

Common Deficiencies – Statistical Considerations

How to Resolve Current Challenges in ANDAs in Transdermal Delivery
System (TDS)

Complex Generic Drug Product Development Workshop

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Outline

- Overview of statistical analysis of skin irritation, sensitization and adhesion (I/S/A) studies
- Common deficiencies identified in the review of I/S/A studies

Overview of Analysis - I/S/A Studies



- Evaluate TDS irritation, sensitization potential and adhesion
- Show performance of proposed generic T not worse than the reference R (non-inferiority test)
- Combined Irritation/Sensitization (I/S)
- Adhesion alone or combined Adhesion/pharmacokinetics

Overview of Analysis (2)



- Irritation: evaluated at the time of each TDS change
- 11- point scale, combination of
 - Dermal response – skin appearance, 0 - 7
 - Other Effects – observation, 0 - 3
- Example – product specific guidance for Rivastigmine

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201278.pdf>

Overview of Analysis (3)

- Adhesion: evaluated at each of multiple time points
- 5-point scale:

0 = $\geq 90\%$ adhered	(essentially no lift off the skin)
1 = $\geq 75\%$ to $< 90\%$ adhered	(some edges only lifting off the skin)
2 = $\geq 50\%$ to $< 75\%$ adhered	(less than half of the TDS lifting off the skin)
3 = $> 0\%$ to $< 50\%$ adhered	(not detached, but more than half of the TDS lifting off the skin without falling off)
4 = 0% adhered	(detached; completely off the skin)

Overview of Analysis (4)



- Comparison of generic with RLD based on mean scores (average for all subjects, all times)
- Irritation: ratio of means - want $T/R < 1.25$
- Adhesion: difference of means - want $T-R < 0.15$

(per current Guidance

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

Information Request (IR)

- Problems are related to
 - Guidance
 - Datasets
 - Calculation

Information Request (IR) (2)

Guidance examples

- per system, not per subject
- for adhesion, unequal sampling time ok

Current guidance: calculate weighted mean

Information Request (IR) (3)

Dataset examples

- Patch detachment in I/S study
- Inconsistent information
- Conflicting study results

Information Request (IR) (4)

Calculation examples

- Evaluation based on means, not medians
- Don't use baseline values

These pull averages towards zero

Common Deficiencies – Statistical Considerations



- Clarification or justification
- Mistakes not irreparable but inefficient and misleading
- Follow guidance or justify other approach

Summary

- Understand the purpose, study design, and **analysis** of I/S/A studies
- Refer to product specific guidances and general guidance on assessing adhesion
- Provide justification in original ANDA submission for alternative approaches