Food and Drug Administration
Center for Drug Evaluation and Research

SUMMARY MINUTES
ARTHRITIS ADVISORY COMMITTEE

July 21, 1999
Holiday Inn Gaithersburg
2 Montgomery Village Avenue, Gaithersburg, MD

Members Present
Steven B. Abramson, M.D., Chair
Daniel J. Lovell, M.D., M.P.H.
David E. Yocum, M.D.
Leona Malone, MSW
Frank Pucino, Jr., Pharm.D.
Janet D. Elashoff, Ph.D.
E. Nigel Harris, M.D.
Yvonne Sherrer, M.D.
Kenneth Brandt, M.D.
Larry Moreland, M.D.

FDA Participants
Robert DeLap, M.D.
Karen Midthun, M.D.
John Hyde, M.D.
Kent R. Johnson, M.D.
James Witter, M.D., Ph.D.

Consultants
Jennifer Anderson, Ph.D.

Guest Experts
Marc Hochberg, M.D.
Paul Dieppe, M.D.
Maxim Dougados, M.D.

Members Absent
Ildy M. Katona, M.D.

Executive Secretary
Kathleen R. Reedy

These summary minutes for the July 21, 1999 meeting of the Arthritis Advisory Committee were approved on 8/25/99.

I certify that I attended the July 21, 1999 meeting of the Arthritis Advisory Committee and that these minutes accurately reflect what transpired.

Kathleen R. Reedy,
Executive Secretary

Steven B. Abramson, M.D.
Chairperson

The Arthritis Advisory Committee met at the Holiday Inn Gaithersburg, 2 Montgomery Village Avenue, Gaithersburg, MD on July 21, 1999 at 8am to discuss the evidence needed to establish that a drug product has a beneficial effect on joint structure in patients with osteoarthritis. The meeting was attended by approximately 150 people. The Advisory Committee members had been provided a background document from the Agency, a draft of a proposed Guidance for Industry: Clinical Development Programs for Drugs, Devices and Biological Products intended for the treatment of Osteoarthritis, and a European Guidance Document; approximately 13 days before the meeting.

The meeting was called to Order at 8:05 by Steven Abramson, M.D., Chair of the Arthritis Advisory Committee, and after all participants at the table were introduced, the Meeting Statement was read by Kathleen Reedy, Executive Secretary of the Arthritis Advisory Committee. Welcome was extended by Karen Midthun, M.D., Acting Division Director of the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drugs.

Introduction of the topic and a presentation discussing Trial Endpoints and Surrogates was presented by James Witter, M.D., Ph.D., Medical Officer, Division of Anti-Inflammatory, Analgesic and Ophthalmic Drugs.

Committee Member Kenneth D. Brandt, M.D., of Indiana University School of Medicine presented and discussed A Design Model of a study being conducted in Indianapolis.

Additions to the agenda and suggestions for discussion from the audience were solicited and there were two responses. One for a discussion of acceptable safety profile parameters regarding improvement in function, paiin and structure. Another for a discussion of arthroscopy.

Philipp Lang, M.D., Department of Radiology, Stanford University School of Medicine presented a study being conducted there to assess joint structure.

Transition and Preamble to the discussion was presented by Kent R. Johnson, M.D., Medical Officer, Division of Anti-Inflammatory, Analgesic and Ophthalmic Drugs. He gave a historical background and possible future directions of assessment of joint structure for consideration for the Guidance Document.

The discussion was conducted in the following format.

Design

Endpoints

1. Joint-space-narrowing (JSN): If a minimum "effective size" is required, (i.e. a minimally clinically important difference), how would this be defined?
2. Symptoms (pain and function): If "no worsening" is required, how would this be defined?

3. Must phase 4 symptom demonstration be done only via continuation of phase 3 trials in which JSN was demonstrated?
4. Is a phase 4 design which specifies withdrawal of placebo patients who show severe JSN (corruption of the negative control) fatally flawed? How can this be avoided?

Should designs address Other Measures up front with face validity

1. Rescue medication use
2. Patient global (including, but not limited to non-signal joints)
3. Other structure assessments (osteophytes, joint instability)
4. Use of assistive devices

Duration

1. One year minimum, in principle, for structure?
2. Duration for (subsequent) symptom demonstration?

The Open Public Hearing had two speakers.
Charles G. Peterfy, M.D., Ph.D., Chief Scientific Officer, Synarc, Inc., San Francisco, and Philipp Lang, M.D., Department of Radiology, Stanford University School of Medicine.
Both presented ongoing studies in the assessment of joint structure.

The Committee discussion continued.
Analysis

Multiplicity: To preserve trial-wide alpha (risk of a positive result of no more than 5% when many analyses are done) should the alpha be distributed in the scenarios below?

All of them?

1. JSN analysis and symptom analysis
2. LOCF x-ray analysis and end-of-trial x-ray analysis
   (Corollary: should dropout (exit) x-rays always be mandated?)
3. Pain analysis and function analysis
   Should there be limits on how to weight these? (Some agents under development are considered likely to affect one disproportionately over the other).
4. Rescue medication use analysis and patient global analysis, and pain and function.
5. Phase 3 analysis and phase 4 analysis.

Missing Information: (dropouts)

1. Best way to analyze, assuming dropouts are "informative" ? (They always are)
   a) Compare dropouts across arms. This is the traditional approach, but it is usually severely limited by the small size of groups.
   b) Determine how deviant the dropouts could have been (how different from the mean change seen between completer cohorts) and still have the overall inference stand ($p<0.05$). This approach was recently used for leflunomide.
   c) Other techniques?
2. Should a dropout exit x-ray always be mandated in the design?

Assembling the Evidence

Distribution of evidence from various OA sites: knee, hip, hands, spine.

1. One trial knee, one trial hip? Separate trials?
2. Predefined knee and hip subset analyses in one large trial of knee and hip patients?
3. Systematic evidence for hand OA, spine OA?

The meeting was adjourned at approximately 3:30 pm.

A verbatim transcript of the meeting is available.