

## Draft Guidance on Clonidine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

**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, two-treatment, two-period crossover in vivo

Strength: 0.3 mg/24 hr

Subjects: Healthy males and non-pregnant, non lactating females, general population.

Additional comments: The transdermal patch should be applied on the chest, back, flank or upper arm, as recommended in the approved reference listed drug (RLD) labeling, and worn for 7 days. The same anatomical site should be used for the entire study. 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.

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2. Type of study: Adhesion Study

Design: Single-dose, two-treatment, two period crossover in vivo

Strength: 0.3 mg/24 hr (A lower strength may be used if adequate justification is provided for the selection 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.

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3. Type of study: Skin Irritation and Sensitization Study

Design: Randomized, evaluator-blinded, in vivo, within-subject repeat test

Strength: 0.1 mg/24 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 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):** Clonidine in plasma (PK-based BE study only)

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

**Waiver request of in vivo testing:** 0.1 mg/24 hr and 0.2 mg/24 hr, based on (i) acceptable bioequivalence studies on the 0.3 mg/24 hr strength, (ii) proportionally similar 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, for transdermal system, dissolution profiles on 12 dosage units each of test and reference products generated using USP apparatuses for transdermal systems in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) 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 0.5, 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. Because addition of the active drug to a placebo patch may potentially result in different irritation or adhesion characteristics, these studies are to be conducted with the actual patches to be marketed and the actual RLD patches. The OGD has considered the safety of administering transdermal clonidine systems to healthy volunteers continuously for 21 days and has determined that this study can safely be conducted using the lowest strength patches (0.1 mg/day) and applying one test product patch and one RLD patch to each subject at the same time. Use of an additional vehicle patch (e.g., having all of the inactive ingredients and being identical to the proposed product in every manner except for the absence of clonidine) is optional. Use of a negative control (e.g., normal saline) is also optional. The patches should be applied to a hairless area of intact skin on the upper outer arm or upper chest, as recommended in the approved reference listed drug (RLD) labeling, and worn for 7 days.

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/24 hr test product, 0.1 mg/24 hr RLD, optional vehicle patch, and optional negative control) are to be applied simultaneously to each subject at different sites, with sequential patch applications to the same skin sites every seven days (the intended duration of wear) for a total of 21 consecutive days. Thus, it is recommended to apply the patches on Days 1, 8, and 15 to the same sites and to have each of them remain in place for 7 days (a total of 21 days altogether). The Day 15 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/24 hr test product, 0.1 mg/24 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 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. An adequate number of subjects should be enrolled to ensure that at least 200 evaluable subjects are included in the PP population.
4. 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.

5. 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.
6. 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.
7. 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.
8. 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 subjects have undergone surgical sterilization OR agree to practice abstinence or contraception during the study.
9. Exclusion Criteria (the sponsor may add additional criteria):
  - a. Taking antihistamines within 72 hours prior to dosing or systemic or topical corticosteroids within 3 weeks prior to dosing.
  - b. Previous exposure to oral or transdermal clonidine or any adverse event or allergic reactions to other alpha 2-adrenergic agonists
  - c. Subject is pregnant, or lactating.
  - d. History of alcohol abuse within the last 2 years.
  - e. Unwilling or unable to refrain from the use of alcohol during the study.
  - f. Medical history of diabetes mellitus, chronic headaches and/or migraines, chronic constipation, tremors or any other condition the Investigator considers may increase risk to the subject or interferes with the evaluation of the data.
  - g. 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. porphyria).
  - h. 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.
  - i. 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.
  - j. Presence of open sores at the application site.

10. Recommend prohibiting use of the following medications during the study for safety reasons:
  - a. Monoamine oxidase inhibitors (MAOI), [e.g. Eldepryl (selegiline). tranylcypromine, phenelzine or isocarboxazid]
  - b. Tricyclic antidepressant medications (e.g. Elavil, Etrafon, Pamelor, Sinequan. Tofranil, Triavil) for depression
  - c. Antihypertensive medication (including all alpha agonists, P-blockers and calcium channel blockers, regardless of indication)
  - d. Drugs that affect the heart rate such as guanethidine, P-adrenergic blocking agents, (e.g. propranolol) cardiac glycosides, or sympathomimetic amines
  - e. Immunosuppressive medication
  - f. Sedative hypnotic medication
  
11. Recommend prohibiting use of the following medications during the study because they may confound the study outcome:
  - a. 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).
  - b. Anti-inflammatory medication except as follows:
    - Aspirin <500 mg/day
    - Ibuprofen <600 mg/day
    - Naproxen sodium <220 mg/day
  
12. Adequate precautions should be taken to ensure patient safety during the study. These should include the following:
  - a. Considering that this is an antihypertensive drug, it should be anticipated that it will result in a decrease in blood pressure, and criteria for exclusion and discontinuation of subjects considered potentially hypertensive or hypotensive should be included in the protocol. The protocol should contain stopping criteria for subjects who may become hypotensive during the course of the study.
  - b. Consider confining patients during the first several days of the study to facilitate frequent monitoring of vital signs.
  - c. Monitor vital signs at least daily throughout the first 7 days of the study and at the time of patch changes thereafter.
  - d. Subjects should return for three days after final patch removal for monitoring of blood pressure and adverse event assessment to evaluate for the possibility of a rebound effect that can result in increased blood pressure following sudden withdrawal of clonidine therapy.
  
13. Subjects who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of a possible sedative effect of clonidine. They should also be informed that this sedative effect may be increased by concomitant use of alcohol, barbiturates, or other sedating drugs.

14. Skin burns have been reported at the patch site in several patients wearing an aluminized transdermal system during a magnetic resonance imaging scan (MRI). Because the RLD contains aluminum, subjects should be advised to remove the test articles before undergoing an MRI.
15. During the induction phase, subjects should return for visits on Days 2, 3, 4, 5, 6, and 7 for adhesion scoring, on Days 8 and 15 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 of scorers and standards for each score.
16. Efforts should be made to blind the evaluation of irritation and sensitization.
17. 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)
18. During both the Induction Phase and Challenge Phase, the skin reactions are to be evaluated and scored according to the following two scales<sup>1</sup>:

**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

<sup>1</sup> 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.

<b>Skin Appearance</b>	<b>Score</b>
Strong reaction spreading beyond the application site.	7

### **Scale 2: Other Effects**

<b>Observation</b>	<b>Score (Numeric equivalent)</b>
Slightly glazed appearance	A (0)
Marked glazed appearance	B (1)
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).

19. 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.
20. Criteria to reinforce the patches with an overlay when a portion of the patch is lifted may be established. 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.
21. 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*

22. 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.

23. 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 and concomitant medications are also to be reported but cannot be distinguished between test articles.

*Skin Irritation Data Tables and Analyses*

24. 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 8; Test Product											
Day 8; RLD											
Day 8; Vehicle Patch (optional)											
Day 8; Negative Control (optional)											
Day 15; Test Product											
Day 15; RLD											
etc.											

25. 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 sites 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).

26. For each test article (0.1 mg/24 hr test product, 0.1 mg/24 hr RLD, positive 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.

27. In addition to the cumulative irritation scores, the following data should be provided for each test article:
- Total number of observations with a combined “Dermal Response” and “Other Effects” irritation score of 3 or more for each product.
  - Number of patches that were moved or removed due to an unacceptable degree of irritation.
  - Number of days until sufficient irritation occurred to preclude repeat application to the same site.
28. 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.,  $\geq 3$ ) 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*

29. 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.
30. 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.
31. 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.

32. 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:
- 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.
  - The subject has a combined “Dermal Response” and “Other Effects” numeric score of at least 2 at their last evaluation during the Challenge Phase.
  - 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.
  - 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 to the RLD.

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

### *Overlay*

Given that the RLD is marketed with an overlay to be used when needed for adhesive support, the generic product should also be provided with an adhesive overlay. OGD requests that the adhesive performance and irritation potential of the test and reference overlays be evaluated separately in the same study (induction phase) along with the active patches but applied at separate skin sites.

### *Data Submission*

34. Study data should be submitted to the OGD in electronic format.
- A list of file names, with a simple description of the content of each file, should be included.
  - 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.
35. 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	RUA	21	2	Y	
101	1	01	54	YEARS	M	1	B	LUA	21	2	Y	
101	2	01	45	YEARS	M	2	A	RUA	21	2	Y	
101	2	01	45	YEARS	M	2	B	LUA	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, E=test overlay, F=reference overlay  
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.

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 8 adhesion scoring due to AE that was not intolerable irritation, B=failed to complete Day 8 adhesion scoring due to lost to follow-up, C=failed to complete Day 8 adhesion scoring due to subject moved 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

36. 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, optional negative control, test overlay, reference overlay)
  - 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 2-8)
  - 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 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	RUA	1	2004-07-01	1	Monday									

ind_n2	ind_c2	ind_n3	ind_c3	ch_n1	ch_c1	potrsens	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, E=test overlay, F=reference overlay
- 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)
- ELTMLB: 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 8)
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

37. 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.

38. Sponsors may submit the protocol for review and comment prior to conducting the study.