Bioequivalence Statistics for Adhesion and Irritation Studies

Somesh Chattopadhyay
Lead Mathematical Statistician
Division of Biometrics VIII, Office of Biostatistics
CDER | US FDA

WEBINAR: A Deep Dive: FDA Draft Guidance on Statistical Approaches to Establishing Bioequivalence – March 14, 2023

Statistical Review of Generic Transdermal Products

- Bioequivalence: Determined using PK studies
- Studies unique for transdermal products:
  - Irritation and sensitization study
  - Patch adhesion study

Statistical Review of Irritation Studies

Goal:

To demonstrate that the potential for a skin irritation or sensitization with the test product is no worse than the reaction with the reference product

Design of Irritation Studies

- 21-day irritation/induction phase
  - Repeated, simultaneous application of the test and reference patches
  - Wear period should be based on the reference label
- 14- to 17-day rest period
- Sensitization/challenge phase
  - Simultaneous application of one test and one reference patch
  - At a naïve site (not used in induction phase)
  - Kept for 48 hours
- A re-challenge phase 4 to 8 weeks after challenge phase if potential sensitization reaction is observed in challenge phase

Irritation Assessments

- Based on an 8-point “dermal response” and a 4-point “other effects” scores
- Irritation score is the sum of these two
- Induction phase assessments
  - Once for each patch after its removal
- Challenge phase assessments
  - 4 assessments after removal of the challenge phase patches
  - At 30 minutes, 24 hours, 48 hours and 72 hours

Statistical Analysis of Irritation Studies

- Irritation analysis:
  - Primary endpoint: Mean irritation score
  - Non-inferiority analysis using mixed model

$$H_0: \mu_T - \mu_R \geq \delta$$

$$H_1: \mu_T - \mu_R < \delta$$

  - Non-inferiority (NI) margin (δ): 0.2
- Sensitization analysis: Descriptive

Statistical Review of Adhesion Studies

Goal:

To show non-inferiority of adhesion characteristics of the test product to those of the reference product

Design of Adhesion Studies

- Single-dose, randomized, two-treatment, two-period crossover study
  - Treatments randomized between periods for each subject

or

- Single-period, two-treatment-per-subject design
  - Treatments randomized between application sites for each subject

Adhesion Assessments

- Based on a 5-point adhesion scale at multiple time points throughout the duration of wear

Percent adhered	Score
≥ 90%	0
≥ 75% to < 90%	1
≥ 50% to < 75%	2
> 0% to < 50%	3
0%	4

Statistical Analysis of Adhesion Studies

- Primary endpoint: Mean adhesion score (mean of adhesion scores post baseline for a patch)
- If adhesion assessments are not equally spaced:
  - A weighted mean should be used for mean adhesion score
  - Weight for an adhesion score

$$= \frac{\text{Time between the current and the preceding assessments}}{\text{Total planned duration of wear}}$$

- At any timepoint the highest adhesion score up to and including that time is used
- Non-inferiority analysis using mixed model
- NI margin: 0.15

References

FDA's 2018 Draft Guidance on Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs:

https://www.fda.gov/media/117569/download

FDA's 2018 Draft Guidance on Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs:

https://www.fda.gov/media/98634/download