

**Draft Guidance on Tazarotene**

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind the FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

**Active ingredient:** Tazarotene

**Form/Route:** Gel/Topical

**Recommended studies:** 1 study

Type of study: Bioequivalence (BE) Study with Clinical Endpoint

Design: Randomized, double blind, parallel, placebo controlled, in vivo

Strength: 0.05%

Subjects: Males and nonpregnant females with clinical diagnosis of plaque psoriasis

Additional comments: Specific recommendations are provided below.

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**Analytes to measure (in appropriate biological fluid):** Not Applicable

**Bioequivalence based on (90% CI):** Clinical Endpoint

**Waiver request of in vivo testing:** Not Applicable

**Dissolution test method and sampling times:** Not Applicable

**Additional comments regarding the BE study with clinical endpoint:**

1. The Office of Generic Drugs (OGD) recommends conducting a bioequivalence study with a clinical endpoint in the treatment of stable plaque psoriasis comparing the test product versus the reference listed drug (RLD) and vehicle control, each administered once daily, in the evening, to psoriatic lesions for 84 days (12 weeks). The primary endpoint is the proportion of subjects with treatment success at the end of treatment (study day 84).
2. Enough gel should be applied ( $2 \text{ mg/cm}^2$ ) to cover only the lesions with a thin film. If a bath or shower is taken prior to application, the skin should be dry before applying the gel. If emollients are used, they should be applied at least an hour before applying the gel.
3. A vehicle (placebo) control arm is recommended to demonstrate that the test product and RLD are active and as a parameter to establish that the study is sufficiently sensitive to detect differences between products. A rescue clause should be included to allow for discontinuation due to lack of treatment response or worsening disease.
4. Inclusion Criteria (the sponsor may add additional criteria)
  - a. Male or nonpregnant females  $\geq 18$  years of age with a clinical diagnosis of stable (at least 6 months) plaque psoriasis involving at least 2% and no more than 20% body surface area (BSA), not including the scalp and intertriginous areas.
  - b. An Investigator's Global Assessment (IGA) of disease severity of at least moderate severity (score  $\geq 3$ , per Table 1) as an overall assessment of all lesions to be treated.

- c. A minimum plaque elevation of at least moderate severity (grade  $\geq 3$ , per Table 2) at the target lesion site. The most severe lesion at baseline should be identified as the target lesion.
  - d. If female of childbearing potential, the subject must have a negative result for a pregnancy test having sensitivity down to at least 50 mIU/mL for hCG within 2 weeks prior to starting treatment, begin treatment during a normal menstrual period, and be willing to use an acceptable form of birth control throughout the study.
5. Exclusion Criteria (the sponsor may add additional criteria)
- a. Females who are pregnant, breast feeding, planning a pregnancy or do not agree to use an acceptable form of birth control throughout the study.
  - b. Females of childbearing potential who do not agree to utilize an adequate form of contraception.
  - c. Current diagnosis of unstable forms of psoriasis in the treatment area, including guttate, erythrodermic, exfoliative or pustular psoriasis.
  - d. Other inflammatory skin disease in the treatment area that may confound the evaluation of the plaque psoriasis (e.g., atopic dermatitis, contact dermatitis, eczema, tinea corporis).
  - e. Presence of pigmentation, extensive scarring, pigmented lesions, or sunburn in the treatment areas, which could interfere with the rating of efficacy parameters.
  - f. History of psoriasis unresponsive to topical treatments.
  - g. History of hypersensitivity or allergy to tazarotene, retinoids and/or any component of the test product or RLD.
  - h. Current immunosuppression.
  - i. Use within six months prior to baseline of biologic treatment for psoriasis (e.g., infliximab, adalimumab, alefacept).
  - j. Use within three months prior to baseline of: 1) chemotherapy, or 2) radiation therapy.
  - k. Use within two months prior to baseline of any immunosuppressive drugs (e.g., tacrolimus, pimecrolimus) or oral retinoids.
  - l. Use within one month prior to baseline of: 1) systemic steroids, 2) systemic antibiotics, 3) systemic antipsoriatic treatment (e.g., methotrexate, cyclosporine, hydroxyurea), 4) PUVA therapy, 5) UVB therapy or 6) systemic anti-inflammatory agents.
  - m. Use within 2 weeks prior to baseline of: 1) topical anti-psoriatic drugs (e.g., salicylic acid, anthralin, coal tar, calcipotriene, tazarotene), 2) topical corticosteroids or 3) topical retinoids.
6. Scales to be used for evaluation of baseline disease severity and treatment effect:

**Table 1. Investigator’s Global Assessment (IGA) of Disease Severity**

Score	Grade	Definition
0	None	No plaque elevation above normal skin level; may have residual non-erythematous discoloration; no psoriatic scale; no erythema
1	Minimal	Essentially flat with possible trace elevation; faint erythema; no psoriatic scale
2	Mild	Slight but definite elevation of plaque above normal skin level; may have up to moderate erythema (red coloration); fine scales with some lesions partially covered
3	Moderate	Moderate elevation with rounded or sloped edges to plaque; moderate erythema (red coloration); somewhat coarse scales with most lesions partially covered
4	Severe	Marked elevation with hard, sharp edges to plaque; severe erythema (very red coloration); coarse, thick scales with virtually all lesions covered and a rough surface
5	Very Severe	Very marked elevation with very hard, sharp edges to plaque; very severe erythema (extreme red coloration); very coarse, thick scales with all lesions covered and a very rough surface

**Table 2. Psoriasis Area Severity Index (PASI) at the Target Lesion Site**

Score	Grade	Erythema	Scaling	Plaque Elevation
0	Clear	No evidence of erythema	No evidence of scaling	No evidence of plaques above normal skin level
1	Almost Clear	Pink discoloration, minimal erythema	Occasional fine scales hardly noticeable	Slight, just discernable elevation above normal skin level
2	Mild	Light red coloration	Slight but definite roughness, fine scale present, no cracking	Discernable elevation above normal skin level upon examination, but not pronounced
3	Moderate	Moderate redness, but not dark	Moderate roughness, somewhat coarse scaling	Definite plaque formation with rounded/sloped edges to plaque
4	Severe	Dark red coloration	Marked roughness, coarse/thick scaling, cracking may be evident	Marked elevation with hard, distinct edges to plaque
5	Very Severe	Very dark red coloration with induration present	Very thick scales covering extensive area severe cracking/fissures may be evident	Very marked elevation, very hard and sharp edges to plaque

7. Body Surface Area (BSA) percentage is no longer requested as an individual component sign in the PASI scale but the information of BSA percentage and distribution should be collected at baseline.
8. Tazarotene gel is designated as pregnancy category X. Therefore, in a bioequivalence study with clinical endpoint, all females of childbearing potential should be maintained on an appropriate method of contraception throughout the study. The informed consent form must clearly discuss the potential risk of teratogenicity.
9. It is recommended to repeat the urine pregnancy test (with sensitivity down to at least 50 mIU/mL hCG) for all females of childbearing potential during the study visits at study day 28 (week 4), study day 56 (week 8) and end of treatment (study day 84; week 12). If a female of childbearing potential discontinues prematurely, the pregnancy test should be performed at the exit visit.
10. 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. Topical product other than the assigned treatment (including moisturizers, new brands of make-up, creams, ointments, lotions, and powders) applied on or near the treatment area.
  - b. Topical or systemic antipsoriatic treatment (e.g., anthralin, coal tar, tazarotene, retinoids, tacalcitol, infliximab, adalimumab, alefacept, PUVA therapy, UVB therapy).
  - c. Topical or systemic corticosteroids.
  - d. Photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides).
  - e. Immunosuppressive drugs.
  - f. More than 10,000 IU/day of Vitamin A supplements.
  - g. Initiation of or changes to non antipsoriatic concomitant medication that could affect psoriasis (e.g., beta blockers, lithium) during the study.
  - h. Tanning booths, sun lamps, or nonprescription UV light sources.
  - i. Phototherapy.
  - j. Application of study treatment to unaffected skin.
  - k. The treated areas should not be bandaged, covered or wrapped as to be occlusive.
  - l. Subjects should be instructed to minimize exposure to natural sunlight. to use sunscreens of at least SPF 15 and wear protective clothing during the day, to not allow the gel to come in

- contact with the eyes, eyelids, or mouth, to not use study treatment on skin that has eczema, and to always wash hands thoroughly after application of study medication.
11. The recommended primary endpoint is the proportion of subjects with treatment success (defined as “absent, very mild, or mild disease, a score of 0, 1 or 2, within the treatment area”) on the IGA at the week 12 visit (study day 84).
  12. The recommended secondary endpoints are:
    - 1) the proportion of subjects with disease severity at the week 12 visit (study day 84) consistent with “absent or very mild, a score of 0 or 1, within the treatment area” on the IGA, and
    - 2) the proportion of subjects with “target site plaque elevation, scaling, and erythema scores of less than or equal to one” on the PASI at the week 12 visit (study day 84).
  13. The protocol should clearly define the per-protocol (PP), modified intent-to-treat (mITT) and safety populations.
    - a. The accepted PP population used for bioequivalence evaluation includes all randomized subjects who meet all inclusion/exclusion criteria, apply a pre-specified proportion of the scheduled applications (e.g., 75% to 125%) of the assigned product for the specified duration of the study, do not miss the scheduled applications for more than 3 consecutive days, and complete the evaluation within the designated visit window (+/- 4 days) 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.
    - b. The mITT population includes all randomized subjects who meet all inclusion/exclusion criteria, apply at least one dose of assigned product and return for at least one post-baseline evaluation visit.
    - c. The safety population includes all randomized subjects who receive study product.
  14. Subjects who are discontinued early from the study due to lack of treatment effect after completing 4 weeks of treatment should be included in the PP population as treatment failures. Subjects whose condition worsens and require alternate or supplemental therapy for the treatment of their plaque psoriasis during the study should be discontinued, included in the PP population analysis, 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).
  15. The start and stop date of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use. The sponsor should clearly explain whether the medication was used prior to baseline visit, during the study, or both.
  16. 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.
  17. 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 these expected application site reactions.
  18. If the inactive ingredients of the test product are different than those contained in the RLD or in significantly different amounts, then the sponsor must clearly describe the differences and

provide information to show that the differences will not affect the safety, efficacy and/or systemic or local availability of the drug.

19. 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.
20. 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.
21. Please refer to 21 CFR 320.38, 320.63 and the Guidance for Industry, "Handling and Retention of BA and BE Testing Samples", regarding retention of study drug samples and 21 CFR 320.36 for requirements for maintenance of records of bioequivalence testing. In addition, the investigators should follow the procedures of 21 CFR 58 and ICH E6, "Good Clinical Practice: Consolidated Guideline", for retention of study records and data in order to conduct their studies in compliance with Good Laboratory Practices (GLP) and Good Clinical Practices (GCP). Retention samples should be randomly selected from the drug supplies received prior to dispensing to subjects. Retention samples should not be returned to the sponsor at any time.
22. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.
23. To establish bioequivalence, the 90% confidence interval of the test - reference difference between products for the primary endpoint (success proportion) must be contained within [-0.20, +0.20] for dichotomous variables (success versus failure), using the PP population.
24. As a parameter for determining adequate study sensitivity, the test product and RLD should be statistically superior to placebo ( $p < 0.05$ , two-sided) for the primary endpoint (success proportion) using the mITT study population and LOCF.
25. The site and size of the treatment area should be tabulated and compared between treatment groups.
26. The following Statistical Analysis Method is recommended for equivalence testing for a dichotomous variable (success/failure):

#### Equivalence Analysis

Based on the usual method used in OGD for binary outcomes, the 90% confidence interval for the difference in success proportions between test and reference treatment must be contained within [-0.20, +0.20] in order to establish equivalence.

The compound hypothesis to be tested is:

$$H_0: p_T - p_R < -0.20 \text{ or } p_T - p_R > 0.20$$

versus

$$H_A: -0.20 \leq p_T - p_R \leq 0.20$$

where  $p_T$  = success rate of test treatment and  $p_R$  = success rate of reference treatment.

Let

$n_T$  = sample size of test treatment group

$c n_T$  = number of successes in test treatment group

$n_R$  = sample size of reference treatment group

$c n_R$  = number of successes in reference treatment group

$$\hat{p}_T = c n_T / n_T, \quad \hat{p}_R = c n_R / n_R,$$

$$\text{and se} = \left( \hat{p}_T (1 - \hat{p}_T) / n_T + \hat{p}_R (1 - \hat{p}_R) / n_R \right)^{1/2}.$$

The 90% confidence interval for the difference in proportions between test and reference was calculated as follows, using Yates' correction:

$$L = \left( \hat{p}_T - \hat{p}_R \right) - 1.645 \text{ se} - (1/n_T + 1/n_R)/2$$

$$U = \left( \hat{p}_T - \hat{p}_R \right) + 1.645 \text{ se} + (1/n_T + 1/n_R)/2$$

We reject  $H_0$  if  $L \geq -0.20$  and  $U \leq 0.20$

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

27. 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. Such a list should include an explanation of the variables included in each of the data sets.
  - 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, covering all variables collected in the Case Report Forms (CRFs) per subject, 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, vital signs, adverse events, disposition (including reason for discontinuation of treatment), concomitant medications, medical history, compliance and comments, etc.
  
28. 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, vehicle control
- i. Location of Treatment Area (i.e., arm, trunk, or legs)
- j. Duration of Treatment (total exposure in days)
- k. Size of Treatment Area (e.g., cm<sup>2</sup>)
- l. Previous use of antipsoriatic treatment (yes/no)
- m. Completed the study (yes/no)
- n. Reason for premature discontinuation of subject
- o. Subject required additional treatment for plaque psoriasis due to unsatisfactory treatment response (yes/no)
- p. Per Protocol (PP) population inclusion (yes/no)
- q. Reason for exclusion from PP population
- r. Modified Intent to Treat (mITT) population inclusion (yes/no)
- s. Reason for exclusion from mITT population
- t. Safety population inclusion (yes/no)
- u. Reason for exclusion from Safety population
- v. Percent (%) Body Surface Area (BSA) involvement at baseline
- w. IGA score at baseline and at week 12
- x. PASI score at baseline and at week 12
- y. Individual component score of erythema, scaling, and plaque elevation at baseline and at week 12
- z. Final designation of treatment outcome (success/failure) based on IGA, with success defined as “absent, very mild, or mild disease, a score of 0, 1 or 2, within the treatment area”
- aa. Final designation of modified treatment outcome (success/failure) based on IGA, with success defined as “absent or very mild, a score of 0 or 1, within the treatment area”
- bb. Final designation of clinical outcome (success/failure) based on PASI, with success defined as “target site plaque elevation, scaling, and erythema scores of less than or equal to one”
- cc. Treatment compliance: number of missed doses per subject
- dd. Concomitant medication (yes/no)
- ee. Adverse event(s) reported (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 a summary dataset containing one line listing for each subject**

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

safety	safety_rs	bsa_b	iga_b	iga_12	pasi_b	pasi_12	eyth_b	eyth_12	scale_b	scale_12	plaq_b	plaq_12	tx_out	m_tx_out	clin_out	complan	CM	AE
Y		8	3	0	3	4	3	2	2	2	3	3				0	Y	Y
Y		10	4	1	3	0	2	2	3	1	4	4				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=vehicle control
EXLOC:	Location of Treatment Area, e.g. F=face, etc.
EXDUR:	Duration of Treatment (total exposure in days)
size_tx:	Size of Treatment area (e.g., cm <sup>2</sup> )
prev_ps:	Previous use of antipsoriatic treatment , e.g., Y=Yes, N=No
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 additional treatment for psoriasis 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.
bsa_b:	Percent (%) of Body Surface Area (BSA) involvement at baseline
iga_b:	IGA score at baseline
iga_12:	IGA score at week 12
pasi_b:	PASI score at baseline
pasi_12:	PASI score at week 12
eryth_b:	Erythema at baseline
eryth_12:	Erythema at week 12
scale_b:	Scaling at baseline
scale_12:	Scaling at week 12
plaq_b:	Plaque Elevation at baseline
plaq_12:	Plaque Elevation at week 12
tx_out	Final designation of treatment outcome (A=success, B=failure) based on IGA, with success defined as “absent, very mild, or mild disease, a score of 0, 1 or 2, within the treatment area”
m_tx_out:	Final designation of modified treatment outcome (A=success, B=failure) based on IGA, with success defined as “absent, or very mild disease, a score of 0 or 1, within the treatment area”
clin_out:	Final designation as clinical outcome (A=success, B=failure) based on PASI, with success defined as “target site plaque elevation, scaling, and erythema scores of less than or equal to one”
complan:	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

29. 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, vehicle control
  - Location of Dose Administration: application site
  - Visit number
  - Visit date
  - Number of days since baseline visit
  - Evaluator: identity of evaluator
  - IGA score
  - Total PASI score
  - Individual erythema PASI score
  - Individual scaling PASI score
  - Individual plaque elevation PASI score
  - Skin reaction scores for each sign and symptom evaluated (e.g., erythema, dryness, burning/stinging, erosion, edema, pain, itching, etc.)
  - 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 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 dataset containing one line listing for each visit per subject**

STUDYID	SUBJID	EXTRT	EXLOC	VISITNUM	SVSTDTTC	ELTMBS	EVAL	iga	pasi_tot	pasi_ery	pasi_sca	pasi_pla	erythema	dryness	burning
101	1	A	F	1	2004-07-01	1							2	2	1

erosion	edema	pain	itching	CMrpt	AErpt	LBtest
1	1	1	Y	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=vehicle control  
 EXLOC: Location of Treatment Area: specific anatomical site of application, e.g., F=face etc.

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  
 iga: IGA score  
 pasi\_tot: Total PASI score  
 pasi\_ery: Individual erythema PASI score  
 pasi\_sca: Individual scaling PASI score  
 pasi\_pla: Individual plaque elevation PASI score  
 erythema: Skin reaction erythema score, e.g. 0=absent, 1=mild (slight, barely perceptible),  
 2=moderate (distinct presence), 3=severe (marked, intense)  
 dryness: Skin reaction dryness score, e.g. 0=absent, 1=mild (slight, barely perceptible),  
 2=moderate (distinct presence), 3=severe (marked, intense)  
 burning: Skin reaction burning score, e.g. 0=absent, 1=mild (slight, barely perceptible),  
 2=moderate (distinct presence), 3=severe (marked, intense)  
 erosion: Skin reaction erosion score, e.g. 0=absent, 1=mild (slight, barely perceptible),  
 2=moderate (distinct presence), 3=severe (marked, intense)  
 edema: Skin reaction edema score, e.g. 0=absent, 1=mild (slight, barely perceptible),  
 2=moderate (distinct presence), 3=severe (marked, intense)  
 pain: Skin reaction pain score, e.g. 0=absent, 1=mild (slight, barely perceptible),  
 2=moderate (distinct presence), 3=severe (marked, intense)  
 itching: Skin reaction itching score, e.g. 0=absent, 1=mild (slight, barely perceptible),  
 2=moderate (distinct presence), 3=severe (marked, intense)  
 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

30. 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 tazarotene.