

Draft Guidance on Nitroglycerin

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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: Nitroglycerin

Dosage Form;Route: Film, extended release; transdermal

Recommended Studies: Three studies

1. Type of study: Bioequivalence (BE) with Pharmacokinetic (PK) Endpoints Study
Design: Single-dose, fasting, two-treatment, two-period crossover in vivo
Strength: 0.4 mg/hr
Subjects: Healthy males and non-pregnant, non-lactating females, general population.
Additional comments: Specific recommendations are provided below. Adequate skin contact is essential for the in vivo performance of the transdermal patch and the PK may be altered when a transdermal patch loses its adherence to the skin. Therefore, the adhesion of each transdermal 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: 0.4 mg/hr (A lower strength may be used if adequate justification is provided for the choice of patch size)
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: Skin Irritation and Sensitization Study
Design: Randomized, evaluator-blinded, in vivo within-subject repeat test
Strength: 0.1 mg/hr (or one-half of a 0.2 mg/hr 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.

Analytes to measure (in appropriate biological fluid): Nitroglycerin and its metabolites, 1,2-dinitroglycerol and 1,3- dinitroglycerol, in plasma (PK-based BE study only). If nitroglycerin plasma concentrations can be reliably measured and its pharmacokinetic parameters accurately determined, you should analyze the nitroglycerin data using the confidence interval approach. The 1,2- dinitroglycerol and 1,3- dinitroglycerol data can be used to provide supportive evidence of comparable therapeutic outcome. It is recommended to use a highly selective assay capable of low pg/mL limit of quantitation.

Bioequivalence based on (90% CI): Nitroglycerin (PK-based BE study only)

Waiver request of in vivo testing: 0.1 mg/hr, 0.2 mg/hr, and 0.6 mg/hr based on (i) an acceptable bioequivalence study on the 0.4 mg/hr strength, (ii) proportion similarity across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

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).

In addition to the method above, dissolution profiles on 12 dosage units each of the test and reference products generated using at least three dissolution media (pH 1.2, 4.5, 6.8 buffer) and water should be submitted in the application. Multipoint dissolution profiles should be obtained using a discriminating agitation speed. Agitation speeds may have to be increased, if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose-dumping) from the formulation.

Additional comments regarding the skin irritation and sensitization study:

1. The Office of Generic Drugs (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, be no more sensitizing than the RLD and adhere at least as well as 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 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, all test articles (i.e., 0.1 mg/hr test product¹, 0.1 mg/hr RLD, optional vehicle patch² and optional negative control³) are to be applied simultaneously to each subject at different sites on the chest, as recommended in the approved reference listed drug (RLD) labeling, with sequential patch applications to the same skin sites every 24 hours for a total of 21 consecutive days. 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 1 day (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 application of the 0.1 mg/hr test product, 0.1 mg/hr RLD, optional 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 also 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.

3. The optimum design of this study will depend on the test product strengths to be marketed and the design of the test product patch. If a 0.1 mg/hr test product is not marketed, one half of a 0.2 mg/hr test product patch and one half of a 0.2 mg/hr RLD patch can be evaluated. Since the RLD has a matrix design that can be safely cut in half, one half of 0.2 mg/hr patch can be used for these studies. If the test product patch also has a design that can be cut to a smaller size, it can also be cut in half and one half of a 0.2 mg/hr test product patch applied simultaneously with one half of a 0.2 mg/hr RLD patch (to separate skin sites). It would not be acceptable to manufacture a separate batch of product in order to use a smaller patch in this study.

¹ The test product evaluated should be the actual patches to be marketed. If the 0.1 mg/hr test product will not be marketed and the test product has a design that can be cut to a smaller size, the 0.2 mg/hr test product and 0.2 mg/hr test product can be cut in half and one-half of a 0.2 mg/hr test product patch applied simultaneously with one half of a 0.2 mg/hr RLD patch (to separate skin sites).

² 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 nitroglycerin.

³ An example of the optional negative control is an occlusion type device with normal saline applied on a polyester pad within the device chamber.

4. If the test product patch has a reservoir design that cannot be cut in half and the 0.1 mg/hr strength of the test product is not to be marketed, then, in order to avoid an unacceptable risk of serious adverse events, the study should be conducted using a parallel design with healthy subjects randomized to receive either the test product or RLD. The study should be powered to show that the test is no more irritating, no more sensitizing compared to the RLD.
5. An adequate number of subjects should be enrolled to ensure that at least 200 evaluable subjects are included in the PP population.
6. The irritation and adhesive properties may be sensitive to climate conditions. Therefore, the OGD prefers that the study be conducted in multiple centers with different climate conditions.
7. 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.
8. 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.
9. 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.
10. Inclusion Criteria (the sponsor may add additional criteria):
 - a. Healthy male and non-pregnant, non lactating female subjects 18-65 years of age inclusive.
 - b. Premenopausal female are to have a negative pregnancy test at screening AND have undergone surgical sterilization OR agree to practice abstinence or contraception during the study.
 - c. Normotensive (resting blood pressure between 120/70 to 140/90, inclusive) with no history of hypotension.
11. Exclusion Criteria (the sponsor may add additional criteria):
 - a. Subject is pregnant or lactating.
 - b. Psychiatric illness requiring treatment.
 - c. 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).

- d. 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).
 - e. 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.
 - f. 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).
 - g. Within 72 hours prior to dosing, use of phosphodiesterase inhibitors, antihistamines or use of topical drugs at patch site.
 - h. 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.
 - i. Presence of open sores at the application site.
12. Provide a listing of the prescription and over-the-counter drug products that are contraindicated during the study, such as:
- a. Antihypertensives
 - b. Narcotics and certain analgesics (e.g., cocaine, meperidine, methadone, pentazocine, propoxyphene, tramadol)
 - c. Nitrates and nitrites other than study medication, (e.g., buccal, intravenous, lingual, sublingual, or topical nitroglycerin, amyl nitrite, isosorbide dinitrate, nitric oxide)
 - d. Phosphodiesterase inhibitors (e.g., sildenafil citrate, tadalafil, vardenafil hydrochloride)
 - e. 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).
 - f. Vasodilators (e.g., alprostadil, ambrisentan, bosentan, dipyridamole, papaverine hydrochloride)
13. Subjects should be advised that the use of alcohol is not recommended while taking study drug due to possible hypotension.
14. Recommend assessing standing and supine blood pressure and pulse at each visit. Due to the risk of hypotension, recommend informing subjects of the symptoms of orthostatic hypotension and cautioning them to rise slowly from supine to seated positions. Recommend discontinuing any subject with significant orthostatic hypotension (decrease of 20 mmHg systolic or 15 mmHg diastolic) from the study.
15. During the induction phase, subjects should 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 most (preferably 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.

16. To ensure adequate adhesion of the test and reference patches in the irritation and sensitization study, adhesion scores are to be recorded just prior to patch removal. The recommended scoring system for adhesion of transdermal 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)

17. During both the Induction Phase and Challenge Phase, the skin reactions are to be evaluated and scored according to the following two scales⁴:

Scale 1: Dermal Response

Skin Appearance	Score
No evidence of irritation	0
Minimal erythema, barely perceptible	1
Definite erythema, readily visible; or 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 test (i.e., application) site	7

Scale 2: Other Effects

Observation	Score (Numeric equivalent)
Slightly glazed appearance	A (0)
Marked glazed appearance	B (1)
Glazing with peeling and cracking	C (2)
Glazing with fissures	F (3)

⁴ 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.

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).

18. For subjects who experience irritation consistent with a combined score of ≥ 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.
19. Criteria may be established for using tape or an overlay to reinforce any 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 should be reported separately from that of the patch application area.
20. 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.

Safety Data and Analyses

21. 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 patient 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.
22. The safety analyses should include all patients 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, change from baseline in blood pressure, and concomitant medications are also to be reported but cannot be distinguished between test articles.

Skin Irritation Data Tables and Analyses

23. 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 1 as an example.

Table 1: Number (%) of Applications by Induction Phase Day and Test Article with a Specific Combined “Dermal Response” and “Other Effect” Score

Induction Phase Scoring Day; Test Article	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.											

24. The Analysis Populations should be defined separately for each parameter and should be defined per patch instead of per subject. The Per-Protocol (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).

25. 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.

26. 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 test article.
- 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.

27. 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

28. 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.
29. 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.
30. The Analysis Populations should be defined separately for each parameter and should be defined per patch instead of per subject. The Per-Protocol (PP) Population 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.
31. For each test article, individually evaluate each Per Protocol 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.

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

Data Submission

- 33. 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.
- 34. 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. PP population inclusion for adhesion analysis (yes/no)
- q. Reason for exclusion from PP population for adhesion analysis
- r. Test article moved (yes/no)
- s. Number of times test article moved
- t. Test article discontinued (yes/no)
- u. Reason for test article discontinuation
- v. Adverse event(s) reported for this treatment arm (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 a summary dataset for each individual test article per subject

STUDYID	SUBJID	SITEID	AGE	AGEU	SEX	RACE	EXTRT	EXLOC	EXDURind	EXDURch	ppirr	ppirr_rs
101	1	01	54	YEARS	M	1	A	RUC	21	2	Y	
101	1	01	54	YEARS	M	1	B	LUC	21	2	Y	
101	2	01	45	YEARS	M	2	A	RUC	21	2	Y	
101	2	01	45	YEARS	M	2	B	LUC	21	2	Y	

ppsen	ppsen_rs	ppadh	ppadh_rs	mv	mv_n	dis	dis_rs	AErpt
Y		Y		Y	1	N		N
Y		Y		Y	1	N		N
N	B	N	B	N		N		N
N	B	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 Draft dated 7/25/07.

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., RUC=right upper chest, LUC=left upper chest
 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.
 ppadh: Per Protocol (PP) population for adhesion analysis, e.g., Y=Yes, N=No
 ppadh_rs: Reason for exclusion from PP population for adhesion analysis, e.g., A=prematurely discontinued prior to completing Day 2 adhesion scoring due to AE that was not intolerable irritation, B=failed to complete Day 2 adhesion scoring due to lost to follow-up, C=failed to complete Day 2 adhesion scoring due to subject travel out of the area, 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

35. For the Irritation, Sensitization and Adhesion 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 scores (e.g., Days 2-22)
- 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 the site
- r. Challenge “Other Effects” letter score for the 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 3 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 3: 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	RUC	1	2004-07-01	1	Monday									

ind_n2	ind_c2	ind_n3	ind_c3	ch_n1	ch_c1	potsens	EVAL	reinf	reinf_tm	mv	mv_n	mv_dt1	mv_dt2	mv_dt3	dis	dis_rs	dis_dt	AErpt

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 Draft dated 7/25/07.

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., RUC=right upper chest LUC=left upper chest
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
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

36. 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 transdermal products.
37. Sponsors may submit the protocol for review and comment prior to conducting the study.