U.S. FOOD & DRUG ADMINISTRATION

Common Deficiencies-OGD 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 skin irritation, sensitization and adhesion (I/S/A) studies
- Common deficiencies identified in the review of I/S/A studies
- Summary

Overview of I/S/A Studies

- Goal: To demonstrate the irritation, sensitization potential and adhesion performance of proposed generic TDS (T) is not worse than the reference TDS (R) (non-inferiority test)

Overview of I/S/A Studies (cont.)

- Combined Irritation/Sensitization (I/S) Study
  - Multi-center, evaluator-blinded, randomized study
  - 6 weeks: Induction phase (21 days), rest period (14-17 days), challenge phase (5 days), re-challenge (if needed)
  - Treatment arms:
    - To-be-marketed T and R (comparison between the T and R)
    - Vehicle TDS (without active) and positive control (e.g., 0.1% sodium lauryl sulfate)

Overview of I/S/A Studies (cont.)

- Adhesion alone study or combined Adhesion/pharmacokinetics (PK) study
  - Single-dose, randomized, two-treatment, two-period crossover study
  - Treatment arms: to-be-marketed T and R
  - Duration: maximum labeled duration of wear of the R

Easily Correctable Deficiency (ECD) or Information Request (IR) in 2015-2017 for I/S/A Studies in ANDAs

	Reasons for ECD or IR	Percentage *
1.	Clarification/Justification	75.8%
2.	Formulation Related Issues	24.2%
3.	Missing Case Report Form	12.1%
4.	Missing Dataset or Dataset Definition Files	9.1%

* The total percentage is higher than 100% because one ECD/IR could contain multiple reasons

ECD/IR for Clarification and Justification

- Patch detachment information in I/S study
- Inconsistent information (e.g., between the study report and case report form, between the dataset and data definition file)
- Conflicting study results when multiple studies were conducted
  - Provide the explanation how the overall conclusion was made

ECD/IR for Clarification and Justification (cont.)

- Different from guidance recommendations
  - Examples:
    - Use different scales: Convert to the scales that guidance recommended and submit the study result
    - Patch moved prior to reaching the excessive irritation score (e.g., irritation score less than 3): Provide explanation when it happens

ECD/IR for Formulation Related Issues

- Formulation and manufacturing process for the proposed generic TDS and vehicle TDS
- Justification of inactive ingredients if different than the Reference Listed Drug
- Clarification on whether the to-be-marketed formulation was used in the studies

ECD/IR for Missing Case Report Forms

- Needed for subjects who were removed from the analysis population, demonstrated protocol deviations or violations, experienced serious adverse events, deaths
- Recommend for all subjects but minimum of 10%

ECD/IR for Missing Dataset and Data Definition Files

- Examples:
  - Datasets in SAS. xpt format
    - Adverse events
    - Concomitant medications
    - Medical history
    - Reasons for subject discontinuation from the study
  - Data definition files for all variables

Summary

- Understand the goal and study design of I/S/A studies
- Refer to product specific guidances and general guidance on the assessment of adhesion
- Other approaches may be acceptable but require justification
- Provide justification/clarification or other information in original ANDA submission

References

- Product Specific Recommendations for Generic Drug Development
- Assessing Adhesion with Transdermal Delivery Systems and Topical Patches for ANDAs
- Guidance for Industry ANDA Submissions – Amendments to Abbreviated New Drug Applications Under GDUFA
- ANDA Submissions-Refuse to Receive Standards Rev.2 Guidance for Industry