

Draft Guidance on Diclofenac Epolamine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Diclofenac epolamine

Dosage Form; Route: Patch; topical

Recommended Studies: Four studies

1. Type of study: Bioequivalence (BE) with pharmacokinetic (PK) endpoints Study
Design: Single-dose, two-treatment, two-period crossover, in vivo
Strength: 1.3%
Subjects: Healthy males and non-pregnant, non-lactating females, general population
Additional comments: One whole topical patch should be applied to clean, dry, intact, healthy skin on the upper inner arm and worn for 12 hours. 24-hour post-dose sampling time should be included in the BE study. Adequate skin contact is essential for the in vivo performance of the topical patch and the PK may be altered when a topical patch loses its adherence to the skin. Therefore, the adhesion of each topical patch should be monitored and recorded throughout the PK study. The PK samples should be collected and analyzed from all subjects at all sampling times regardless of the adhesion scores of the patch. Overlays should not be used during the study.
2. Type of study: Adhesion Study
Design: Single-dose, two-treatment, two period crossover in vivo
Strength: 1.3%
Subjects: Healthy males and non-pregnant, non-lactating females, general population
Additional comments: The sponsor may elect to evaluate the PK BE (study 1) and the adhesion (study 2) in a single multi-purpose study or in independent studies. In either case, studies should be adequately powered to evaluate the BE with appropriately selected PK endpoints, and independently, the comparative assessment of adhesion. The sponsor should follow FDA's current thinking in the guidance "Assessing Adhesion with Transdermal Delivery Systems and Topical Patches for ANDAs" for the design and conduct of the independent adhesion study or the multi-purpose study to evaluate both the PK BE and adhesion.
3. Type of study: BE with clinical endpoint
Design: Randomized, double-blind, parallel, placebo-controlled, in vivo
Strength: 1.3%
Subjects: Males and non-pregnant, non-lactating females with ankle sprain
Additional comments: Specific recommendations are provided below.

4. Type of study: Skin irritation and sensitization
Design: Randomized, evaluator-blinded, in vivo within-subject repeat test
Strength: 1.3% (Dose: one-fourth of 1.3% patch)
Subjects: Healthy males and non-pregnant, non-lactating females, general population
Additional comments: Specific recommendations are provided below. Adequate skin contact is essential for maximal induction of irritation and sensitization and it may be altered when a patch loses its adherence to the skin. Therefore, the adhesion of each patch should be monitored and recorded throughout the irritation and sensitization study. Any loss of adhesion that develops due to skin irritation or sensitization should be evaluated.
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Analytes to measure (in appropriate biological fluid): Diclofenac in plasma (PK-based BE Study 1 only)

Bioequivalence based on (90% CI): Diclofenac (PK-based BE Study 1 only); Clinical endpoint (Study 2)

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods web site, available to the public at the following location: <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

General comments:

1. These recommendations are specific to this product and may not be appropriate for bioequivalence studies of any other product, including any other dosage form or strength of diclofenac.
2. Please note that the Reference Listed Drug (RLD) name is designated as diclofenac epolamine topical patch, 1.3%. This designation is based on the concentration of diclofenac epolamine in the adhesive, which is 1.3%. Please formulate your product to contain 1.3% of diclofenac epolamine in the adhesive and to have the same active surface area as the RLD.
3. The Office of Generic Drugs (OGD) recommends that the test patch have a design that can be safely cut to a smaller size.
4. The OGD recommends conducting both a BE study with PK endpoints and a BE study with a clinical endpoint because the scientific literature does not currently support a direct correlation between plasma levels of diclofenac and the arrival of diclofenac at the local sites of action. Diclofenac Epolamine Topical Patch, 1.3% is approved for the

indication “topical treatment of acute pain due to minor strains, sprains, and contusions”. For this indication, the site of action is in substantially deeper tissues than the dermal/epidermal junction, where drug is absorbed into the systemic circulation. The site of action for a sprain is in or around the injured ligament(s) that surround a joint and connect bone to bone . The site of action for a strain is in or around the injured or torn muscle(s) and/or tendon(s) that connect muscle to bone. A contusion is a bruise caused by trauma to an injured area when blood vessels break and blood pools around the injured area. Thus, the site of action for a contusion is the injured tissue, e.g., skin, subcutaneous tissue, muscle, ligament, tendon, or bone

Additional comments regarding the BE study with a clinical endpoint:

1. The OGD recommends conducting a bioequivalence study with a clinical endpoint in the treatment of acute ankle pain due to a minor ankle sprain. Subjects are to be randomized to receive a diclofenac epolamine topical patch test product, the RLD, or placebo control applied as one whole patch every 12 hours for 3 days (i.e., total of 6 patches) to the most painful area of the ankle. The primary endpoint is the change from baseline to 72 hours after application of the first patch in the self-evaluation of pain on active mobilization measured in mm on the Visual Analog Scale (VAS).
2. Inclusion Criteria (the sponsor may add additional criteria)
Males and non-pregnant, non-lactating females aged 18 to 65 years with a minor ankle sprain that occurred within 48 hours of beginning the treatment phase AND baseline self-evaluation of acute ankle pain on active mobilization by the VAS \geq 50 mm.
3. Exclusion Criteria (the sponsor may add additional criteria)
 - a. Pregnant or lactating female.
 - b. Sprain occurred > 48 hours prior to study enrollment.
 - c. Ankle sprain requires an orthopedic or surgical treatment.
 - d. Ankle sprain treated prior to study entry by topical, oral, or parenteral NSAID, physiotherapy, ultrasound, physical therapy or acupuncture.
 - e. Baseline self-evaluation of pain on active mobilization by the VAS < 50 mm.
 - f. Non-intact or damaged skin within the area to be treated, e.g., eczema, psoriasis, exudative dermatitis, infected lesion, burn or wound.
 - g. Medical history of asthma, urticaria, angioedema, bronchospasm, ulcer disease, gastrointestinal bleeding, hypertension, edema, heart failure or cardiovascular disease.
 - h. Medical history of any chronic pain disorder.
 - i. Coagulation defects.
 - j. Severe cardiac, renal or hepatic impairment.
 - k. Severe systemic disease (e.g., cancer, severe acute infection)
 - l. Use within one month prior to randomization of 1) immunomodulators or immunosuppressive therapies, 2) interferon, 3) oral or parenteral corticosteroids or 4) cytotoxic drugs.
 - m. Use within 7 days prior to randomization of any topical agent on the affected ankle.
 - n. Use within 7 days prior to randomization of topical, oral or parenteral treatment with NSAIDs or aspirin.

- o. Use within 12 hours prior to randomization of an analgesic.
 - p. Known allergy or hypersensitivity to diclofenac, aspirin or other NSAIDs, or any excipient in the test product or RLD.
4. The protocol should include a list of the prescription and over-the-counter drug products, procedures, and activities that are prohibited during the study, such as:
 - a. Any therapy for treatment of pain, e.g., oral, topical, or parenteral NSAIDs, aspirin or narcotic pain medication, other than study treatment.
 - b. Anticoagulants, lithium, digoxin, antidiabetic agents, quinolone antimicrobials, diuretics, ACE inhibitors, immunomodulators or immunosuppressive therapies, interferon, oral, systemic or topical corticosteroids, or cytotoxic drugs.
 - c. Topical product other than the assigned treatment (including moisturizers, sun screen, creams, ointments, lotions, and powders) applied on or near the treatment area.
 - d. Treatment to affected ankle, e.g., physiotherapy, ultrasound, physical therapy or acupuncture.
 - e. Subjects should be advised to avoid exposing the patch application site(s) to external sources of direct heat, e.g., heating pads or electric blankets, heat lamps, saunas, hot tubs, heated water beds, and prolonged direct sunlight, while wearing the patch.
 5. The recommended primary endpoint of the study is the mean change from baseline to study day 3 (i.e., 72 hours after the first patch application) in the self-evaluation of pain on active mobilization by the Visual Analog Scale (VAS) in mm.
 6. The protocol should clearly define the per-protocol (PP), modified intent-to-treat (mITT) and safety populations.
 - a. The PP population includes all randomized subjects who met all inclusion/exclusion criteria, applied a prespecified proportion of the scheduled applications (e.g., 75% to 125%) of the assigned product for the specified duration of the study, did not miss more than 4 consecutive scheduled applications, and completed the primary endpoint evaluation within the designated visit window (+/- 24 hours) with no protocol violations that would affect the treatment evaluation. The protocol should specify how compliance will be verified, e.g., by the use of subject diaries, and the protocol violations that would affect the treatment evaluation.
 - b. The mITT population includes all randomized subjects who met all inclusion/exclusion criteria, received study treatment, and returned for at least one post-baseline visit. The mITT population should be used to compare both test and reference products to placebo.
 - c. The safety population includes all randomized subjects who received study treatment.
 7. Subjects whose condition worsens and require alternate or supplemental therapy for the treatment of ankle pain during the study should be discontinued, included in the PP population analysis using LOCF, and provided with effective treatment. Subjects discontinued early for other reasons should be excluded from the PP population, but included in the mITT population, using Last Observation Carried Forward (LOCF).

8. All adverse events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of AEs should include date of onset, description of the AE, severity, relation to study medication, action taken, outcome and date of resolution. This information is needed to determine if the incidence and severity of adverse reactions is different between the test product and RLD.
9. Application site reactions such as erythema, dryness, burning/stinging, erosion, edema, pain and itching are to be recorded at each visit to allow a comparison between treatment groups. A descriptive analysis comparing the application site reactions for each treatment group is recommended. It is important to ensure that the test product is not worse than the reference product with regard to the expected and unexpected application site reactions.
10. Adhesion data should be collected during the course of the study to document that adhesion of the products is adequate. Adhesion may be self-evaluated on non-visit days. You may consider establishing criteria for using tape to reinforce any patches that are lifting during the study.
11. Please evaluate adhesion using a scale such as the following:
 - 0 = \geq 90% adhered (essentially no lift off of the skin)
 - 1 = \geq 75% to $<$ 90% adhered (some lifting off of the skin e.g., edges only)
 - 2 = \geq 50% to $<$ 75% adhered (less than half of the system lifting off of the skin)
 - 3 = $<$ 50% adhered by not detached (more than half the system lifting off of the skin without falling off)
 - 4 = patch detached (patch completely off the skin)
12. The method of randomization should be described in the protocol. It is recommended that an independent third party generate and hold the randomization code throughout the conduct of the study in order to minimize bias. The sponsor may generate the randomization code if not involved in the packaging and labeling of the study medication. A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity of each subject.
13. A detailed description of the blinding procedure is to be provided in the protocol. The packaging of the test, reference and placebo products should be similar in appearance to make differences in treatment less obvious to the subjects and to maintain adequate blinding of evaluators. When possible, neither the subject nor the investigator should be able to identify the treatment. The containers should not be opened by the subject at the study center.
14. Please refer to the Guidance for Industry, “Handling and Retention of BA and BE Testing Samples”, regarding retention of study drug samples and for maintenance of records of bioequivalence testing.

15. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.
16. To establish bioequivalence, the 90% confidence interval of the test/reference ratio of mean change from baseline to study day 3 (i.e., 72 hours after the first patch application) for the primary endpoint [mean change from baseline to study day 3 (i.e., 72 hours after the first patch application) in the self-evaluation of pain on active mobilization by the VAS in mm] should be within [0.80, 1.25], using the PP population.
17. As a parameter for determining adequate study sensitivity, the test product and RLD should both be statistically superior to placebo ($p < 0.05$, two-sided) for the primary endpoint [mean change from baseline to study day 3 (i.e., 72 hours after the first patch application) in the self-evaluation of pain on active mobilization by the VAS in mm], using the mITT study population and LOCF.
18. The following Statistical Analysis Method is recommended for equivalence testing for a continuous variable:

Equivalence Analysis For A Continuous Variable

The compound hypothesis to be tested is:

$$H_0: \mu_T / \mu_R \leq \theta_1 \text{ or } \mu_T / \mu_R \geq \theta_2 \text{ versus } H_A: \theta_1 < \mu_T / \mu_R < \theta_2$$

Where μ_T = mean of test treatment, and μ_R = mean of reference treatment

Typically, we reject H_0 with a type I error $\alpha = 0.05$ (two 1-sided tests), if the 90% confidence interval for the ratio of means between test and reference products (μ_T / μ_R) is contained within the interval $[\theta_1, \theta_2]$, where $\theta_1 = 0.80$ and $\theta_2 = 1.25$.

Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products.

19. Study data should be submitted to the OGD in electronic format.
 - a. A list of file names, with a simple description of the content of each file, should be included.
 - b. Please provide a “pdf” document with a detailed description of the codes that are used for each variable in each of the SAS datasets (for example, Y=Yes, N=No for analysis population).
 - c. All SAS transport files should include .xpt as the file extension and should not be compressed. A simple SAS program to open the data transport files and SAS files should be included.
 - d. Primary data sets should consist of two data sets: No Last Observation Carried Forward (NO-LOCF-pure data set) and Last Observation Carried Forward (LOCF-modified data set).

- e. Please provide a separate dataset for variables such as demographics, baseline admission criteria, adverse events, reasons for discontinuation of treatment, concomitant medications, medical history, compliance and comments, etc.
20. Please provide a summary dataset containing a separate line listing for each subject (if data exist) using the following headings, if applicable:
- a. Study identifier
 - b. Subject identifier
 - c. Site identifier: study center
 - d. Age
 - e. Age units (years)
 - f. Sex
 - g. Race
 - h. Name of Actual Treatment (exposure): test product, RLD, placebo
 - i. Location of Treatment Area
 - j. Duration of Treatment (total number of patch applications)
 - k. Completed the study (yes/no)
 - l. Reason for premature discontinuation of subject
 - m. Subject required acetaminophen or additional treatment for ankle pain due to unsatisfactory treatment response (yes/no)
 - n. Per Protocol (PP) population inclusion (yes/no)
 - o. Reason for exclusion from PP population
 - p. Modified intent to Treat (mITT) population inclusion (yes/no)
 - q. Reason for exclusion from mITT population
 - r. Safety population inclusion (yes/no)
 - s. Reason for exclusion from Safety population
 - t. VAS (in mm) on Day 0 (baseline)
 - u. VAS (in mm) on Day 3 (72 hours after first patch application)
 - v. Any patch removed due to strong skin irritation reaction (yes/no)
 - w. Total number of patches removed due to strong skin irritation reaction
 - x. Any patch reinforced with tape (yes/no)
 - y. Total number of patches reinforced with tape
 - z. Treatment compliance: number of missed doses per subject
 - aa. Concomitant medication (yes/no)
 - bb. Adverse event(s) reported (yes/no)

Please refer to Table 1 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 1: Example of a summary dataset containing one line listing for each subject

STUDYID	SUBJID	SITEID	AGE	AGEU	SEX	RACE	EXTRT	EXLOC	EXDUR	completd	disc_rs	add_trt	pp	pp_rs	mitt	mitt_rs
101	1	01	54	YEARS	F	1	A	RA	14	Y		N	Y		Y	
101	2	01	58	YEARS	F	1	B	LA	14	Y		N	Y		Y	

safety	safe_rs	vas_0	vas_3	remov	nu_remov	reinf	nu_reinf	complan	CM	AE
Y		50	14	N	0	N	0	0	Y	Y
Y		60	24	N	0	N	0	0	N	N

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final dated 11/12/08.

- STUDYID: Study Identifier
- SUBJID: Subject Identifier for the Study
- SITEID: Study Site Identifier
- AGE: Age
- AGEU: Age units (years)
- SEX: Sex, e.g., M=Male, F=Female, U=Unknown
- RACE: Race, e.g., 1=White, 2=Black or African American, 3=Asian, 4=American Indian or Alaska Native, 5=Native Hawaiian or Other Pacific Islanders
- EXTRT: Name of Actual Treatment (exposure), e.g., A=test product, B= RLD, C=placebo
- EXLOC: Location of Treatment Area, e.g. RA=right ankle, LA=left ankle
- EXDUR: Duration of Treatment (total number of patch applications)
- completd: Subject completed the study, e.g., Y=Yes, N=No
- disc_rs: Reason for premature discontinuation from the study, e.g., A=adverse event, B=death, C=lost to follow-up, D=non-compliance with treatment, E=treatment unblinded, F=subject moved out of area, G=unsatisfactory treatment response, H=withdrew consent, I=protocol violation, K=other event
- add_trt: Subject required acetaminophen or additional treatment for ankle pain due to unsatisfactory treatment response, e.g., Y=Yes, N=No
- pp: Per Protocol (PP) population inclusion, e.g., Y=Yes, N=No
- pp_rs: Reason for exclusion from PP population, e.g., A=prematurely discontinued, B=lost to follow-up, C=subject moved out of the area, D=noncompliant, etc.
- mitt: Modified Intent to Treat (mITT) population inclusion, e.g., Y=Yes, N=No

mitt_rs: Reason for exclusion from mITT population, e.g., A=never treated, etc.
 safety: Safety population inclusion, e.g., Y=Yes, N=No
 safe_rs: Reason for exclusion from Safety population, e.g., A=never treated, etc.
 vas_0: VAS (in mm) on Day 0 (baseline)
 vas_3: VAS (in mm) on Day 3 (72 hours after first patch application)
 remov: Any patch removed due to strong skin irritation reaction (yes/no)
 nu_remov: Total number of patches removed due to strong skin irritation reaction
 reinf: Any patch reinforced with tape (yes/no)
 nu_reinf: Total number of patches reinforced with tape
 complian: Treatment compliance, e.g., number of missed doses per subject
 CM: Concomitant medication, e.g., Y=Yes, N=No
 AE: Adverse event(s) reported, e.g., Y=Yes, N=No

21. Please provide a dataset containing a separate line listing for each visit per subject (if data exist) using the following headers, if applicable:
- Study identifier
 - Subject identifier
 - Name of Actual Treatment (exposure): test product, RLD, placebo control
 - Visit number
 - Visit date
 - Number of days since baseline visit
 - Evaluator: identity of evaluator
 - VAS (in mm) at that visit [e.g., for Day 0 (baseline), 1, 2 or 3]
 - Adhesion score at that visit (e.g., for Day 1, 2 or 3)
 - Concomitant medication reported during this visit (yes/no)
 - Adverse event reported during this visit (yes/no)
 - Laboratory testing during this visit (yes/no)

Please refer to Table 2 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 2: Example of dataset containing one line listing for each visit per subject

STUDYID	SUBJID	EXTRT	VISITNUM	SVSTDTTC	ELTMBS	EVAL	vas_0	vas_1	vas_2	vas_3	adh_1	adh_2	adh_3	CMrpt	AErpt	LBtest
101	1	A	2	2004-07-01	1			40			0			Y	Y	N

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final dated 11/12/08.

STUDYID: Study Identifier
 SUBJID: Subject Identifier for the Study

EXTRT:	Name of Actual Treatment (exposure), e.g. A=test product, B=RLD, C=placebo control
VISITNUM:	Visit Sequence Number
SVSTDTC:	Visit date: (SVSTDTC=Subject Visit Start Date Time-Character)
ELTMBL:	Elapsed Time since Baseline (days)
EVAL:	Evaluator: identity of the evaluator
vas_0:	VAS (in mm) at baseline (e.g., Visit 1)
vas_1:	VAS (in mm) on Day 1 (e.g., Visit 2)
vas_2:	VAS (in mm) on Day 2 (e.g., Visit 3)
vas_3:	VAS (in mm) on Day 3 (e.g., Visit 4)
adh_1:	Adhesion score for Day 1 (e.g., Visit 2)
adh_2:	Adhesion score for Day 2 (e.g., Visit 3)
adh_3:	Adhesion score for Day 3 (e.g., Visit 4)
CMrpt:	Concomitant Medication reported during this visit, e.g., Y=Yes, N=No
AErpt:	Adverse Event reported during this visit, e.g., Y=Yes, N=No
LBtest:	Laboratory Testing performed during this visit, e.g., Y=Yes, N=No

Additional comments regarding the skin irritation and sensitization study:

1. The OGD recommends evaluating skin irritation and sensitization in a single study. To support approval, the test product should be no more irritating than the RLD and be no more sensitizing than the RLD. Each parameter is to be evaluated with a separate analysis. The primary endpoints should be considered as co-primary endpoints, e.g., for each of them, the study should demonstrate that the test product is no worse than the RLD. The analysis for each parameter, and the primary endpoint(s) and any secondary endpoint(s) for each analysis, are to be clearly defined in the protocol prior to the start of the study. A clear, objective definition of a sensitization reaction is also to be prespecified in the protocol.
2. The RLD patch has a design that can be safely cut and if the test patch also has a design that can be cut to a smaller size, one fourth of each patch should be used for these studies.¹
3. The recommended study consists of two phases, a 21-day Induction Phase, followed by a 14 to 17 day rest period, and a Challenge Phase.

During the Induction Phase when using one fourth patches, all test articles (i.e., one-fourth of the test product², one-fourth of the RLD, optional one-fourth of the vehicle

¹ Because of the low systemic exposure of diclofenac with the topical patch, it appears unlikely that wearing two whole patches for 21 consecutive days during the Induction Phase of the skin irritation and sensitization study would be a safety issue. However, because of the large size of the patch, the lack of PK data for patches worn longer than 12 hours, and none of the RLD clinical trials evaluating the safety of simultaneously wearing more than one whole patch, it is recommended to use partial one-fourth patches, each applied for 24 hours for 21 consecutive days during the Induction Phase of the skin irritation and sensitization study.

² The test product evaluated should be the actual patches to be marketed.

patch³ and optional negative control⁴) are to be applied simultaneously to each subject on dry, intact skin at different sites, with sequential patch applications to the same skin sites every 24 hours for a total of 21 consecutive days. The irritation evaluation is to be conducted during the Induction Phase, with assessment of “Dermal Response” and “Other Effects” at the time of each patch change. The patches should be applied to clean, dry, hairless, intact healthy skin. Thus, it is recommended to apply the patches daily on Days 1-21 to the same sites and to have each of them remain in place for 24 hours (a total of 21 days altogether). The Day 21 patches would be removed on Day 22. The irritation evaluation is to be conducted during the Induction Phase, with assessment of “Dermal Response” and “Other Effects” at the time of each patch change.

The Challenge Phase consists of a single 48-hour challenge patch application of one-fourth of the test product, one-fourth of the RLD patch, optional one-fourth of the vehicle patch and optional negative control to a naïve site followed by an assessment of “Dermal Response” and “Other Effects” at 30 minutes and at 24, 48, and 72 hours after challenge patch removal, with a narrative description of any reactions observed, together with the opinion of the investigator as to whether such reactions are felt to be indicative of a contact sensitization. A re-challenge test four to eight weeks following the original challenge, conducted in the same manner, is recommended for all subjects with a potential sensitization reaction.

Adhesion should be monitored and recorded prior to patch removal and throughout the entire study period to ensure adequate skin contact for maximal induction of irritation and sensitization.

4. Inclusion Criteria (the sponsor may add additional criteria):
Healthy male and non-pregnant, non-lactating female subjects 18-65 years of age inclusive.
5. Exclusion Criteria (the sponsor may add additional criteria):
 - a. Pregnant or lactating female.
 - b. Known allergy to diclofenac, aspirin or NSAIDs.
 - c. Known allergy or hypersensitivities to medical adhesives or any component of the test product or RLD.
 - d. Medical history of asthma, urticaria, angioedema, bronchospasm, ulcer disease, gastrointestinal bleeding, coagulation defects, hypertension, edema, heart failure or cardiovascular disease.
 - e. Medical history of condition that would significantly influence the immune response (e.g., primary or acquired immunodeficiencies such as human immunodeficiency virus (HIV) positive or AIDS, allergic diseases such as anaphylaxis, asthma or generalized drug reaction, neoplasms such as lymphoma or leukemia, rheumatoid arthritis or systemic lupus erythematosus).

³ The optional vehicle patch should have all of the inactive ingredients and be identical to the test product in every manner except for the absence of diclofenac epolamine.

⁴ An example of the optional negative control is an occlusion type device with normal saline applied on a polyester pad within the device chamber.

- f. Medical history of significant dermatologic diseases or conditions, such as atopy, psoriasis, vitiligo or conditions known to alter skin appearance or physiologic response (e.g. diabetes, porphyria).
 - g. History of significant dermatologic cancers (e.g. melanoma, squamous cell carcinoma), except basal cell carcinomas that were superficial and did not involve the investigative site.
 - h. Within 3 weeks prior to dosing, use of medications or treatments that would significantly influence or exaggerate responses to the test product or that would alter inflammatory or immune response to the product (e.g. cyclosporine, tacrolimus, systemic or topical corticosteroids, cytotoxic drugs, immune globulin, Bacillus Calmette-Guerin (BCG), monoclonal antibodies, radiation therapy).
 - i. Within 72 hours prior to dosing, use of antihistamines or use of topical drugs at patch site.
 - j. Subject has an obvious difference in skin color between arms or the presence of a skin condition, excessive hair at the application sites, scar tissue, tattoo, or coloration that would interfere with placement of test articles, skin assessment, or reactions to drug.
 - k. Presence of open sores, exudative dermatitis, eczema, infected lesion, burns or wounds at the application site.
6. During both the Induction Phase and Challenge Phase, the skin reactions are to be evaluated and scored according to the following two scales⁵:

Scale 1: Dermal Response

Skin Appearance	Score
No evidence of irritation	0
Minimal erythema, barely perceptible	1
Definite erythema, readily visible; minimal edema or minimal papular response	2
Erythema and papules	3
Definite edema	4
Erythema, edema, and papules	5
Vesicular eruption	6
Strong reaction spreading beyond the application site.	7

Scale 2: Other Effects

Observation	Score (Numeric equivalent)
Slightly glazed appearance	A (0)
Marked glazed appearance	B (1)

⁵ Berger RS and JP Bowman. A reappraisal of the 21-day cumulative irritation test in man. *J. Toxicol.-Cut. & Ocular Toxicol.* 1982; 1 (2); 109-115.

Glazing with peeling and cracking	C (2)
Glazing with fissures	F (3)
Film of dried serous exudates covering all or part of the patch site	G (3)
Small petechial erosions and/or scabs	H (3)

When an “Other Effects” score is observed, each score should be reported as a number and letter combination score and also as a numerical total (i.e. numerical “Dermal Response” score + numeric equivalent for the “Other Effects” lettered score).

7. To ensure adequate adhesion of the test articles, adhesion scores are to be recorded just prior to patch removal. The recommended scoring system for adhesion of topical patches is indicated as follows:
 - 0 = \geq 90% adhered (essentially no lift off the skin)
 - 1 = \geq 75% to $<$ 90% adhered (some lifting off the skin e.g., edges only)
 - 2 = \geq 50% to $<$ 75% adhered (less than half of the patch lifting off the skin)
 - 3 = $>$ 0% to $<$ 50% adhered but not detached (more than half of the patch lifting off the skin without falling off)
 - 4 = 0% adhered - patch detached (patch completely off the skin)
8. During the induction phase, subjects should have the first patch placed on Day 1 and return for daily visits on Days 2-21 for adhesion scoring, patch removal, irritation scoring, and patch replacement and on Day 22 for adhesion scoring, patch removal and irritation scoring. After wearing the challenge patch for 48 hours (or until removal due to intolerable reaction), subjects should return for adhesion scoring, patch removal and irritation scoring at 30 minutes and at 24, 48, and 72 hours after challenge patch removal. Scoring of patch adherence and skin reactions should be performed by a trained and blinded observer at each patch removal. All efforts should be made to ensure that the same scorer is used for all observations. If the same scorer is not used in all cases, inter-scorer variability needs to be addressed in the protocol, specifying the training and standards for each score.
9. For subjects who experience irritation consistent with a combined score of \geq 3, or who experience symptomatic intolerable irritation, the patch may be moved to a new site in order to complete the 21-day Induction Phase and continue with the sensitization part of the study. In this circumstance the highest score observed (not truncated to 3) prior to discontinuation of the first patch site should be carried forward for all remaining observations in the irritation analysis.
10. Whereas this study using partial patches can not be used for a definitive assessment of adhesion performance of the active product, criteria may be established for using tape or an overlay to reinforce any patches that are lifting. This may be preferable to replacing detached patches, since shorter application intervals could give different irritation results. If the patch is reinforced with tape or an overlay, skin irritation associated with the tape or overlay area should be reported separately from that of the patch application area.

11. If a patch completely detaches, it should be replaced within 24 hours and the subject should continue in the study. During the 21-day Induction Phase, if a patch is completely detached for more than 24 hours (unless the patch was removed for an unacceptable degree of irritation), the subject should be excluded from both the irritation and sensitization analyses for that product. During the 48-hr Challenge Phase, if a patch is completely detached for more than 24 hours, the subject should be excluded from the sensitization analysis. The subject should note the date and time of detachment as soon as it occurs.
12. The irritation and adhesive properties may be sensitive to climate changes. Therefore, OGD prefers that the study be conducted in multiple centers with different climate conditions.
13. The protocol should include a list of the prescription and over-the-counter drug products, procedures, and activities that are prohibited during the study, such as:
 - a. Nonsteroidal anti-inflammatory drugs (NSAIDs)
 - b. Anticoagulants, lithium, digoxin, antidiabetic agents, quinolone antimicrobials, diuretics, ACE inhibitors, immunomodulators or immunosuppressive therapies, interferon, oral, systemic or topical corticosteroids, or cytotoxic drugs.
 - c. Use of medications or treatments that would significantly influence or exaggerate responses to the test product or that would alter inflammatory or immune response to the product (e.g. antihistamines, systemic or topical corticosteroids, cyclosporine, tacrolimus, cytotoxic drugs, immune globulin, Bacillus Calmette-Guerin (BCG), monoclonal antibodies, radiation therapy).
 - d. Subjects should not apply make-up, creams, lotions, powders, or other topical products to the skin area where the patch will be placed, as this could affect adhesive performance or irritation potential.
 - e. Subjects should be advised to avoid exposing the patch application site(s) to water or to external sources of direct heat, e.g., heating pads or electric blankets, heat lamps, saunas, hot tubs, heated water beds, and prolonged direct sunlight, while wearing the patch.
14. Assignment of the test product, RLD, optional vehicle patch and optional negative control to skin sites should be randomized. The method of randomization should be described in the protocol. It is recommended that an independent third party generate and hold the randomization code throughout the conduct of the study in order to minimize bias. A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity for each application site on each subject.
15. Efforts should be made to blind the evaluation of irritation and sensitization.
16. Please refer to the Guidance for Industry, "Handling and Retention of BA and BE Testing Samples", regarding retention of study drug samples and for maintenance of records of bioequivalence testing.

17. An adequate number of subjects should be enrolled to ensure that at least 200 evaluable subjects are included in the PP population.

Safety Data and Analyses

18. All application site reactions are to be reported in the data tables and in the detailed narrative description for each subject’s response in both phases of this study in the study report. These would include subject complaints such as dryness, itching, burning, pain, or soreness, etc., identifying to which application site the complaint applies. These reports are to be compared between test articles.
19. The safety analyses should include all subjects who received a dose of study medication. Safety analyses should include comparing the test product, RLD, optional vehicle patch, and optional negative control with regard to the occurrence and severity of application site adverse events (AEs). Systemic drug-related AEs and concomitant medications are also to be reported but cannot be distinguished between test articles.

Skin Irritation Data Tables and Analyses

20. For each day during the Induction Phase, when the skin is evaluated for irritation, please provide a frequency table showing the number of applications of each test article with each combined “Dermal Response” and “Other Effect” score using Last Observation Carried Forward for subjects who discontinued a test article because of unacceptable irritation. Please refer to Table 3 as an example.

Table 3: Number (%) of Subjects by Induction Phase Day and Drug Product with a Specific Combined “Dermal Response” and “Other Effect” Score

Induction Phase Day; Product	Combined “Dermal Response” and “Other Effect” Score										
	0	1	2	2A	2B	3	3A	3B	3C	3F	etc.
Day 2: Test Product											
Day 2: RLD											
Day 2: Vehicle Patch (optional)											
Day 2: Negative Control (optional)											
Day 3: Test Product											
Day 3: RLD											
etc.											

21. The Analysis Populations should be defined separately for each parameter and should be defined per patch instead of per subject. The PP Population for evaluation of skin irritation should be defined as follows:

Irritation Analysis– the test articles need to be applied sequentially to the same site for the entire 21 day induction phase (without any period of detachment longer than 24 hours) to be evaluated for the cumulative irritation effect OR if a patch is moved or removed due to excessive irritation, it should be included using Last Observation Carried Forward (LOCF).

22. For each test article (test product, RLD, optional vehicle patch and optional negative control), the mean cumulative irritation score is to be calculated as the sum of all combined “Dermal Response” and “Other Effects” scores observed at each observation divided by the total number of observations.
23. In addition to the cumulative irritation scores, the following data should be provided for each test article:
 - a. Total number of observations with a combined “Dermal Response” and “Other Effects” irritation score of 3 or more for each product.
 - b. Number of patches that were moved or removed due to an unacceptable degree of irritation.
 - c. Number of days until sufficient irritation occurred to preclude repeat application to the same site.
24. To demonstrate non-inferiority of the test product compared to the RLD with regard to the cumulative irritation scores, the upper bound of the one-sided 95% CI of the mean test product score minus 1.25 times the mean RLD score should be less than or equal to 0. For the irritation evaluation, the OGD also considers other clinically relevant data including the number of applications that reach a maximal irritation score and the number of subjects that discontinue the product applications because of unacceptable irritation.

The same mean cumulative score could be reached with a small number of high scores (e.g., ≥ 3) as with a larger number of low scores (e.g., 1, which are of little clinical significance). Thus, it is difficult to determine the clinical meaningfulness of a given cumulative score or a given difference between products with regard to mean cumulative scores. Therefore, in addition to cumulative scores, it is necessary to also evaluate the proportion of subjects with a meaningful degree of irritation for each product. The proportion of subjects with a meaningful degree of irritation should be no higher for the test product than for the RLD, and irritation should not occur earlier in the application period for the test product than for the RLD. To be approved, the test product should be non-inferior with regard to cumulative irritation scores and also show no meaningful difference with regard to degree of irritation.

Sensitization Data Tables and Analyses

25. Please provide a frequency table showing the number of applications of each test article during the Challenge Phase with a specific combined “Dermal Response” numerical score and “Other Effect” letter score by each evaluation time point.

26. For all subjects with at least one combined score of 2 or more at 48 or 72 hours after patch removal in the Challenge Phase, please provide a table showing the actual scores for each subject at each evaluation time point during the Induction and Challenge Phases.
27. The Analysis Populations should be defined separately for each parameter and should be defined per patch instead of per subject. The PP Population for evaluation of sensitization should be defined as follows:

Sensitization Analysis – includes all test articles worn (without any period of detachment longer than 24 hours) for the full 21 day induction phase AND the entire 48-hour challenge phase AND the subject should return for at least one of the scheduled evaluations at 48 and 72 hours after removal of the challenge patch. If a test article is removed prior to the end of the 48-hour challenge phase due to an intolerable reaction, the application site should be evaluated at 24, 48, and 72 hours after patch removal and be included in the sensitization analysis using LOCF.

28. For each test article, individually evaluate each PP subject with a combined score of 2 or greater at 48 or 72 hours after patch removal during the Challenge Phase for potential sensitization. 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 a contact sensitization. Consider a subject to be potentially sensitized if all of the following criteria are met:
 - a. The subject has at least one evaluation occurring at more than 24 hours (e.g., at 48 or 72 hours) after the removal of the Challenge Phase patch.
 - b. The subject has a combined “Dermal Response” and “Other Effects” numeric score of at least 2 at their last evaluation during the Challenge Phase.
 - c. The combined “Dermal Response” and “Other Effects” numeric scores obtained during the Challenge Phase evaluations are generally higher than the combined “Dermal Response” and “Other Effects” numeric scores obtained during the Induction Phase.
 - d. If the subject completed a Rechallenge Phase, the above 3 criteria were met during both the Challenge Phase and the Rechallenge Phase.

Scores that resolve before 48 hours are generally considered to be due to irritation instead of sensitization. Provide the total number of subjects considered sensitized to the test product and RLD.

29. The sponsor should provide descriptive statistics comparing the proportion of subjects sensitized or potentially sensitized to each test article.

Adhesion Data Table

30. To ensure adequate skin contact for maximal induction of irritation and sensitization, please provide a frequency table showing the adhesion score for each patch per study visit. For patches that fall off, provide information about the duration of patch wear before the patch falls off.

Data Submission

31. Study data should be submitted to the OGD in electronic format.
 - a. A list of file names, with a simple description of the content of each file, should be included.
 - b. Please provide a “pdf” document with a detailed description of the codes that are used for each variable in each of the SAS datasets (for example, Y=yes, N=no for analysis population).
 - c. All SAS transport files should include .xpt as the file extension and should not be compressed. A simple SAS program to open the data transport files and SAS files should be included.
 - d. Primary data sets should consist of two data sets: No Last Observation Carried Forward (NO-LOCF-pure data set) and Last Observation Carried Forward (LOCF-modified data set).
 - e. Please provide a separate dataset for each study to include such variables as demographics, baseline admission criteria, baseline vital signs, adverse events, reasons for discontinuation of treatment, concomitant medications, medical history, compliance and comments, etc.

32. Please provide a summary dataset containing a separate line listing for each test article per subject (if data exist) using the following headings, if applicable:
 - a. Study identifier
 - b. Subject identifier
 - c. Site identifier: study center
 - d. Age
 - e. Age units (years)
 - f. Sex
 - g. Race
 - h. Name of Actual Treatment (exposure): test article (i.e., test product, RLD, optional vehicle patch and optional negative control)
 - i. Location of Dose Administration: patch application site
 - j. Duration of Treatment (total exposure in days) during Induction Phase: time from first application to discontinuation of test article during Induction Phase
 - k. Duration of Treatment (total exposure in days) during Challenge Phase: time from first application to discontinuation of test article during Challenge Phase
 - l. Per Protocol (PP) population inclusion for irritation analysis (yes/no)
 - m. Reason for exclusion from PP population for irritation analysis
 - n. PP population inclusion for sensitization analysis (yes/no)
 - o. Reason for exclusion from PP population for sensitization analysis

- p. Test article moved (yes/no)
- q. Number of times test article moved
- r. Test article discontinued (yes/no)
- s. Reason for test article discontinuation
- t. Adverse event(s) reported for this treatment arm (yes/no)

Please refer to Table 4 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 4: Example of a summary dataset for each individual test article per subject

STUDYID	SUBJID	SITEID	AGE	AGEU	SEX	RACE	EXTRT	EXLOC	EXDURind	EXDURch	ppirr	ppirr_rs	ppsen	ppsen_rs	mv	mv_n	dis	dis_rs	AErpt
101	1	01	54	YEARS	M	1	A	RUA	21	2	Y		Y		Y	1	N		N
101	1	01	54	YEARS	M	1	B	LUA	21	2	Y		Y		Y	1	N		N
101	2	01	45	YEARS	M	2	A	RUA	21	2	Y		N	B	N		N		N
101	2	01	45	YEARS	M	2	B	LUA	21	2	Y		N	B	N		N		N

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final dated 11/12/08.

- STUDYID: Study Identifier
- SUBJID: Subject Identifier for the Study
- SITEID: Study Site Identifier
- AGE: Age
- AGEU: Age units (years)
- SEX: Sex, e.g., M=Male, F=Female, U=Unknown
- RACE: Race, e.g. 1=White, 2=Black or African American, 3=Asian, 4=American Indian or Alaska Native, 5=Native Hawaiian or Other Pacific Islanders
- EXTRT: Name of Actual Treatment (exposure), e.g. A=test product, B= RLD, C=optional vehicle patch, D=optional negative control
- EXLOC: Location of Dose Administration (exposure): specific anatomical site of patch application, e.g., RUA=right upper arm, LUA=left upper arm
- EXDURind: Duration of Treatment during Induction Phase (exposure in days; 21 days exposure planned during Induction Phase)
- EXDURch: Duration of Treatment during Challenge Phase (exposure in days; 2 days exposure planned during Challenge Phase)
- ppirr: Per Protocol (PP) population for irritation analysis, e.g., Y=Yes, N=No
- ppirr_rs: Reason for exclusion from PP population for irritation analysis, e.g., A=prematurely discontinued prior to completing irritation phase due to AE that was not intolerable irritation, B=failed to complete irritation phase due to

lost to follow-up, C=failed to complete irritation phase due to subject moved out of the area, etc.

ppsen: PP population for sensitization analysis, e.g., Y=Yes, N=No

ppsen_rs: Reason for exclusion from PP population for sensitization analysis, e.g., A=prematurely discontinued prior to completing challenge phase due to AE that was not intolerable irritation, B=failed to return for at least one of the two challenge visits at 48 and 72 hours, etc.

mv: Test article moved, e.g., Y=Yes, N=No

mv_n: Number of times test article was moved, e.g., 1, 2, 3, etc.

dis: Discontinuation of the test article, e.g., Y=Yes, N=No

dis_rs: Reason for test article discontinuation, e.g., A=irritation, etc.

AErpt: Adverse event(s) reported for this treatment arm, e.g., Y=Yes, N=No

33. For the Irritation and Sensitization Analyses, please provide a separate line listing for each individual test article per subject, per each visit (if data exist) using the following headers, if applicable:
- a. Subject identifier
 - b. Treatment: test article (i.e., test product, RLD, optional vehicle patch and optional negative control)
 - c. Application Sequence: number of particular test article application (i.e., 1=first, 2=second, 3=third)
 - d. Location of Dose Administration: test article application site
 - e. Visit number
 - f. Visit date
 - g. Number of days since baseline visit
 - h. Application day of week (i.e., Sunday, Monday, Tuesday, etc.)
 - i. Application date and time
 - j. Date and time of removal or complete detachment
 - k. Duration of Treatment: time (hours) from individual test article application to removal or complete detachment
 - l. Reason for exclusion of data from this individual test article from analysis
 - m. Scoring date
 - n. Adhesion score
 - o. Induction “Dermal Response” numeric score for each site
 - p. Induction “Other Effects” letter score for each site
 - q. Challenge “Dermal Response” numeric score for each site
 - r. Challenge “Other Effects” letter score for each site
 - s. Potentially sensitized (yes/no)
 - t. Identity of the evaluator
 - u. Was the individual test article reinforced with tape or overlay (yes/no)
 - v. If individual test article was reinforced, time from individual test article application to reinforcement
 - w. Individual test article moved (yes/no)
 - x. Number of times individual test article moved
 - y. Date of each move of individual test article
 - z. Individual test article discontinued (yes/no)

- aa. Reason for discontinuation
- bb. Date individual test article discontinued
- cc. Adverse event reported during this visit (yes/no)

Please refer to Table 5 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 5: Example of dataset containing one line listing for each individual test article per visit per subject

SUBJID	EXTRT	EXSEQ	EXLOC	VISITNUM	SVSTDTC	ELTMBS	day_wk	itaSTDTC	itaENDTC	itaDUR	exc_rs	scr_date	adh_2	adh_3	ind_n1	ind_c1
1	A	1	RUA	2	2004-07-01	1	Tuesday			24			0		0	0

ind_n2	ind_c2	ind_n3	ind_c3	ch_n1	ch_c1	potsens	EVAL	reinf	reinf_tm	mv	mv_n	mv_dt2	mv_dt3	dis	dis_rs	dis_dt	AErpt
								N		N				N			N

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final dated 11/12/08.

- SUBJID: Subject Identifier for the Study
- EXTRT: Name of Actual Treatment (exposure), e.g. A=test product, B=RLD, C=optional vehicle patch, D=optional negative control
- EXSEQ: Sequence Number of exposure to particular test article (e.g. application number 1, 2, 3, etc.)
- EXLOC: Location of Dose Administration (exposure): specific anatomical site of patch application, e.g., RUA=right upper arm, LUA=left upper arm
- VISITNUM: Visit Sequence Number
- SVSTDTC: Visit date: (SVSTDTC=Subject Visit Start Date Time-Character)
- ELTMBL: Elapsed Time since Baseline (days)
- day_wk: Day of week of individual test article application (i.e., Sunday, Monday, Tuesday, etc.)
- itaSTDTC: Individual test article application date and time: start date/time of individual test article
- itaENDTC: Individual test article removal date and time: end date/time of individual test article

itaDUR:	Individual test article exposure duration (hours) (i.e., time from individual test article application to removal)
exc_rs:	Reason for exclusion of data from this individual test article from analysis, e.g., A=subject did not show for appointment, B=test article detached for more than 24 hours, C=protocol/exclusion criteria violation, etc.
scr_date:	Scoring date
adh_2:	Adhesion score for Day 2
adh_3:	Adhesion score for Day 3 (etc. to Day 22)
ind_n1:	Numeric “Dermal Response” score for the first site during Induction
ind_c1:	Character “Other Effects” score for the first site during Induction
ind_n2:	Numeric “Dermal Response” score for the second site (if application site moved due to excessive irritation) during Induction
ind_c2:	Character “Other Effects” score for the second site during Induction
ind_n3:	Numeric “Dermal Response” score for the third site during Induction
ind_c3:	Character “Other Effects” score for the third site during Induction
ch_n1:	Numeric “Dermal Response” score for the Challenge site
ch_c1:	Character “Other Effects” score for the Challenge site
potsens:	Potentially sensitized, e.g., Y=Yes, N=No
EVAL:	Evaluator: identity of the evaluator
reinf	Individual test article reinforced with tape or overlay e.g., Y=Yes, N=No
reinf_tm	If individual test article was reinforced, time (hours) from individual test article application to reinforcement
mv:	Individual test article moved, e.g., Y=Yes, N=No
mv_n:	Number of times individual test article was moved, e.g., 1, 2, etc.
mv_dt1:	Date of first move of individual test article
mv_dt2:	Date of second move of individual test article
mv_dt3:	Date of third move of individual test article
dis:	Discontinuation of the individual test article, e.g., Y=Yes, N=No
dis_rs:	Reason for individual test article discontinuation, e.g., A=irritation, etc.
dis_dt:	Date individual test article discontinued
AErpt:	Adverse Event reported during this visit, e.g., Y=Yes, N=No

34. Please note that the guidance provided here supersedes information provided in the *Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products*, which has been withdrawn. The information given here is general in nature and represents the current thinking of the OGD for this product and may not be appropriate for other topical or transdermal products.