetry line) that consistently *passed* NI by *both* the historical and new approaches
3) Red Dots: 5 (*14%*) involve moderately- adhering TDS with either *Inferior* adhesion (above the symmetry line), or adhesion that is comparable to RLD (around the symmetric line) but with an *insufficient* sample size, that consistently *failed* by *both* the old and new approaches
4) Purple Dot: 1 (3%) involves a poorly-adhering generic TDS with *inferior* adhesion to RLD (above the symmetric line) that *passed* the *historical* approach but *failed* the *new* approach.

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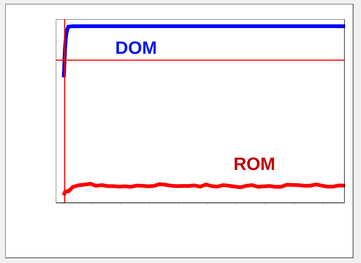
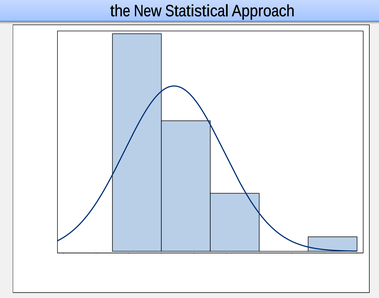
Figure 4. A Hypothetical Study. Key Features Mimic an ANDA with Near Perfect Adhering TDS: Sample Size Reduction for Historical vs. New Statistical Approach



TEST Mean: 0.04
RLD Mean: 0.03
Intra-subject SD: 0.13
Historical Approach:
> 2000 subjects
New Approach:
22 subjects

Figure 5. Distribution of Sample Size Among 29 Adhesion Studies that Passed NI by the New Statistical Approach



Among the 29 adhesion studies that passed NI based on the new statistical approach recommended by the new guidance,

- 18 (*62%*) studies had ≤ *60* subjects.
- 6 (*21%*) studies had *60-80* subjects.
- 5 (17%) studies had 80-180 subjects.

The five studies with > 80 subjects likely would have passed NI even with fewer subjects.

Conclusions

These meta-analysis results suggest that:

- The new statistical approach *effectively corrected* the *low power* for *well-adhering* TDS products of the historical statistical approach recommended by the old product-specific guidance, and therefore, *achieved the objective* of developing an efficient, appropriate approach to evaluate NI for TDS adhesion.
- The NI *margin of 0.15* associated with the current statistical approach is *reasonable*, and not overly stringent.
- The current approach does not necessitate an unreasonably large sample size. Instead, the new approach *significantly reduces* the *sample* size that was needed to pass NI by the old approach - as large as thousands of subjects for non-inferior TEST TDS products in situations where the reference TDS had almost perfect adhesion.
- The new statistical approach retains *reasonably comparable power to* and *corrects the overly high power* of the old approach for *poorly-adhering* products.

Impact on Generic Drugs

An analysis of the results suggests that

- The statistical approach recommended in the 2016 draft guidance *corrects* the lower power of the historical approach for well-adhering TDS
- Thereby *enhances* the *approvability* of well-adhering generic TDS products, and
- *Promotes* the *approvability, availability, and access to* high quality, affordable generic TDS products for patients

References

United States Food and Drug Administration Guidance for Industry on Assessing Adhesion with Transdermal Delivery Systems and Topical Patches for ANDAs. June, 2016. Accessible at:

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM504157.pdf.