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December 15, 2005

Division of Dockets Management
Food and Drug Administration
5620 Fishers Lane
Room 1061 (HFA-305)
Rockville, MD 20852

Re: Docket No. 2005D-0340
Draft Guidance of Industry on Acne Vulgaris: Developing Drugs for Treatment

Dear Sir or Madam:

Galderma is a leading worldwide pharmaceutical company with a focus on research and development of dermatological products. Our corporate mission is to contribute to the treatment of dermatologic diseases and conditions by developing quality products that meet the needs of dermatologists and patients.

Galderma supports the Agency's efforts to develop guidances for sponsors regarding the issues to be considered when developing drug products. With our focus on the development of topical dermatologic products, we have considerable research and development experience that have bearing on the issues affected by this draft guidance. We are pleased to have the opportunity to provide comments on the "Guidance for Industry, Acne Vulgaris: Developing Drugs for Treatment" as published in the September 19, 2005 Federal Register for the Agency's consideration.

We have included specific information extracted from the guidance document with sections and line numbers from the draft guidance in order to facilitate the Agency's review. We provide our comments immediately following the information from the guidance document.

Indication :

Section III.A.3 (Targeted Acne Therapy) of the draft guidance states that *"If a product is developed specifically for either inflammatory lesions or noninflammatory lesions of acne, labeling should reflect the specific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. (...) 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."*

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Our opinion is that dichotomization of noninflammatory acne and inflammatory acne may appear too theoretical and not necessarily reflect pathogenesis of acne and clinical reality. Since both types of lesions arise from microcomedone (which is not visible clinically), it seems reasonable to assume that a beneficial effect on one type of lesions would at least be linked to a partial effect on the other type of lesions. The lack of proven efficacy on one type of lesions during clinical development would therefore not necessarily mean that the lack of efficacy on this type of lesion is proven. Moreover, from a medical practice point of view, patients usually visit their doctor for their acne only when the disease becomes visible, i.e. when inflammatory lesions appear on their face. An anti-acne drug with an indication restricted to noninflammatory lesions would therefore have very limited chance to be prescribed although proven to be efficacious.

As a consequence, we propose that the indication section of the labelling of topical anti-acne therapies should simply read "*Topical treatment of acne vulgaris*". This rule should apply to both single drug products and fixed combination products. Such approach is consistent with our suggestion to use Success Rate (based on IGA scale) as the single primary efficacy endpoint, since it allows for a global clinical and statistical evaluation of the disease which is close to the real medical situation and which is more reliable and less variable than lesion counting.

Nevertheless, we agree that the labeling should somewhere reflect the effects of the drug on the different types of lesions and would propose that this information should be best placed in the CLINICAL STUDIES section. The inclusion of the results for both change and percent change in lesion counts *versus* vehicle in this section would provide the health care provider with the useful information on the efficacy pattern of the drug (i.e. predominantly active on one type of lesions or active on both types).

In the specific case of fixed dose combination products, we also agree that the failure for a product to achieve a significant superiority on one type of lesions *versus* one of its monads would also need to be reflected in the CLINICAL STUDIES section of the labeling. However, such a failure should not prevent the Applicant to claim an efficacy of the fixed dose combination product on both types of lesions as long as a significant superiority of the combination *versus* the vehicle has been demonstrated on both types of lesions.

Clinical endpoints:

We propose that the primary efficacy parameter should be the percentage of patients with success at the end of treatment (defined as dichotomization success / failure based on the IGA scale (Investigator's global assessment)). The study would be claimed positive, for the indication "Acne vulgaris", if the test products are significantly superior to the chosen comparator.

It is our opinion, that success rate based on IGA, is the most relevant clinical parameter to evaluate drug effects in the treatment of acne vulgaris. The IGA is a static, qualitative evaluation of overall acne severity. It closely mimics the health care provider's

evaluation of patients in everyday clinical practice, it is well established with dermatologists and is more reliable and less variable than lesion counting.

The proposed IGA scale include as an example in the draft guidance (Table 1, section IV) has some drawbacks. The definition of 0 and 1 seems to be close clinically and does not allow unambiguously to represent each of these two grades. Also, the definition of “Mild” (grade 2) seems to be closer to an almost clear status than representing a diagnosis of mildly severe acne vulgaris. Moreover, line 143 of the draft guidance states that “no numerical range of lesions for categorizing the IGA is recommended”, whereas grade 1 and 3 of the proposed scale do so.

In addition, the footnote (line 363-364), is not consistent since the proposed scale does not provide for a grade more severe than 4 and worsening beyond grade 4 should be considered as lack of efficacy rather than a safety concern and treated as such in the study report.

We would therefore propose an alternate scale (Table 1):

Table 1 : Proposed IGA scale

Investigator’s Global Assessment Scale		
0	Clear	Residual hyperpigmentation and erythema may be present.
1	Almost Clear	A few scattered comedones and a few small papules.
2	Mild	Easily recognizable; less than half the face is involved. Some comedones and some papules and pustules.
3	Moderate	More than half of the face is involved. Many comedones, papules and pustules.
4	Severe	Entire face is involved. Covered with comedones, numerous papules and pustules and few nodules and cysts.

It is our opinion, that among the two proposed options to define success, the first one (success defined as clear/almost clear as grades 0 and 1) is some how redundant with the second one (two grades improvement as success). We would therefore propose that the latter be the standard to define success, i.e. as an improvement of two grades from baseline score at a pre-specified endpoint, which allows the subjects with severe acne vulgaris (grade 4) to be considered as successful even if they do not achieve a clear or almost clear state.

Section V.A.2,Line 514-516 states: “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)."

We would propose to examine robustness of the results in success rate based on sensitivity analyses that impute missing data in all groups as failure on one hand and as success on the other hand.

It is not clear, how consistency that is described in line 141-142 (*"The baseline score of the IGA severity scale should be consistent with the baseline lesion counts"*) may be established, since lesion count measurement and IGA scale are not measuring the same endpoint in the same way. In particular, as the agency underlines further, IGA *"takes into account the quality, as well as the quantity, of the acne lesions"* (line 145-146).

Lesion count

We would like to clarify the morphological criteria to define papules and nodules. The guidance refers (line 74) to nodules being defined as lesions > 5mm in diameter. However, in our understanding that the current definition of nodule is > 1 cm. It should also be noted that acne lesions evolve over time and from the proposed guidance it is not clear how initially inflamed comedones are evaluated in clinical trials. These may not be captured by the definition of papules and pustules alone.

As stated in line 321 to 332 of the draft guidance, the problems and limitations associated with counting are well documented. In particular, we agree that lesion counting plays is not used in clinical practice for the evaluation of acne and subsequently therapeutic decision making. Hence, we are convinced that lesions counts should be considered as secondary endpoints only and not as co-primary endpoints as proposed in the draft guideline. For instructive purposes to the prescribing physician, inflammatory and non-inflammatory lesions counts will be summarized in the clinical section of the labeling. Consequently, the secondary statistical analyses will be performed each at the 0.5 level without adjustment for multiplicity. This would considerably simplify the clinical and statistical evaluation of study results while providing valuable, relevant information to the medical professional.

Lines 160 to 164 of the draft guidance state that *"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."*

It can be reasonably assumed that the non-inferiority margin chosen for the non-targeted lesion should be smaller than the expected difference to show superiority on the targeted lesion. This implies that the sample size would be driven by the non-inferiority comparison and not on the superiority, which remains the main objective of the study.

The agency proposes several co-primary endpoints. The choice of several primary clinical endpoints may render interpretation of the results difficult. The agency should provide further guidance on hierarchy of these proposed co-primary clinical endpoints to support under which circumstances the study would be considered positive ("win for approval").

Photographs :

Reference is made to the following paragraphs:

Section IV. A. (line 355-357) *"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."*

Section V. B. (line 534-536) *"Electronic photographic records should be submitted to the Agency such as that they can be readily evaluated (e.g. sufficient resolution to allow for clinical re-evaluation)..."*

In both chapters it remains unclear, how the Agency will use and assess the provided photographs. At the best of our knowledge, it remains unknown, whether clinical evaluation directly on the patient or photographic evaluation is correlated and to what extent (two dimension for photos versus three dimensions in the clinical examination). In addition, this correlation is expected to vary depending on the parameters chosen (success rate, global severity or lesion count). It is in our experience very difficult to judge on non-inflammatory lesions and depending on the angle and lighting conditions inflammatory lesion may not be evaluated properly. The clinical assessment should be based on the clinical examination by a competent investigator. It remains very difficult in our opinion, to use photographs, due to the mentioned limitations, for clinical evaluation or re-evaluation.

In conclusion, we appreciate the opportunity to comment on this guidance document. We believe that the comments Galderma has provided will further enhance the clarity and value of the guidance document.

Should you have any question regarding these comments please don't hesitate to contact the undersigned by phone at (817) 961-5355.

Respectfully,



William H. Carson
Vice-President, Medical and Regulatory Affairs
Galderma USA