Guidance for Industry

Acne Vulgaris: Developing Drugs for Treatment

DRAFT GUIDANCE

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For questions regarding this draft document contact (CDER) Frank Cross at 301-827-2020.

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Clinical/Medical

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Office of Training and Communications
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
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I. INTRODUCTION

This document is intended to provide guidance to the pharmaceutical industry on the development of drug products for the treatment of acne vulgaris other than nodulocystic acne. The information presented will help applicants plan clinical studies, design clinical protocols, implement and appropriately monitor the conduct of clinical trials, collect relevant data for analysis, and perform appropriate types of analyses of study data.

This guidance does not address systemic retinoid therapies, which may not have appropriate risk-benefit profiles for non-nodulocystic acne therapy. Development programs for these treatments should be discussed with the review division before initiation.

The recommendations in this guidance are based on careful assessment of important issues raised in the review of clinical trials for acne vulgaris. Applicants are encouraged to discuss development plans with the review division before embarking on studies to ensure that the clinical trial design and analysis plan meet defined objectives. The FDA's

[1] This guidance has been prepared by the Division of Dermatologic and Dental Drug Products in the Office of New Drugs (OND) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

Paperwork Reduction Act of 1995: This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collection of information in this guidance has been approved under OMB Control Number 0910-0001.

guidance for industry *Format and Content of the Clinical and Statistical Sections of an Application*[2] and ICH E9[3] contain additional information.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. CLINICAL BACKGROUND

Acne vulgaris is a chronic disease of sebaceous follicles that is multifactorial in etiology and varies in severity as evidenced by lesion type, size, numbers, scarring, and post-inflammatory pigmentary changes. The severity of acne vulgaris (i.e., amount of inflammation and number of lesions) can wax and wane in a given patient. A variety of drug products, topical and systemic, are currently available to treat acne. Acne occurs more frequently on the face, but can also occur on nonfacial skin (e.g., back, shoulders, chest).

A. Lesion Types

There are two major types of acne lesions: noninflammatory and inflammatory. Although most drug products for acne are intended for the broad indication of acne vulgaris, some products have been developed that only target one of these two specific subsets of acne vulgaris lesions.

Noninflammatory lesions of acne are the open (blackheads) or closed (whiteheads) comedones. Closed comedones may be more difficult to detect visually and may require stretching of the skin to aid in visualization. These lesions, especially closed comedones, may be precursors to the larger inflammatory lesions and therefore are of clinical importance.

Inflammatory lesions are divided into papules, pustules, and nodules/nodulocystic lesions, depending on the severity and location of the inflammation within the dermis. The papules and pustules have surrounding halos of erythema allowing for their characterization as inflammatory. Nodules are typically erythematous and often tender and/or painful. Additionally, they are deep-seated in the skin (i.e., centered in the dermis or subcutis). Nodules have been defined as being greater than 5 mm in diameter. The borders of these lesions may be difficult to determine because of the associated erythema/inflammation.

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[2] We update guidances periodically. For the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

[3] See ICH guidance for industry *E9 Statistical Principles for Clinical Trials* (http://www.fda.gov/cder/guidance/index.htm)

B. Overall Acne Severity

There is no single uniform, standardized, and reproducible grading system for severity of acne. Acne severity is dependent on the numbers and types of lesions present and the extent of involvement (i.e., the body areas affected). (See Section III.A.2., Baseline Lesion Counts.)

A number of acne grading systems have been described, some with inherent difficulties with regard to use. Such difficulties include inadequately defined grades of severity or excessively small differences between grades to be objectively evaluated. An Investigator's Global Assessment (IGA) scale that may be useful for assessing overall acne severity is described in Section IV.A.1.

C. Patient Population

Acne vulgaris is primarily a disease beginning with and extending beyond puberty, but can persist past the third decade of life. Although acne vulgaris affects both genders, severity may be greater in male patients. Acne vulgaris occurs in all races and across the United States.

III. DRUG DEVELOPMENT PLAN

A. Clinical Considerations

1. General

The Agency recommends that phase 2 clinical studies provide sufficient information to optimize dose and duration of treatment chosen for phase 3 evaluation (with adequate consideration given to both safety and efficacy before end-of-phase 2 discussion). In general, a minimum treatment duration of 12 weeks is needed to demonstrate efficacy. We recommend considering a post-treatment follow-up period to evaluate recurrences following treatment discontinuation.

It is important that all drug products for acne be evaluated for safety and efficacy in the treatment of facial acne. Applicants are encouraged to demonstrate the safety and efficacy of the investigational drug in at least two adequate and well-controlled studies. We recommend that these trials be randomized, blinded, multicenter trials with suitable comparator arms, which usually include a vehicle or placebo control. Additional assessments for safety and efficacy in the treatment of nonfacial acne can be included for topical products and should be included for all systemic acne medications.

Patients are often recruited for study entry at their worst severity and usually improve during the course of therapy, whether the therapy is active or placebo (vehicle in the case

of topical drugs). A demonstration of superiority against a placebo arm is generally needed for clinical studies.

We recommend that applicants enroll a population that is representative of the age, race, gender, and geographic location of acne patients in the United States. (See also ICH guidance for industry *E5 Ethnic Factors in the Acceptability of Foreign Clinical Data* and guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials*.)

2. Baseline Lesion Counts

Baseline acne severity is a key element of the enrollment criteria. Baseline lesion counts are expected to have a major influence on efficacy outcomes in acne trials. Since change in lesion counts from baseline may not always translate into a successful IGA outcome, it is recommended that power calculations be based on both endpoints (see Section IV., Study Design). As the range of baseline lesion counts is expected to affect the success rates of the outcomes, and may vary from drug to drug, applicants are encouraged to investigate the optimal range of baseline lesion counts to demonstrate success before initiation of phase 3 studies.

The baseline score of the IGA severity scale should be consistent with the baseline lesion counts. However, no numerical range of lesions for categorizing the IGA is recommended. This is because the IGA is the investigator's or physician's overall general assessment of the patient's condition and is considered to be more subjective than the purely numerical lesion count. It also takes into account the quality, as well as the quantity, of the acne lesions.

3. Targeted Acne Therapy

If a drug product is developed specifically for either inflammatory lesions or noninflammatory lesions of acne, labeling should reflect the specific type of lesion studied with reference to lack of proven efficacy for the lesion type not studied.

For drugs specifically intended to treat either inflammatory or noninflammatory lesions, it is appropriate for both lesion counts and the IGA to be assessed. Superiority will need to be demonstrated for both the targeted lesion type and the IGA. We recommend that the IGA allow for a clinical and statistical evaluation of the investigator's overall qualitative assessment of the acne severity in each patient. However, emphasis in the IGA regarding the lesion type not being targeted may be modified. To show that there is no worsening of the nontargeted lesion type, we recommend the endpoint for the nontarget lesion count demonstrate noninferiority of the active treatment to the vehicle at the prespecified time point. It is important that an appropriate noninferiority margin be selected to maintain a substantial proportion of the expected improvement from baseline for the nontargeted lesions in the vehicle or placebo treatment group.

At the end of phase 2 and before initiation of phase 3 trials, we recommend that the applicant specify if a drug product would be indicated for only inflammatory, only noninflammatory, or both types of lesions of acne.

If the drug product under development is expected to be used together with another marketed drug therapy for acne, it is important that the clinical study design reflect such co-use or adjuvant use. We recommend consultation with the Agency before the conduct of these types of trials.

As there are specific informational needs with regard to many treatments for nodular acne, it is recommended that applicants seek additional guidance from the Agency regarding treatments targeted for nodular/nodulocystic acne.

4. Fixed Combination Drug Products for Acne Vulgaris

Fixed combination topical products for the treatment of acne vulgaris are considered under 21 CFR 300.50 and require evidence for the contribution of each active component that is claimed to provide for additional safety or efficacy. In study design, we recommend consideration be given to active components that may target a specific lesion type.

Although evidence for efficacy may rely on comparison with a reference-listed combination drug product, comparison of only test and reference-listed combination drug product may be insufficient. The contribution to efficacy of different active ingredients may vary among different vehicles. Because of the complexity of clinical trial design, we recommend applicants seek further guidance from the Agency before the conduct of studies for fixed combination drug products.

5. Safety Considerations

For topical drug products, dermal safety studies with the final to-be-marketed drug product are recommended. It is important for these trials to provide information regarding cumulative irritancy (at least 30 evaluable subjects), contact sensitization (at least 200 evaluable subjects), phototoxic (at least 30 evaluable subjects), and photocontact allergic potential (at least 50 evaluable subjects). These trials are usually conducted simultaneously with phase 3 clinical trials, although preliminary dermal safety evaluations could be conducted during development of the to-be-marketed formulation.

Dermal provocative irritation studies may be waived if phase 2 safety data demonstrate that the product is irritating and the Agency determines that this information is adequate for labeling purposes. Dermal irritation and sensitization (allergenicity) studies can be combined as long as a sufficient number of subjects are included for sensitization evaluation. Phototoxicity and photosensitization studies may be waived if there is no absorption of the drug product by UVB, UVA, or visible light (280 to 700 nm).

Safety assessments, for short-term use, of both oral and topical acne drug products can include routine chemistry and hematology profiles. Other safety parameters may be appropriate depending upon any safety signals found in preclinical studies.

Given the natural history of acne vulgaris, acne drug products have the potential for chronic use. Therefore, we recommend addressing long-term safety. Applicants are referred to the ICH E1A guidance[4] for assistance in determining the number of subjects exposed and duration of treatment needed to provide an acceptable safety database.

B. Biopharmaceutical Considerations

Pharmacokinetic studies to assess the degree of and/or potential for systemic absorption may be needed to fulfill the requirements of 21 CFR part 320 (Bioavailability and Bioequivalence Requirements). Under this section, a new drug application (NDA) must either contain an assessment of in vivo bioavailability or sufficient information which would allow the Agency to issue a waiver of in vivo bioavailability testing. In general, waivers of in vivo biostudies are the exception and are only granted in specific cases. Because of the variable dosing nature of topical products, we recommend that studies of the in vivo assessment of systemic exposure be done under so-called *maximal use conditions*. The recommended elements of such a maximal use study are as follows:

1) A formulation identical to the clinically studied/to-be-marketed formulation should be used.

2) The study should be done in an adequate number of patients with area of involvement and disease severity index/measuring toward the upper end of that in the proposed indication to include at least the face, shoulders, chest, and back.

3) The topical dosing used should represent the maximal dosing anticipated in both phase 3 trials and in the proposed package insert for the following:

    a) Frequency of dosing
    b) Duration of treatment
    c) Use of highest proposed strength
    d) Extent of involved area to be treated at one time
    e) Amount applied per square centimeter
    f) Method of application/site preparation

4) The analytical method should be properly validated for both parent compound and metabolites.

The objective of this study is to maximize those elements affecting dermal penetration such that systemic absorption can be determined. We recommend, when possible, that

[4] See ICH guideline for industry *E1A The Extent of Population Exposure to Access Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions* (http://www.fda.gov/cder/guidance/index.htm)

the resulting pharmacokinetic data be analyzed using standard pharmacokinetic metrics (AUC, C_{max}, T_{max}). It is also recommended that the study protocols incorporate evaluations for cutaneous safety.

IV. STUDY DESIGN

The Agency recommends that the study protocol for evaluation of acne vulgaris clearly specify the objectives of the trial, the patient population, study drug dosage and duration of treatment, primary endpoints, and key planned analyses. In addition, we recommend the study design support the proposed claims by taking into consideration the following factors:

1) **Sample size:** It is important that the sample size be sufficiently large to support the overall safety and efficacy claims. We recommend the study be powered to ensure at least 80 percent power with a 2-sided Type I error rate of 0.05. It is important that the protocol provide details concerning sample size calculations for each of the co-primary endpoints: changes from baseline in inflammatory and noninflammatory lesion counts and success according to the IGA. We also recommend the study be adequately powered for all co-primary endpoints. For each of these co-primary endpoints, it is important that the protocol specify estimated treatment effect for each comparator. For noninferiority trials, it is also important for the noninferiority margin to be prespecified and discussed with the Agency. Unequal treatment allocation of patients to the various treatment arms might help keep the sample size manageable. Such unequal treatment allocation can be particularly useful for evaluation of combination drug products (see Section III, Drug Development Plan).

2) **Randomization and stratification:** Randomization is intended to allocate patients to treatment groups to reduce bias and to ensure that the statistical procedures can be appropriately applied. As baseline lesion counts are expected to have a significant effect on outcomes, it is important to make a considerable effort to ensure random allocation of subjects to treatment arms to reduce bias. Although randomization is intended to balance treatment allocation for confounding factors, there is always a chance that randomization may fail to achieve balance, particularly in smaller trials.

   If there are known factors that are expected to have a large influence on outcome, stratification can be used to balance patient assignments for these factors instead of relying solely on simple randomization. However, we recommend that stratification be limited to the most influential factors to avoid having a large number of strata and consequently a small number of subjects per cell. Because stratification implies constraints on randomization, the statistical analysis for studies that have been stratified for certain factors should account for these factors. Since some degree of variation in efficacy across patients of different

sites or geographic areas is expected, we recommend randomization by study site to balance the treatment arms in acne trials.

3) **Blinding:** Because efficacy assessments of acne, in particular the IGA, have a high degree of subjectivity, it is important that the highest degree of patient and assessor blinding be sought to achieve credible inference. Blinding may be compromised if there is a marked difference in the adverse event profile between the comparators. Every effort should be taken to preserve blinding, such as using an independent assessor (a qualified independent clinical assessor would provide the scoring of record for those aspects of clinical assessment to be blinded).

A. Primary Endpoints

Many methods exist for assessing the severity of acne and almost all of them use an ordinal scale for assessing global severity (Lehmann et al. 2002). The primary difficulty in developing a standardized ordinal scale is the pleomorphic nature of acne, as is pertinent to the mixture of lesion types, sites of involvement, the variable characteristics of the lesions (especially the inflammatory types), and the variability in the progression of acne lesions. However, this inherent difficulty provides the basis for the categorical utility of having such a global assessment (Allen 1980; Feinstein 1977; Plewig et al. 1992).

Use of lesion count assessments alone as an endpoint may be less than reliable because of the lack of appreciation for the variable expression of acne vulgaris with a strictly quantitative definition (e.g., size of lesions, intensity of inflammation, and location of lesions). Although reduction in lesion counts may indicate improvement of acne severity, clinical perception of a given lesion count reduction (e.g., 50 lesions less) is different for various baseline lesion counts (e.g., 100 versus 53 lesions). In addition, precision achieved with lesion counts can be difficult and can vary even among clinicians who are experienced in counting lesions of acne vulgaris. Variability of lesion counts among raters has been shown to increase as the number of acne lesions on a patient increase (Lucky et al. 1996). Finally, although individual lesion counts have often been employed successfully in the investigational setting, their practicality and value for use in the clinical setting have been questioned (Pochi et al. 1991).

Combining the two approaches of ordinal global assessment scale and lesion count assessments allows for a balanced approach toward the evaluation of acne severity. The Agency continues to evaluate new metrics and alternative methods as they are developed for evaluating acne severity.

We recommend for clinical studies investigating the effect of a therapy on acne severity, co-primary endpoints that evaluate an IGA, and acne lesion counts.

1. Investigator's Global Assessment

The Agency recommends that the IGA be a static evaluation of qualitative overall acne severity. To accomplish this, the global assessment scale should be an ordinal scale with approximately five severity grades (reported only in integers, e.g., 0 to 4). Each grade should be defined by a distinct and clinically relevant morphologic description that minimizes interobserver variability. The grades on the scale should be sufficiently defined to appropriately and unambiguously represent each severity grade on the scale. Photographic examples of each grade that have been agreed upon with the Agency before their use may be provided to investigators. It is recommended that measures to ensure blinding of investigators as to any previous or baseline scores with each evaluation be submitted for review by the Agency. For consistency, it is important that the same IGA scale be used throughout the study, including study enrollment, evaluation at endpoint, and for assessment of relapse. The Agency recommends that each subject's improvement be verifiable (e.g., via photographic records of baseline and assessment time point) by Agency staff for auditing purposes. Table 1 is an example of an IGA scale that may be useful.

Table 1. Sample IGA Scale for Acne Vulgaris

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 and inflammatory lesions, but no more than a few nodular lesions

* 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 patients not include patients with nodulocystic acne. Patients who worsen beyond Grade 4 are to be described in the safety evaluation.

For assessment of efficacy, the Agency recommends that the IGA scale be dichotomized to *success* or *failure* using one of the following two criteria to be selected *a priori*.

1) **Clear or almost clear (Grades 0 or 1) as *success*:** Success is defined as "Clear" (Grade 0) or "Almost clear" (Grade 1) at the prespecified primary time point. For patients whose baseline score is Grade 2, the clinically meaningful criterion for IGA success is achieving a score of Grade 0 at the prespecified primary time point because of limitations inherent to an ordinal scale.

2) **Two grade improvement as *success*:** Success is defined as improvement of two grades from the baseline score at a prespecified primary time point. Since under

this alternative definition of success not all subjects with "Severe" (Grade 4) acne will achieve the "Clear" or "Almost clear" state, if the product under study is approved, these outcomes would provide useful information in product labeling.

We recommend that the IGA success criterion not selected *a priori* for primary evaluation be evaluated as a secondary endpoint. A study that fails on the primary IGA success criterion selected would not be rescued with the other success criterion, as this would not control for Type I error.

For targeted acne therapy (i.e., treatment of inflammatory or noninflammatory lesions of acne alone), the IGA selected for use may modify emphasis for the lesion type not being evaluated.

Applicants are encouraged to discuss other alternative IGA grading scales and study designs with the Agency before implementation.

2. Lesion Counts

For the acne vulgaris indication, noninflammatory and inflammatory acne lesion counts are co-primary endpoints along with the IGA. When counting facial acne lesions, it is important that all lesions be counted, including those present on the nose.

Even if the indication is limited to only one type of lesion (i.e., either noninflammatory or inflammatory lesions of acne), as described in Section III.A., Clinical Considerations, we recommend obtaining lesion counts for both types, but only declaring one as primary in the prespecified analysis plan.

B. Patient-Reported Outcomes

The Agency is interested in *patient-reported outcome* information; however, such information should not be used as a substitute for objective data or as a surrogate for efficacy. For patient-reported outcome assessments, objective measures could be helpful tools, which may inform both the patient and clinician.

V. DATA ANALYSIS

It is important that the tools for statistical evaluation be appropriate for analysis of the efficacy endpoints. We recommend that the statistical analysis plan prespecify the primary efficacy variables, the study population, the hypothesis to be tested, and the statistical methodology to be used. It is important to consider the following points in the statistical analysis plan:

1) The primary efficacy analyses for an acne indication should be:

    a) Change from baseline in the inflammatory lesion count;

b) Change from baseline in the noninflammatory lesion count; and
c) The proportion of success according to the dichotomized IGA.

Secondary efficacy variables should be those clinically relevant outcomes that support the validity of the primary efficacy variables.

2) For a general acne indication, we recommend the test drug be superior to its vehicle with respect to change, both in inflammatory and noninflammatory lesions, in addition to success according to the IGA (see above). It is also important to provide secondary analysis for percent change of lesion counts.

   On the other hand, for an acne indication specific to a certain lesion type (see Section III.A.3., Targeted Acne Therapy), we recommend the test drug be superior to its vehicle with respect to the specified lesion type, and be noninferior to its vehicle for the other lesion type. It is important that the noninferiority margin be discussed and agreed upon with the Agency before study initiation. In addition, it is important to demonstrate superiority for success according to the IGA.

3) Prespecification of the statistical analysis is a key factor for obtaining consistent and convincing evidence of product efficacy, as data-driven analyses should not be used to support efficacy claims. We recommend the protocol have sufficient description of the statistical analyses of the primary efficacy endpoints so that an independent statistician could perform the analyses in the protocol. The description should include: specifying the hypotheses to be tested, indicating the level of significance to be used, and whether it is 1- or 2-sided, denoting the mathematical expression of the statistical models, and identifying methods for controlling Type I error rates for multiplicity or interim analyses if needed.

4) It is important that the protocol prospectively identify the covariates to be used in the analysis. We recommend using all prespecified covariates that are selected. It is also important that the number of covariates be kept to a minimum and limited to those whose influence on the outcome is suspected to be strong, such as stratification factors like study center.

5) We recommend addressing in the protocol possible center-by-treatment interaction along with planned sensitivity analyses to ensure robustness of the efficacy results.

6) If multiple assessments are taken (e.g., over time) it is important that the protocol prespecify how they will be evaluated for efficacy. If the claim is that a win occurs if any assessment wins, an adjustment needs to be made for multiplicity, but, if a win occurs only if all assessments win, no adjustment in significance level is warranted. We recommend that the method for multiplicity adjustment be planned and specified in the protocol. This would also include assessments for any validated patient-reported outcome endpoints.

7) If interim analyses are planned, it is important that the protocol prespecify early stopping rules and penalties for such interim analyses.

8) We recommend provisions be made for analysis of clinically relevant secondary endpoints and subgroup efficacy analysis, along with safety evaluations. A multiplicity adjustment could be appropriate if the efficacy results from multiple secondary endpoints are intended to appear in the label.

9) It is important that the study protocol clearly define the study population to be analyzed, and provisions be made to handle dropouts (see Section V.A., Handling Dropouts). We recommend efficacy evaluation be carried out for the intent-to-treat (ITT) population, defined as all subjects randomized and dispensed study medication. We also recommend that a supportive analysis be carried out for the per-protocol (or completers) population and criteria for defining the per-protocol population be specified in the protocol.

A. Handling Dropouts

We recommend that efficacy and safety evaluation be carried out on all patients randomized and dispensed study medication. Every effort should be made to follow all enrolled subjects until the end of the study and until the resolution of any adverse event. However, in clinical trials, it is anticipated that a certain percentage of enrolled subjects will drop out.

Dropouts are common in acne trials and lead to information loss. It is unlikely that dropouts occur randomly, and they rarely occur completely independent of the treatment being tested, so there is always the possibility that dropouts introduce bias. The extent of this bias is expected to be related not only to the magnitude of the information loss due to dropout but also to the distribution of the dropouts among the various treatment arms. Several methods for handling dropouts have been proposed, but none is fully adequate.

1) The Agency's current approach for acne vulgaris trials is based on using the intent-to-treat analysis with imputation of the last observation carried forward (ITT/LOCF), along with the per-protocol (completers) analysis. Although consistency in efficacy findings from the two analyses can increase confidence in the efficacy results, this does not resolve the problem of handling dropouts. The LOCF might not be the optimal approach for handling dropouts; however, it is frequently applied because of simplicity. If other or additional approaches for handling dropouts are proposed, we recommend they be prespecified in the protocol.

2) It is important that the effect of dropouts be addressed in all clinical trials and analyses, and analyses be carried out to demonstrate that the study conclusions are robust with regard to handling dropouts. An approach that can be used to check robustness of study findings is the worst-case rule (assigning the best possible

score to all dropouts on placebo arm and the worst score to all dropouts on the active arm and then performing an analysis including these scores).

B. Data Quality and Format

We recommend that all data from clinical trials be validated and their quality assured. We also recommend that all data be submitted in electronic format per Agency guidance.[5] It is important to consider the following points during database formulation:

1) In addition to efficacy and safety data, it is important that demographic and baseline data be submitted to the Agency. It is also important that data for derived variables be provided along with the algorithm to generate these variables.

2) Efficacy and safety summaries can be consolidated. We recommend data from multiple studies use the same format, so that data from one trial can be easily merged with data from another to allow subset analyses based on gender, age, race, and, when appropriate, other subgroups.

3) Electronic photographic records should be submitted to the Agency such that they can be readily evaluated (e.g., sufficient resolution to allow for clinical re-evaluation), clearly labeled (e.g., with regard to subject, study number, center, and time taken), and organized in a retrievable fashion for storage and archiving purposes.

[5] See guidance for industry *Providing Regulatory Submissions in Electronic Format — General Considerations* and guidance for industry *Providing Regulatory Submissions in Electronic Format — NDAs* (http://www.fda.gov/cder/guidance/index.htm)

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