ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

SEPTEMBER 23, 1999
CDER Advisory Committee Conference Room
5630 Fishers Lane
Rockville, MD

MEMBERS
Goldberg, Arthur H., Ph.D.
Robert A. Branch, M.D., F.R.C.P.
Stephen R. Byrn, Ph.D.
Kathleen R. Lamborn, Ph.D.
Mary J. Berg, Pharm.D.
John Doull, M.D., Ph.D.
Judy P. Boehlert, Ph.D.
Vincent H.L. Lee, Ph.D.
Gloria L. Anderson, Ph.D.

FDA Reresenatives
Mei-Ling Chen, Ph.D.
Larry Lesko, Ph.D.
Roger Williams, M.D.
Vinod Shah, Ph.D.

INTERNATIONAL OBSERVER
Norman J. Pound, Ph.D.

Guests
Les Benet
Bill Barr
Sandy Bolton
Laszlo Endrenyi
Thomas Gretter
Kam Midha
Nevine Zariffa
Avi Yacobi

These summary minutes for the September 23, 1999, meeting of the Advisory Committee for Pharmaceutical Science were approved on 11/20/99.

I certify that I attended the September 23, 1999, meeting of the Advisory Committee for Pharmaceutical Science and that these minutes accurately reflect what occurred.

Kimberly L. Topper
Executive Secretary

Stephen Byrn, Ph.D.
Chairperson

Minutes of the Advisory Committee for Pharmaceutical Science
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The meeting was called to order at 8:30 am by Stephen Byrn , Ph.D., Acting Chairman, the Conflict of Interest Statement was read and the committee introduced themselves. There were 193 people in attendance.

Roger L. Williams, M.D. introduced the subject and provided a brief history on the issue of Average and Individual Bioequivalence Criteria to Compare Bioequivalence Measures. Tom Gretter, M.D. presented the clinical perspective, William Barr, Ph.D. presented the pharmaceutical scientist perspective, and Leslie Z. Benet, Ph.D. provided the Expert Panel Report.

The Population and Individual Bioequivalence Working Group presented the work completed since the last meeting. Walter Hauck, Ph.D. explained the motivation behind the IBE process, Mei-Ling Chen, Ph.D. presented the Criteria and Update of Guidance, Larry Lesko, Ph.D., explained the Mechanistic Understanding and Roger Williams, M.D. covered Replicate and Non-Replicate Datasets. Vinod Shah, Ph.D. then gave an overview of the General BA/BE Guidance of Orally Administered Drugs.

The Open Public Hearing was held with presentations by the following registered speakers: Steven Schachter, M.D., Chairman, Professional Advisory Board, Epilepsy Foundation, 4351 Garden City Drive, Landover, MD 20785-2267; A. Lawrence Gould, Ph.D., Senior Director, Scientific Staff, Merck Research Laboratories, BL3-2, West Point, PA 19486; Michael Spino, Pharm.D., Chairman, Scientific Advisory Committee, IGPA, Sr. V.P. Scientific Affairs, Apotex Inc., 150 Signet Dr., Weston, Ontario, M9L1T9 Canada; Laszlo Endrenyi, University of Toronto, Department of Pharmacology, Medical Sciences Building, Room 4207, 8 Taddle Creek Road, Toronto, Ontario, M5S 1A8; Russell J. Rackley, Ph.D., Director, Biopharmaceutics, Purepac Pharmaceutical Co., 200 Elmore Ave Elizabeth, NJ 07207; Leon Shargel, Ph.D., Vice President and Technical Director, National Association of Pharmaceutical Manufacturers, 320 Old Country Road, Garden City, NJ 11530-1752; Nevine Zariffa, Pharmaceutical Research and Manufacturers of America, Smith Kline Beecham, 1 Franklin Plaza, SG0415, P.O.Box 7929, Philadelphia, PA 19101. There were two requests to speak from the floor: Les Benet, Ph.D., University of California at San Francisco, Department of Biopharmaceutical Science, 533 Parnassus Ave, Z-68, San Francisco, CA

94143-0446 and Bob Buice, Bioequivalence Focus Group for the American Association of Pharmaceutical Scientists.
Roger Williams introduced the discussion topics.

Discussion Topic 1
Is it reasonable and appropriate for FDA to recommend replicate study designs for specified drug products for an interim two year period?

The question was rewritten by the Committee to read : Is it reasonable and appropriate for FDA to recommend replicate study designs for some drug products for an interim two-year period under conditions yet to be discussed? The new question was discussed, and the committee believed that it was reasonable. The committee asked for reassurance that the recommendation would be withdrawn if it was determined to be inappropriate after discussion of the conditions described in the topics below. This was not the case (see below).

Discussion Topic 2
The Advisory Committee is asked to comment on inclusion and exclusion criteria for these specific drug products in the interim study period if the answer to Topic 1 is affirmative.

The Committee favors including MR drug products and wording to strongly encourage inclusion of BCS II, III, IV drug substance/drug products to increase the number of potential compounds for which replicate study designs are recommended. They strongly encourage industry to do this during the interim study period. The committee also endorsed the Expert Panel recommendation for replicate study designs for modified release dosage forms.

Discussion Topic 3
Are there scientific and technical reasons why the proposed individual bioequivalence criterion should not be used to allow market access for specified drug products in the interim study period?

The Committee had concerns with the new criterion and recommended use of average bioequivalence criterion for market access, unless there was a compelling reason for use of individual bioequivalence criterion.

Discussion Topic 4
The proposed criterion allows scaling of the bioequivalence limit (goalpost) by the within-subject variance of the reference product. To avoid large mean T and R differences, constraints on the allowable mean difference may be placed. The Advisory Committee is asked to consider this approach for the interim study

period.

The Committee believed that this issue could be deferred pending a decision to use the proposed criterion.

Discussion Topic 5

The FDA proposal, as well as the Expert Panel, recommends BE studies in certain types of subjects. The Advisory Committee is asked to comment on these recommendations.

The Committee recommends that key variables related to subject-by-formulation interaction be considered in selecting study populations for bioequivalence studies. Studies should recommend that subgroups be included, and the Committee encourages diversity. Studies should address age, minority, and male/female subjects. Sponsors should be encouraged to provide failed studies as well as successful ones so all data may be used to achieve further resolution. The Committee felt that the Expert Panel recommendation was a good one for the study population for bioequivalence studies of modified release products.

Discussion Topic 6

The Advisory Committee is asked to comment on plans for further research programs and projects associated with use of average and individual criteria to allow comparison of bioavailability measures.

The Committee endorsed plans proposed by FDA for better mechanistic understanding, clinical pharmacology studies (›proof of concept‹ and ›goalpost‹ studies) and other approaches as well. The Committee recommended that outliers should be studied as a means of identifying important causes for a subject by formulation interaction. The Committee endorsed creation of a research document to guide the interim study period and to request a review of this document by the Expert Panel.

The meeting was adjourned at 4:42.

A verbatim transcript, speakers overheads, agenda and the FR Notice are available on the FDA home page at:

www.fda.gov/ohrms/dockets/ac/cder99t.htm#Pharmaceutical Science Advisory Committee