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5630 Fishers Lane, Rm 1061
Rockville, MD 20852
<http://www.fda.gov/dockets/ecomments>

**Comments on Docket No. 2005D-0340
Draft Guidance for Industry on Acne Vulgaris: Developing Drugs for Treatment;
Availability**

December 13, 2005

The Global Alliance to Improve Outcomes in Acne would like to present comments on Docket No. 2005D-0340. The Global Alliance is an international group of dermatologists formed in 2001 with the goal of harmonizing the treatment of acne across the world. The group published recommendations for acne management as a supplement to the July 2003 issue of the *Journal of the American Academy of Dermatology* (volume 49). As clinical investigators and experts involved in many acne studies, the group appreciates the opportunity to comment on the draft guidance. It is our belief that the document contains substantive errors regarding acne and the evaluation of acne therapies. It is our further belief that these guidelines, if adopted in their present form, will severely hamper the development and approval of new therapies. The Global Alliance *strongly recommends* that these guidelines not be adopted.

CLINICAL BACKGROUND
Lesion Types

- 1) In the draft guidance page 2, lines 65-67, it is stated that “These lesions, especially closed comedones, may be precursors to the larger inflammatory lesions and therefore are of clinical importance.”

This statement shows a poor understanding of the pathophysiology and clinical expressions of acne vulgaris and should be deleted. (Gollnick et al. *J Am Acad Dermatol* 2003; 49). Closed comedones *rarely* become inflammatory lesions. Rather, a microscopic, preclinical lesion—the microcomedone—is the precursor to both comedones and inflammatory lesions. If a statement about the precursor lesion in acne is included, it should be added at the end of page 2, line 58, and should read “both types of lesions arise from the microcomedone, which is not visible clinically.”

- 2) In the draft guidance page 2, lines 71 and 72 define papules and pustules.

We recommend assessing based on the size of papules and pustules to small (<5 mm) and large (>5 mm). This would be particularly useful for clinical trials that are designed to evaluate the response to systemic antibiotic treatment.

In addition, only some papules and pustules have halos or erythema.

- 3) In the draft guidance page 2, line 74, nodules are “defined as being greater than 5 mm in diameter.”

This definition is incorrect, and should be changed to “1 cm or larger.” The classic textbook definition of a nodule refers to lesions 1 cm or larger (Shalita AR. *Clin Dermatol.* 2004;22:385-386; Fitzpatrick TB, Johnson R, Wolff K, Suurmond R, eds. *Color Atlas & Synopsis of Clinical Dermatology.* 4th ed. New York: McGraw-Hill Professional; 2000); this definition is used not only for acne, but for other diseases as well and should be consistent. Large papules greater than 5 mm exist in patients who do not have the most severe inflammatory form of acne—nodulocystic acne. Nodulocystic acne is not defined as greater than 2 nodules. Rather widespread, numerous nodular lesions in association with large papules and/or pustules are seen in this type of acne.

DRUG DEVELOPMENT PLAN

Clinical Considerations

- 1) In the draft guidance page 3, lines 109-110, a posttreatment follow-up period is recommended.

As it is well established that acne is a chronic and relapsing disease, a posttreatment follow-up seems less justified, unless data from phase I or II clinical studies suggest a drug-candidate has a prolonged effect.

- 2) In the draft guidance page 3, lines 115 to 116, inclusion of “suitable comparator arms, which usually include a vehicle or placebo control” is recommended.

The comparator should be vehicle in acne studies involving topical drugs, unless the sponsor intends to submit a 505 (b)2 application.

- 3) The draft guidance page 4, line 151, suggests that “labeling should reflect the specific type of lesion studied with reference to lack of proven efficacy for the lesion type not studied.”

We suggest striking the section “3. Targeted Acne Therapy” and specific indications; the indication for anti-acne therapies should be simply acne

vulgaris. We believe it will be difficult to specify the contribution of each active ingredient in particular with agents that include 2 or more active agents. In addition, the Investigator’s Global Assessment (IGA), as currently defined, does not quantify noninflammatory lesions (this will be discussed in more detail below).

- 4) The draft guidance, page 5, lines 179-192, discusses the need to reestablish the contributions of individual ingredients to a fixed combination drug product for acne vulgaris when a “new formulation” is studied.

The current system of showing non-inferiority of a new formulation to the original combination is a well-established method that should be maintained.

STUDY DESIGN

- 1) Lines 270 to 272, page 7, indicate that sample size calculations should be made “for each of the co-primary endpoints: changes from baseline in inflammatory and noninflammatory lesion counts and success according to the IGA.”

Percent change in lesion counts should be the only primary endpoint.

Absolute change in lesion counts and IGA should be used as secondary endpoints. Change all mention of “co-primary endpoints” to “primary endpoints” in this paragraph (lines 273 and 274).

Primary Endpoints

- 1) In the draft guidance page 8, lines 321 through 340, the utility of co-primary endpoints (acne lesion counts and IGA) is discussed.

Percent change in lesion counts should be the only primary endpoint for judging efficacy.

Absolute change in lesion counts and IGA should be used as secondary endpoints. We agree with the FDA that there is no standardized and reproducible grading system for the severity of acne (line 80) and that such a system is more subjective than lesion counts (lines 144 and 145) and has a high degree of variability (line 303). For these reasons, it was the recommendation of the Dermatology Advisory Committee (November 2002) and the invited speakers that an IGA *not* be a primary end point in assessing efficacy of anti-acne drugs. We note that the Generic Division of the FDA has taken that advice and now uses the IGA as a secondary end point. We urge the Dermatology Division to do likewise. The guidance document states that an IGA is necessary in order to capture an appreciation of the size, intensity, and location of lesions (lines 322), yet the proposed IGA would make no comment on these aspects of inflammation. Furthermore, the FDA comments that describing lesion counts does not give an

overall view of improvement for patients with a range of baseline counts. This is true for the proposed change of using actual counts rather than percent change. The latter gives a clear view of degree of improvement, has been the method of analysis for more than 25 years, and is understood by dermatologists. The guidance document provides no comment on why a change from percent change to actual lesion count is proposed.

- 2) Page 9, lines 342-364, discussion of IGA.

IGA does not include any assessment of noninflammatory lesions and cannot be used as a primary endpoint for any study of noninflammatory lesions.

The proposed scale encompasses only non-acne and mild disease and is different from the grading scale currently recommended by the FDA. Our objections to the new scale are as follows: Grades 0 and 1 are the same clinically and, as such, fail to meet the FDA recommendations on line 349 that grades be defined “unambiguously” to represent each severity grade. Grades 0 and 1 should be combined as “Clear.” The given definition of Grade 2 is, in our opinion, “Almost clear.” The grade 3 definition actually describes mild acne. Patients with moderately severe inflammatory acne typically will have more than 20 to 35 inflammatory lesions, not “some.” The grade 4 definition, severe, describes moderate inflammatory disease.

The proposed scale also is totally inappropriate for evaluating a drug with potential benefit only in the noninflammatory phase of acne.

- 3) On page 9 of the draft guidance, lines 355-357, photographic documentation of each subject’s improvement for Agency “auditing purposes” is discussed.

Currently, there is no standardized photographic methodology for visualizing comedones, particularly closed comedones, which are difficult to see (lines 64 and 65). At the November 2002 Dermatological Advisory Committee, there was discussion concerning development of a photographic methodology to complement lesion counting. We urge the Agency not to ask for photographic documentation until a methodology for visualizing noninflammatory comedones is developed.

- 4) Page 9, lines 366 and 367, definition of success.

The statistical reduction in lesion counts should be included as a success measure.

- 5) Page 10, lines 381 through 388, discussion of IGA success criterion.

The IGA should be used as a secondary endpoint and is not appropriate for evaluation of noninflammatory lesions. As indicated above, the group does not recommend “targeted acne therapy” studies or indications.

- 6) In the draft guidance page 10, line 397, the guidance suggests that “all lesions be counted, including those present on the nose.”

Lesion counts on the nose should not be included in clinical trials.

Historically, the nose has not been included in clinical trials because it is very difficult to count lesions on this body area in clinical practice. In addition, comedones are common on the nose in younger individuals, but older individuals (15 years and older) more typically have open pores that may mimic comedones to inexperienced clinicians. Finally, the nose is rarely involved with inflammatory acne and thus would inherently not be involved in any studies targeting inflammatory acne.

- 7) Page 10, lines 399 to 402, discussing lesion counts for indications limited to one type of lesion.

For the reasons detailed above, the group does not recommend “targeted acne therapy” studies or indications. In addition, we recommend showing total lesion counts (the combined counts of inflammatory and noninflammatory lesions).

DATA ANALYSIS

- 1) Pages 10 and 11, lines 420 through 424, discussing primary efficacy analyses.

The dichotomized IGA should be a secondary efficacy analysis.

In addition, as described above, the IGA scale needs to be revised.

- 2) Page 11, lines 434 to 440, discussing acne indication specific to a certain lesion type.

For the reasons detailed above, the group does not recommend “targeted acne therapy” studies or indications.

In closing, it is our judgment that the substantive errors in the proposed guidance document will result in serious impediment to the development of new acne therapies, particularly for moderately severe and severe inflammatory acne. We hope that you will

take these comments into consideration when developing any further guidance from FDA on conduct of studies to evaluate anti-acne therapies.

Cordially,

The Steering Committee of the Global Alliance to Improve Outcomes in Acne
On behalf of the group

Harald Gollnick, MD – Chair

Otto-von-Guericke-Universität
Magdeburg Universitätsklinik
Für Dermatologie und Venerologie
Leipziger Strasse 44
Magdeburg 39120
Germany
49 (391) 671-5249 - phone
49 (391) 671-5249 - fax
Harald.gollnick@medizin.uni-magdeburg.de

Diane Thiboutot, MD – Co-Chair

Department of Dermatology
Pennsylvania State University
College of Medicine
UPC III/Room 4300
500 University Drive
Hershey, PA 17033
USA
(717) 531-7437 - phone
(717) 531-4821 - fax
dthiboutot@psu.edu

Vincenzo Bettoli, MD

Clinica Dermatologica
Azienda Ospedaliera
Arcispedale S. Anna
University of Ferrara
Corso Giovecca 189
Ferrara 44100
Italy
39 (05) 32 20 67 91 - phone
39 (05) 32 20 58 25 - fax
bettoli.minzoni@libero.it

Diane Berson, MD

Assistant Professor of Dermatology
Department of Dermatology
Weill Medical College of Cornell University
425 East 61st Street
10th Floor
New York, NY 10021
Phone: (212) 821-0761
Fax: (212) 821-0765
dsberson@aol.com

Brigitte Dréno, MD, PhD

Hotel Dieu
Place Alexis Ricordeau
Nantes, F-44093
France
33 (2) 40-08-3118 - phone
33 (2) 40-08-3118 - fax
bdreno@wanadoo.fr

Alison Layton, MB, ChB, FRCP

Department of Dermatology
Harrogate District Hospital
Lancaster Park Road
Harrogate, HG2-7SX
United Kingdom
01423 553094 - phone
01423 553094 - fax
Alison.layton@hhc-tr.northy.nhs.uk

James J. Leyden, MD

Department of Dermatology
University of Pennsylvania
School of Medicine
26 Spruce Street
Philadelphia, PA 19104
USA
(215) 662-6151 - phone
(215) 649-9384 - fax
jjleyden@mindspring.com

Alan R. Shalita, MD

Department of Dermatology
State University of New York
Downstate Medical Center
450 Clarkson Avenue, Box 46
Brooklyn, NY 11203
USA
(718) 270-1229 - phone
(718) 270-2794 - fax
ashalita@downstate.edu

Alejandro Cordero, MD

Avenida del Libertador 736
Capital Federal
Buenos Aires 1001
Argentina
54 (11) 48 15 11 98 - phone
54 (11) 48 15 17 60 - fax
acordero@lazar.com

Andrew Finlay, MSc

Department of Dermatology
Wales College of Medicine
Cardiff University
Heath Park
Cardiff, CF14-4XN
Wales
United Kingdom
44 29 2074 2615 - phone
44 29 2074 4312 - fax
finlayAY@cardiff.ac.uk

**Chee Leok Goh, MD, MRCP,
FRCP, FAMS**

National Skin Centre, Singapore
1 Mandalay Road
Singapore 308205
Singapore
(65) 6253 4455 - phone
(65) 6253 3225 - fax
nsc@pacific.net.sg

María Isabel Herane, MD

Department of Dermatology
West Unit
University of Chile
Hospital San Juan de Dios
Guardia Vieja 255 of. 901
Providencia, Santiago
Chile
56 2 3310449 - phone
56 2 3310450 - fax
giderm@yahoo.es

Sewon Kang, MD, MPH

University of Michigan Medical Center
1910 Taubman Health Care Center
Ann Arbor, MI 48109
USA
734-936-4192 - phone
734-936-6395 - fax
swkang@umich.edu

Raj Kubba, MD

108, Aurobindo Place
Hauz Khas
India
26 964 924 - phone
26 517 988 - fax
kubba@touchtelindia.net

Montserrat Perez, MD

Hospital de San Pablo
c/o San Antonio M Claret, n 167
Barcelona 8025
Spain
34 93 291 90130 - phone
10630mpl@comb.es

Jaime Piquero Martin, MD

Center Clinico
P-1, Cons. 12
Mexico Avenue
The Candlemas
Venezuela
571 1802 - phone
Piquero1@telcel.net.ve

Marcia Ramos-e-Silva, MD, PhD

Centro Medico Sorocaba
Rua Sorocaba 464/205
205 Batafogo
Rio de Janeiro 22271-220
Brazil
55 (21) 535-1459
ramos.e.silva@dermato.med.br

Jo-Ann See, MBBS, FACD

Level 3
193 Macquarie Street
Sydney 2000
Australia
02 9221 1477 - phone

Neil Shear, MD, FRCPC

Sunnybrook and Womens College
Health Sciences Centre
2075 Bayview Avenue, Room M1-737
Toronto, Ontario M4N 3M5
Canada
(416) 480-4078 - phone
(416) 480-6025 - fax
neil.shear@swchsc.on.ca

Vicente Torres Lozada, MD

Olmo #62
Jardines de Santa Monica
Tlalnepantla 54050
Edo de Mexico
Mexico
(525) 362-8817 - phone
(525) 362-8818 - fax
vitorres@prodigy.net.mex

John Wolf, Jr, MD

Department of Dermatology
Baylor College of Medicine
One Baylor Plaza
Houston, TX 77030
USA
(713) 798-7620 - phone
(713) 798-6923 - fax
jwolf@bcm.tmc.edu