DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

-4 P1:35

MINUTES OF A MEETING
November 19, 2003

Meeting Type: Public Feedback Meeting

Docket No.: 77N-0094 / CP16

Subject: Bayer HealthCare
Citizen's Petition
Proposed Amendment to the Final Rule for Aspirin Professional Labeling:
Primary Prevention of Myocardial Infarction

Project Manager: Walter J. Ellenberg, Ph.D.
Meg Pease-Fye

FDA Participants:
Center for Drug Evaluation and Research (CDER)
Robert Temple, M.D., Director, Office of Drug Evaluation I
Douglas C. Throckmorton, M.D., Director, Division of Cardio-Renal Drug Products
Norman Stockbridge, M.D., Ph.D., Deputy Director, Division of Cardio-Renal Drug Products
Charles Le, Ph.D., Statistician, Division of Biometrics I, Office of Biostatistics, Office of Pharmacoepidemiology and Statistical Science
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Charles Ganley, M.D., Director, Division of Over-the-Counter Drug Products
Debbie Lumpkins, Team Leader, Division of Over-the-Counter Drug Products
Michelle Jackson, Ph.D., Interdisciplinary Scientist, Division of Over-the-Counter Drug Products
Walter Ellenberg, Ph.D., Regulatory Health Project Manager, Division of Over-the-Counter Drug Products
Keith Olin, R.Ph, Regulatory Health Project Manager, Division of Over-the-Counter Drug Products

Bayer HealthCare Participants:
William Carson, Former Head, Research and Development
Judy Doyle, Associate Director Regulatory Affairs
Erica Peitler, Acting Head, Research and Development
Stephen Wecsman, Consultant, Innovative Science Solutions

Other Attendees:
Chris Walker, Reporter, The Tan Sheet
Jeff Baggish, M.D., Medical Affairs, McNeil Consumer Health Care

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Background

On November 19, 2003, the FDA held a public feedback meeting to discuss the issues raised during the review of Bayer's Citizen Petition submitted February 12, 2003. Specifically, the Petition requests the FDA to amend the final rule for professional labeling for aspirin to include the use of 75 mg and 325 mg aspirin for primary prevention of myocardial infarction in those individuals at significant risk. The following studies were provided for review in the Citizen's Petition:

- Physician's Health Study, 1988;
- British Doctor's Trial, 1998;
- Hypertensive Optimal Treatment Study (HOT), 1998;
- The Thrombosis Prevention Trial, 1989,
- The Primary Prevention Project, 2001.

The Citizen's Petition provides a summary of the major trials in primary prevention under consideration. The material submitted in this Citizen's Petition will be the topic of discussion during the upcoming Cardio-Renal Advisory Committee scheduled for December 8, 2003.

Discussion

FDA convened this meeting to provide Bayer and other interested parties with information on the format of the forthcoming Cardio-Renal Advisory Committee meeting as well as the issues for discussion. The history and background of monographs and Over-the-Counter professional labeling will be presented by Michelle Jackson, Ph.D. Charles Le, Ph.D. will present the statistical background and analysis of the key study (HOT).

During the meeting, the FDA distributed a draft summary of the review issues (see attachment). This information was submitted to Docket 77N-0094 on November 24, 2003. This preliminary information summarized each trial under consideration and defined the primary endpoints of each study. The FDA expressed its concern in evaluating the results of the HOT study targeted populations, specifically, the demographic subgroups referring to age, gender and race differences of people taking aspirin. These differences involve efficacy, risk assessment, dosing regimen, and defining a target population that would benefit from aspirin therapy.

One of the FDA's major concerns is focused on interpreting of the rates of "silent MIs" (asymptomatic MIs). In the HOT study, the original protocol included silent MIs in the primary endpoint. This was changed and the publication focused on the results excluding these events. When they are included, the effect of aspirin becomes less impressive. The FDA questioned the rationale for leaving the silent MI data out of the study. Although the result of the HOT study indicated a favorable trend for aspirin for the combined endpoint including silent MIs, the results were neither statistically significant nor did it show an effect on stroke.

The FDA will also be interested in having the Advisory Committee comment on how to look at results from these heterogenous trials, as the quality and type of data are different from what would typically be submitted to the Agency.

Conclusions

At the conclusion of the meeting, the floor was opened for other discussions and specific questions. None were raised. The meeting was then closed.

Attachment: draft written overview

Chair: _____

Douglas C. Throckmorton, M.D.

Drafted 11.10.03 Finaled 12.01.03

Here are some issues relating to the use of aspirin for the primary prevention of myocardial infarction. These data are considered in response to a Citizen Petition, filed 11 February 2003 by Bayer Healthcare, requesting an amendment to the professional labeling for aspirin. The Petition cites the five studies summarized in the table below.

The British Doctors' Trial (BDT; British Medical Journal, 1988) was conducted between 1978 and 1984 among 5139 healthy male British doctors. age 50 to 78. The comparison was between aspirin 500 mg daily and no treatment. The primary end point was fatal or non-fatal MI, stroke, or TIA; p=NS.

The Physician's Health Study (PHS; New England Journal of Medicine, 1989) was conducted between 1982 and 1987 among 22071 healthy male US physicians, age 40 to 84. The comparison was between aspirin 325 mg every other day and placebo. The primary end point was cardiovascular mortality; p=0.87.

The Thrombosis Prevention Trial (TPT; Lancet, 1998) was conducted between 1984 and 1989 among 5085 British males at high risk, age 45 to 69. The comparison was between controlled-release aspirin 75 mg daily and placebo. The primary end point was "coronary death and fatal and non-fatal MI"; p=0.04 (p=0.07 including silent MI).

The Hypertension Optimal Treatment study (HOT; Lancet, 1998) was conducted in 26 countries between 1992 and 1997 among 19196 men and women with mild-to-moderate hypertension and no stroke or MI within 12 months. The comparison was between aspirin 75 mg daily and placebo. The primary end point was cardiovascular death and non-fatal MI or stroke; p=0.17 (p=0.03 excluding silent MI).

The Primary Prevention Project (PPP; Lancet 2001) was conducted in Italy between 1994 and 1998) among 4495 men and women over age 50 with some additional cardiovascular risk. The comparison was between enteric aspirin 100 mg daily and no treatment. The primary end point was cardiovascular death and non-fatal MI or stroke; p=NS.

Of the 5 studies, a study protocol and source data were available for only HOT, and the FDA review of HOT suggests a substantially weaker result than is published. The primary end point in HOT included silent MI, while in TPT silent MI was assessed (but it unclear whether it is included in the reported analyses) and in the other 3 studies silent MI was, apparently, not collected. Assessed end points in the published studies are shown in the

table below:

	BDT	PHS	TPT	PPP
All-cause mortality	√	√	√	√
Cardiovascular mortality	√	√	√	√
CV death + MI + stroke	√			√
Fatal MI + fatal stroke	√			
Fatal or non-fatal MI	√	√	√	√
Fatal or non-fatal stroke	√	√	√	√
Non-fatal MI	√	√	√	√
Non-fatal stroke	√	√	√	√
Silent MI			√	

1. Are there other studies that should be considered?

2. In considering how to interpret these trials with respect to primary prevention of MI, whether by formal or informal meta-analysis, ...
   2.1. ...what is the significance of each of the following?
      2.1.1. The study protocol is available for only one study.
      2.1.2. The source data are available for only one study.
      2.1.3. No study had primary prevention of MI as a primary end point.
      2.1.4. Only one study appears to have denied its null hypothesis.
      2.1.5. The studies varied with respect to what MIs were captured.
      2.1.6. The dose, regimen, and biopharmaceutical properties of aspirin varied.
      2.1.7. The baseline risk factors varied.
   2.2. ...do you conclude that a meaningful synthesis is possible?

3. Aspirin has a claim for *secondary* prevention of myocardial infarction.
   3.1. How much, if at all, does this lower the evidentiary burden for *primary* prevention of myocardial infarction?
   3.2. Aspirin also has secondary prevention claims related to strokes and overall cardiovascular mortality. Since effects of aspirin on strokes and cardiovascular mortality are not evident in these primary prevention studies, how much, if at all, does this discrepancy *raise* the evidentiary burden for primary prevention of myocardial infarction?

4. What do the available data say was the effect of aspirin on primary prevention of myocardial infarction? If a consistent effect was seen, ...
   4.1. ...name that effect and define what constituted a myocardial infarction.

4.2. ...what was the effect in relevant demographic subgroups (gender, age, and race)?

5. What do the available data say about the safety of aspirin in primary prevention setting? What do you know about ...
   5.1. ...risks in demographic subgroups (gender, age, race)?
   5.2. ...interactions with underlying disease?
   5.3. ...use with various concomitant drugs?

6. Should professional labeling for aspirin recommend its use for primary prevention of MI?
   6.1. If so, ...
      6.1.1. ...what patient population can expect to benefit from aspirin?
      6.1.2. ...what dose, regimen, and form of aspirin should be recommended?
   6.2. If not, describe the study that would provide compelling evidence for this indication.

7. If aspirin were to be approved for primary prevention of myocardial infarction, comment on the petitioner's proposal to identify a target population using an integrated risk assessment score.
   7.1. How confident are you that the proposed scoring system appropriately identifies patients most likely to benefit from aspirin?
   7.2. Can physicians use this?
   7.3. Can patients understand it?

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE:

FROM: Director
Division of OTC Drug Products, HFD-560

SUBJECT: Material for Docket No. 77N-0094

TO: Dockets Management Branch, HFA-305

☑ The attached material should be placed on public display under the above referenced Docket No.

☑ This material should be cross-referenced to Comment No. CP 16

Charles J. Ganley, M.D.

Attachment