Guidance for Industry

Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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I. INTRODUCTION

This guidance is intended to assist sponsors of abbreviated new drug applications (ANDAs) by recommending study designs and scoring systems that can be used to test skin irritation and sensitization during development of transdermal products.

To fully evaluate the equivalence of a transdermal product for an ANDA to a reference listed drug (RLD), skin irritation and sensitization should be assessed because the condition of the skin may affect the absorption of a drug from a transdermal system.[2] More severe skin irritation may affect the efficacy or safety of the product.

Transdermal products have properties that may lead to skin irritation and/or sensitization. The delivery system, or the system in conjunction with the drug substance, may cause these reactions. In the development of transdermal products, dermatologic adverse events are evaluated primarily with animal studies and safety evaluations in the context of large clinical trials generally associated with the submission of new drug applications (NDAs). Separate skin irritation and skin sensitization studies also are used for this purpose. These latter studies are designed to detect irritation and sensitization under conditions of maximal stress and may be used during the assessment of transdermal drug products for ANDAs.

II. STUDY DESIGNS

Recommended designs for skin irritation and skin sensitization studies for the comparative evaluation of transdermal drug products for an ANDA are delineated below. Other proposals for studies may be

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[1] This guidance has been prepared by the Office of Generic Drugs in conjunction with the Division of Dermatological and Dental Drug Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on studies to assess skin irritation and sensitization of proposed generic transdermal drug products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

[2] This guidance does not address the bioequivalence studies that would be needed for a particular transdermal drug product. These will vary according to the active ingredient in the product. The Office of Generic Drugs (OGD) should be contacted with questions regarding bioequivalence studies.

suggested, but potential applicants are advised to consult the Office of Generic Drugs about alternative study designs prior to the initiation of such a study.

A. Recommendations for a Cumulative Skin Irritation Study

1. Sample size: 30 subjects

2. Exclusion criteria: Dermatologic disease that might interfere with the evaluation of test site reaction

3. Duration of study: 22 days

4. Study design: A randomized, controlled, repeat patch test study that compares the test patch to the innovator patch. Placebo patches (transdermal patch without active drug substance) and/or high- and low-irritancy controls (e.g., sodium lauryl sulfate 0.1% and 0.9% saline) can be included as additional test arms.

5. Patch application: Each subject applies one of each of the patches to be tested. Test sites should be randomized among patients. Patches should be applied for 23 hours (plus or minus 1 hour) daily for 21 days to the same skin site. At each patch removal, the site should be evaluated for reaction and the patch reapplied.

   Application of a test patch should be discontinued at a site if predefined serious reactions occur at the site of repeated applications. Application at a different site may subsequently be initiated.

6. Evaluations: Scoring of skin reactions and patch adherence should be performed by a trained and blinded observer at each patch removal, using an appropriate scale.

   Dermal reactions should be scored on a scale that describes the amount of erythema, edema, and other features indicative of irritations. (See Appendix A for an example of a scoring system that can be used.) The percent adherence of the transdermal patches should be assessed using a 5-point scale (see Appendix B).

7. Data presentation and analysis: Individual daily observations should be provided, as well as a tabulation that presents the percentage of subjects with each grade of skin reaction and degree of patch adherence on each study day.

The mean cumulative irritation score, the total cumulative irritation score, and the number of days until sufficient irritation occurred to preclude patch application for all the study subjects should be calculated for each test product, and a statistical analysis of the comparative results should be performed (see Appendix C).

B. Recommendations for a Skin Sensitization Study (Modified Draize Test)

1. Sample size: 200 subjects

2. Exclusion criteria:

   a. Dermatologic disease that might interfere with the evaluation of the test site reactions.

   b. Use of systemic or topical analgesics or antihistamines within 72 hours of study enrollment or systemic or topical corticosteroids within 3 weeks of study enrollment.

3. Duration of study: 6 weeks

4. Study design: A randomized, controlled study on three test products: the test transdermal patch, the innovator patch, and the placebo patch (transdermal patch without the active drug substance).

5. Patch application: Test sites should be randomized among patients. The study is divided into three sequential periods:

   - Induction Phase: Applications of the test materials should be made to the same skin sites 3 times weekly for 3 weeks, for a total of 9 applications. The patches should remain in place for 48 hours on weekdays and for 72 hours on weekends. Scoring of skin reactions and patch adherence should be performed by a trained and blinded observer at each patch removal, using an appropriate scale.

     Dermal reactions should be scored on a scale that describes the amount of erythema, edema, and other features indicative of irritation. (See Appendix A for an example of a scoring system that can be used.) The percent adherence of the transdermal patches should be assessed using a 5-point scale (see Appendix B).

- **!** Rest Phase: The induction phase is followed by a rest phase of 2 weeks, during which no applications are made.

- **!** Challenge Phase: The patches should be applied to new skin sites for 48 hours. Evaluation of skin reactions should be made by a trained blinded observer at 30 minutes and at 24, 48, and 72 hours after patch removal. (See Appendix A for an example of a scoring system that can be used.)

6. Data presentation and analysis: The individual daily observations should be provided, as well as a tabulation of the percentage of subjects with each grade of skin reaction and degree of patch adherence on each study day. The mean cumulative irritation score and the total cumulative irritation score for all the study subjects should be calculated for each test product, and a statistical analysis of the comparative results should be performed.

   A narrative description of each reaction in the challenge phase should be provided, together with the opinion of the investigator as to whether such reactions are felt to be indicative of contact sensitization.

C. Combined Studies

Alternatively, the cumulative skin irritation study and the skin sensitization study can be combined into a single study. The study design would be identical to that described for the skin sensitization study (see section B), except that patch application during the induction phase should be daily for 23 hours (plus or minus 1 hour) each day over 21 days.

APPENDIX A

Skin Irritation Scoring Systems

The following scoring system for irritation and/or sensitization reactions is included as an example of a scoring system that can be used for these studies. Other validated scoring systems can be used in quantifying skin reactions. The inclusion of this system should not be interpreted as an endorsement of the system by the Agency. It is provided as an example only.[3]

I. Dermal response:

0 = no evidence of irritation
1 = minimal erythema, barely perceptible
2 = definite erythema, readily visible; minimal edema or minimal papular response
3 = erythema and papules
4 = definite edema
5 = erythema, edema, and papules
6 = vesicular eruption
7 = strong reaction spreading beyond test site

II. Other effects:

A = slight glazed appearance
B = marked glazing
C = glazing with peeling and cracking
F = glazing with fissures
G = film of dried serous exudate covering all or part of the patch site
H = small petechial erosions and/or scabs

[3] This is the system used by Hill Top Research, Inc.

APPENDIX B

Adhesion Score

The following scoring system is included as an example of a scoring system that can be used for this type of study. Other validated scoring systems may be equally effective in quantifying comparative adhesion of transdermal systems. The inclusion of this system is not to be interpreted as an endorsement of the system by the Agency. It is provided as an example only. [4]

An estimate of the adherence of the transdermal system will be rated as follows:

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

[4] This is the system used by Hill Top Research, Inc.

APPENDIX C

To be considered equivalent for a particular response, the average response for the generic (μ_T) should be between 80% and 125% of the average response for the innovator (μ_R). It is recommended that the response of the generic be equivalent to or better than the innovator. This implies a one-sided test.

For a variable for which low scores are better, such as mean irritation score or total cumulative irritation score, the hypotheses would be

$$H_0: \mu_T/\mu_R > 1.25$$
$$H_1: \mu_T/\mu_R \# 1.25$$

which (assuming that $\mu_R > 0$) implies

$$H_0: \mu_T - 1.25\mu_R > 0$$
$$H_1: \mu_T - 1.25\mu_R \# 0$$

The null hypothesis H_0 will be rejected when the upper limit of the 90% confidence interval (that is, the 95% upper confidence bound) for the quantity $\mu_T - 1.25\mu_R$ is less than or equal to zero.

For a variable for which high values are better, such as time to removal score, the hypotheses would be

$$H_0: \mu_T/\mu_R < 0.80$$
$$H_1: \mu_T/\mu_R \$ 0.80$$

which (assuming that $\mu_R > 0$) implies

$$H_0: \mu_T - 0.80\mu_R < 0$$
$$H_1: \mu_T - 0.80\mu_R \$ 0$$

The null hypothesis H_0 will be rejected in this case when the lower limit of the 90% confidence interval (that is, the 95% lower confidence bound) for the quantity $\mu_T - 0.80\mu_R$ is greater than or equal to zero.

In either case, if the null hypothesis H_0 is rejected the generic should be considered equivalent or better than the innovator.

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