Contains Nonbinding Recommendations

Draft Guidance on Tazarotene

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 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: Cream/Topical

Recommended studies: 1 study

Type of study: Bioequivalence (BE) Study with Clinical Endpoint
Design: Randomized, double blind, parallel, placebo controlled, in vivo
Strength: 0.1%
Subjects: Males and nonpregnant females with acne vulgaris
Additional comments: Specific recommendations are provided below.

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 single bioequivalence study with clinical endpoint in the treatment of acne vulgaris comparing the tazarotene topical cream, 0.1% test product versus the reference listed drug (RLD) and placebo control, each applied once daily in the evening for 12 weeks. The two co-primary endpoints, percent change from baseline in the inflammatory (papules and pustules) and non-inflammatory (comedones) lesion counts, are to be evaluated at the end of treatment (study day 84; week 12).

2. A 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.

3. Inclusion Criteria (the sponsor may add additional criteria)
   a. Healthy male or nonpregnant female aged ≥ 12 and ≤ 40 years with a clinical diagnosis of acne vulgaris.
   b. On the face, ≥ 25 non-inflammatory lesions (i.e., open and closed comedones) AND ≥ 20 inflammatory lesions (i.e., papules and pustules) AND ≤ 2 nodulocystic lesions (i.e., nodules and cysts).
   c. Investigator’s Global Assessment (IGA) of acne severity grade 2, 3, or 4 (per Table 1).
   d. Willing to refrain from use of all other topical acne medications or antibiotics during the 12-week treatment period.

e. 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.

4. 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. Presence of any skin condition that would interfere with the diagnosis or assessment of acne vulgaris (e.g., on the face: rosacea, dermatitis, psoriasis, squamous cell carcinoma, eczema, acneform eruptions caused by medications, steroid acne, steroid folliculitis, or bacterial folliculitis).
   c. Facial sunburn.
   d. Excessive facial hair (e.g. beards, sideburns, moustaches, etc.) that would interfere with diagnosis or assessment of acne vulgaris.
   e. History of hypersensitivity or allergy to tazarotene, retinoids and/or any component of the test product or RLD.
   f. Use within 6 months prior to baseline of oral retinoids (e.g. Accutane®) or therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed).
   g. Use for less than 3 months prior to baseline of estrogens or oral contraceptives; use of such therapy must remain constant throughout the study.
   h. Use on the face within 1 month prior to baseline or during the study of 1) cryodestruction or chemodestruction, 2) dermabrasion, 3) photodynamic therapy, 4) acne surgery, 5) intralesional steroids, or 6) x-ray therapy.
   i. Use within 1 month prior to baseline of 1) spironolactone, 2) systemic steroids, 3) systemic antibiotics, 4) systemic treatment for acne vulgaris (other than oral retinoids, which require a 6-month washout), or 5) systemic anti-inflammatory agents.
   j. Use within 2 weeks prior to baseline of 1) topical steroids, 2) topical retinoids, 3) topical acne treatments including over-the-counter preparations, 4) topical anti-inflammatory agents, or 5) topical antibiotics.

5. Scale to be used for evaluation of baseline disease severity and treatment effect:

Table 1. Sample IGA Scale for Acne Vulgaris[1]

Grade	Description
0	Clear skin with no inflammatory or noninflammatory lesions
1	Almost clear; rare noninflammatory lesions with no more than one small inflammatory lesion
2	Mild severity; greater than Grade 1; some noninflammatory lesions with no more than a few inflammatory lesions (papules/pustules only, no nodular lesions)
3	Moderate severity; greater than Grade 2; up to many noninflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion
4*	Severe; greater than Grade 3; up to many noninflammatory lesions and may have some inflammatory lesions, but no more than a few nodular lesions

[1] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Draft Guidance for Industry: Acne Vulgaris: Developing Drugs for Treatment. Clinical/Medical. September 2005. Accessed at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071292.pdf

* The Case Report Forms for acne studies can allow for reporting by investigators of lesion worsening beyond Grade 4 with treatment. It is recommended that enrollment of acne vulgaris subjects not include subjects with nodulocystic acne. Subjects who worsen beyond Grade 4 are to be described in the safety evaluation.

6. Tazarotene cream 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.

7. 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.

8. Subjects should gently clean and dry the face and then apply the product onto the affected areas of the face once daily, in the evening, avoiding contact with the eyes, eyelids and mouth.

9. 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. Medicated soaps used on face.
   b. 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.
   c. Photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides).
   d. Application of study treatment to unaffected skin.
   e. More than 10,000 IU/day of Vitamin A supplements.
   f. Spironolactone.
   g. Oral retinoids, therapeutic vitamin A supplements of greater than 10,000 units/day (multivitamins are allowed) or other systemic treatment for acne vulgaris.
   h. Systemic (e.g., oral or injectable) antibiotics.
   i. Systemic steroids, systemic anti-inflammatory agents or immunosuppressive drugs.
   j. Antipruritics, including antihistamines, within 24 hours of study visits.
   k. Use on the face of 1) cryodestruction or chemodestruction, 2) dermabrasion, 3) photodynamic therapy, 4) acne surgery, 5) intralesional steroids, or 6) x-ray therapy.
   l. The treated areas should not be bandaged, covered or wrapped as to be occlusive.
   m. Tanning booths, sun lamps, or nonprescription UV light sources.
   n. Phototherapy.
   o. 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 cream 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.

10. The recommended two co-primary endpoints of the study are percent change from baseline to week 12 in the inflammatory (papules and pustules) lesion counts and in the noninflammatory (open and closed comedones) lesion counts. The protocol should clearly define papules, pustules, open comedones, closed comedones, nodules and cysts. When counting facial acne lesions, it is important that all lesions be counted, including those present on the nose. Counts of nodules and cysts should be reported separately and not included in the inflammatory or non-inflammatory lesion counts.

11. The dichotomized IGA severity scale should be treated as a secondary endpoint for supportive evidence. This secondary endpoint for bioequivalence should be evaluated as the proportion of subjects with a clinical response of "success" at week 12. Success should be defined as an IGA score that is at least 2 grades less than the baseline assessment. Failure should be defined as an IGA score that is the same, higher or one grade lower than the baseline assessment.

12. 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 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 the 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.

13. 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 acne vulgaris 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 LOCF.

14. 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.

15. 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.

16. Application site reactions such as erythema, dryness, burning/stinging, erosion, edema, pain and itching are to be recorded at each visit to allow a comparison between treatment groups. A descriptive analysis comparing the application site reactions for each treatment group is recommended. It is important to ensure that the test product is not worse than the reference product with regard to the expected and unexpected application site reactions.

17. 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.

18. 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.

19. 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.

20. 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.

21. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.

22. To establish bioequivalence, the 90% confidence interval of the test/reference ratio of the mean percent change from baseline to week 12 in the inflammatory (papules and pustules) and noninflammatory (open and closed comedones) lesion counts must be contained within [0.80, 1.25], using the PP study population.

23. As a parameter for determining adequate study sensitivity, the test product and RLD should be statistically superior to placebo ($p<0.05$) with regard to percent change from baseline to week 12 in the inflammatory (papules and pustules) and non-inflammatory (comedones) lesion counts using the mITT study population and Last Observation Carried Forward (LOCF).

24. The following Statistical Analysis Method is recommended for equivalence testing for a continuous variable:

    Equivalence Analysis
    The compound hypothesis to be tested is:

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

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

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

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

25. 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: $p_T - p_R < -0.20$ or $p_T - p_R > 0.20$

versus

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

where p_T = cure rate of test treatment and p_R = cure rate of reference treatment.

Let

n_T = sample size of test treatment group

cn_T = number of successes in test treatment group

n_R = sample size of reference treatment group

cn_R = number of successes in reference treatment group

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

and se = $(\hat{p}_T(1 - \hat{p}_T)/n_T + \hat{p}_R(1 - \hat{p}_R)/n_R)^{½}$.

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

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

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

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.

26. 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, lesion counts, vital signs, adverse events, disposition (including reason for discontinuation of treatment), concomitant medications, medical history, compliance and comments, etc.

27. Please provide a summary dataset containing a separate line listing for each subject (if data exist) using the following headings, if applicable:
    a. Study identifier
    b. Subject identifier
    c. Site identifier: study center
    d. Age
    e. Age units (years)
    f. Sex
    g. Race
    h. Name of Actual Treatment (exposure): test product, RLD, placebo control
    i. Location of Treatment Area
    j. Duration of Treatment (total exposure in days)
    k. Completed the study (yes/no)
    l. Reason for premature discontinuation of subject
    m. Subject required additional treatment for acne vulgaris due to unsatisfactory treatment response (yes/no)
    n. Per Protocol (PP) population inclusion (yes/no)
    o. Reason for exclusion from PP population
    p. Modified Intent to Treat (mITT) population inclusion (yes/no)
    q. Reason for exclusion from mITT population
    r. Safety population inclusion (yes/no)
    s. Reason for exclusion from Safety population
    t. Total number of inflammatory lesions on the face at baseline
    u. Total number of non-inflammatory lesions on the face at baseline
    v. Total number of nodules/cysts on the face at baseline
    w. IGA score at baseline
    x. Total number of inflammatory lesions on the face at week 12
    y. Total number of non-inflammatory lesions on the face at week 12
    z. Total number of nodules/cysts on the face at week 12
    aa. IGA score at week 12
    bb. Final designation for IGA (success/failure)
    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 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 containing one line listing for each subject

STUDYID	SUBJID	SITEID	AGE	AGEU	SEX	RACE	EXTRT	EXLOC	EXDUR	completd	disc_rs	add_trt	pp	pp_rs	mitt	mitt_rs
101	1	01	21	YEARS	F	1	A	Face	14	Y		N	Y		Y	
101	2	01	30	YEARS	F	1	B	Face	14	Y		N	Y		Y	

safety	safe_rs	numinfb	numnonb	numnodb	iga_b	numinf12	numnon12	numnod12	iga_12	iga_f	complian	CM	AE
Y		32	45	0	3	16	30	0	2	F	0	Y	Y
Y		25	36	1	3	10	18	1	1	S	0	N	N

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

STUDYID:	Study Identifier
SUBJID:	Subject Identifier for the Study
SITEID:	Study Site Identifier
AGE:	Age
AGEU:	Age units (years)
SEX:	Sex, e.g., M=Male, F=Female, U=Unknown
RACE:	Race, e.g., 1=White, 2=Black or African American, 3=Asian, 4=American Indian or Alaska Native, 5=Native Hawaiian or Other Pacific Islanders
EXTRT:	Name of Actual Treatment (exposure), e.g., A=test product, B= RLD, C=placebo control
EXLOC:	Location of Treatment Area, e.g. F=face, etc.
EXDUR:	Duration of Treatment (total exposure in days)
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 acne 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.
numinfb:	Total number of inflammatory lesions on face at baseline
numnonb:	Total number of noninflammatory lesions on face at baseline
numnodb:	Total number of nodular/cystic lesions on face at baseline

iga_b:	IGA score at baseline, e.g., 0=Clear, 1=Almost Clear, 2=Mild, 3=Moderate
numinf12:	Total number of inflammatory lesions on face at week 12
numnon12:	Total number of noninflammatory lesions on face at week 12
numnod12:	Total number of nodular/cystic lesions on face at week 12
iga_12:	IGA score at week 12, e.g., 0=Clear, 1=Almost Clear, 2=Mild, 3=Moderate
iga_f:	Final designation for IGA, e.g., S=Success; F=Failure
complian:	Treatment compliance, e.g., number of missed doses per subject
CM:	Concomitant medication, e.g., Y=Yes, N=No
AE:	Adverse event(s) reported, e.g., Y=Yes, N=No

28. Please provide a dataset containing a separate line listing for visit per subject (if data exist) using the following headers, if applicable:
    a. Study identifier
    b. Subject identifier
    c. Name of Actual Treatment (exposure): test product, RLD, placebo control
    d. Location of Dose Administration: application site
    e. Visit number
    f. Visit date
    g. Number of days since baseline visit
    h. Evaluator: identity of evaluator
    i. Total number of inflammatory lesions
    j. Total number of noninflammatory lesions
    k. Total number of nodular/cystic lesions
    l. IGA score
    m. Skin reaction scores for each sign and symptom evaluated (e.g., erythema, dryness, burning/stinging, erosion, edema, pain, itching, etc.)
    n. Concomitant medication reported during this visit (yes/no)
    o. Adverse event reported during this visit (yes/no)
    p. Laboratory testing 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 visit per subject

STUDYID	SUBJID	EXTRT	EXLOC	VISITNUM	SVSTDTC	ELTMBS	EVAL	numinf	numnon	numnod	iga
101	1	A	F	1	2004-07-01	1		35	28	1	3

erythema	dryness	burning	erosion	edema	pain	itching	CMrpt	AErpt	LBtest
1	0	0	1	0	0	0	Y	Y	N

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

STUDYID:	Study Identifier
SUBJID:	Subject Identifier for the Study
EXTRT:	Name of Actual Treatment (exposure), e.g., A=test product, B=RLD, C= placebo control
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
numinf:	Total number of inflammatory lesions on face
numnon:	Total number of noninflammatory lesions on face
numnod:	Total number of nodular/cystic lesions on face
iga:	IGA score, e.g., 0=Clear; 1=Almost clear, 2=Mild, 3=Moderate, 4=Severe
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/stinging 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

29. If the Tazarotene Cream/Topical, 0.1% test product demonstrates bioequivalence for the acne vulgaris indication, it is not necessary to conduct an additional BE study with clinical endpoint for the psoriasis indication. If a sponsor requests approval of their Tazarotene Cream/Topical, 0.1% test product for both reference listed drugs (RLDs), submits the appropriate labeling for both RLDs, and their test product demonstrates bioequivalence in the acne vulgaris indication, it is not necessary to conduct an additional BE study with clinical endpoint for the indication “as an adjunctive agent for use in the mitigation (palliation) of facial fine wrinkling, facial mottled hyper- and hypopigmentation, and benign facial lentigines in patients who use comprehensive skin care and sunlight avoidance programs”.

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.