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Background Information: An Amendment to the Final Rule for Professional Labeling for Aspirin

A Joint Meeting of the

Cardiovascular and Renal Drugs & Nonprescription Drugs Advisory Committee December 8, 2003

Purpose:

Bayer HealthCare submitted a Citizen's Petition (TAB 1) dated February 11, 2003, requesting FDA's approval for expanded cardiovascular indications and labeling for the use of a daily aspirin regimen (75 mg to 325 mg) in individuals: 1) with a 10 percent or greater risk of coronary heart disease (CHD) over 10 years or 2) for whom there is a positive benefit-risk as assessed by their healthcare providers.

In support of their request, the petition provided results of five clinical trials in primary prevention:

1) Physician's Health Study (PHS) - 1988
2) British Doctor's Trial (BDT) - 1988
3) Thrombosis Prevention Trial (TPT) - 1998
4) Hypertensive Optimal Treatment Study (HOT) - 1998
5) Primary Prevention Project (PPP) - 2001

Background:

Professional Labeling

The petition is seeking to amend the current regulation, CFR 21 343.80 (TAB 2), "Professional Labeling of Aspirin, Buffered Aspirin, and Aspirin in Combination with Antacid Drug Products for OTC Internal Analgesic, Antipyretic, and Antirheumatic Drug Products." TAB 3 contains the enlarged dosage and administration chart for the professional labeling of aspirin that includes the indications, recommended daily dose, and duration of therapy.

Professional labeling contains comprehensive prescribing information (similar to that found on prescription labels) for the use of aspirin for vascular indications, in patients who have undergone certain revascularization procedures, and for rheumatologic diseases.

The regulation constitutes FDA's approved labeling for this use of aspirin and is the labeling that is required to be provided to healthcare professionals by manufacturers if they choose to promote aspirin for this use.

- This information may not appear in the OTC label.

OTC Drug Review

The professional labeling regulation was developed as part of the OTC drug review. The review is a fourstep notice and public comment rulemaking process:

OTC Drug Review	Description of the Process
Advisory Review Panel	Evaluation of data submitted in response to FDA's call for data on an OTC drug Product category, e.g., analgesic/antipyretic drug products.
Advance Notice of Proposed Rulemaking (ANPR)	Publication of the Panel's recommendations along with FDA's proposed regulation based on these recommendations with an opportunity for comment and submission of new data.

Tentative Final Monograph (TFM)	FDA's proposed regulation based on FDA's consideration of the Panel's recommendations and comments and new data received with an opportunity for comment and submission of new data.
Final Rule (FR)	FDA's regulation.

October 6, 1989 - FDA's Cardiovascular and Renal Drugs Advisory Committee (TAB 4)

The Committee met to consider a claim for aspirin for the prevention of primary (first) heart attack based on the findings of the U.S. Physicians' Health Study. The Committee was aware of the findings of the BDT study, but only the findings from the PHS were presented in detail.

Advisory Committee Meetings

- The Committee did not have confidence in efficacy for prevention of fatal MI alone, although combined fatal and not-fatal MI appeared to be reduced. Aspirin had no effect on total cardiovascular mortality. The number of fatal strokes was too small to reach a conclusion. The Committee was divided 4-no, 3-yes whether there was a significant effect for increased hemorrhagic stroke in the aspirin group. The committee was also divided on the weight of the BDT. They voted 4-no, 3-yes that this outcome influenced their evaluation of the PHS.
- The Committee recommended (by a 6 to 2 vote) that, although some claim should be considered for some high-risk group of patients, aspirin should not be used routinely in patients without risk factors or in women, until such patients had been studied. The Committee minority was concerned about the toxicity of aspirin and the number of normal individuals at low risk of having a heart attack who would be treated long-term.
- The Committee recommended (by a 6 to 2 vote) that some type of primary claim for some group of patients could be developed. The committee was concerned that aspirin would be used in healthy people or inappropriate patient populations and would be promoted for such use.
- The Committee unanimously agreed that patients should ask their doctor before beginning prophylactic therapy.

January 23, 1997 - Cardiovascular and Renal Drugs Advisory Committee and Nonprescription Drugs Advisory Committee (TAB 5)

The Committee met to discuss a Citizen's Petition from the Aspirin Strategy Group, seeking broadened indications for professional labeling for aspirin to include anyone at risk for heart attack and stroke.

The Committee unanimously recommended that results from the Swedish Angina Pectoris Antiplatelet Trial supported the benefits for low-dose aspirin in patients with stable angina pectoris.

- The Committee unanimously recommended that low-dose aspirin be extended to patients with arterial revascularization procedures, i.e., CABG or PTCA.
- The Committee recommended (by an 11 to 2 vote) that professional labeling should not include an indication for use in peripheral vascular disease because the evidence did not meet usual standards for approval.

FEDERAL REGISTER Notices

The active ingredient aspirin and its use for professional indications has been extensively evaluated in the review. We have included Federal Register documents related to the development of the rulemaking for internal analgesic, antipyretic, and antirheumatic drug products for OTC human use. This provides a frame of reference for the information available in the public record and the rationale behind past decisions.

Federal Register Notice	Information in Notice	Section
Jul 8, 1977 42 FR 35346 Establishment of a Monograph for OTC Internal Analgesic, Antipyretic, and Antirheumatic Drug Products	FDA published the recommendations of the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products (Internal Analgesic Panel). • Pages 35384-35386 contain the Panel's extensive discussion on the effects of aspirin on platelet aggregation and increased bleeding time.	TAB 6
November 16, 1988 (53 FR 46204) TFM for OTC Internal Analgesic, Antipyretic, and Antirheumatic Drug Products	In the TFM (pages 46258-46260), the Agency proposed professional labeling in § 343.80 for the use of aspirin for rheumatologic diseases, for reducing the risk of recurrent transient ischemic attacks (TIA's) or stroke in men who have had transient ischemia of the brain due to fibrin platelet emboli, and for reducing the risk of death or nonfatal myocardial infarction (MI) in patients with a previous infarction or unstable angina pectoris. • The Agency also proposed professional labeling for the use of carbaspirin calcium, choline salicylate, magnesium salicylate, or sodium salicylate for rheumatologic diseases.	TAB 7
June 13, 1996 61 FR 30002) Amendment to the TFM for OTC Internal Analgesic, Antipyretic, and Antirheumatic Drug Products	Amendment to the TFM to include an indication for the use of aspirin in treating acute MI: an initial dose of 160 to 162.5 mg to be continued daily for at least 30 days.	TAB 8
October 23, 1998 63 FR 56802) FR for Professional Labeling of Aspirin, Buffered Aspirin, and Aspirin in Combination with Antacid Drug Products for OTC Internal Analgesic, Antipyretic, and Antirheumatic Drug Products	In the final rule (pages 56803-56804), the Agency concluded that the available data did not support the professional labeling of aspirin for the prevention of first MI; some of the reasons included the following: • The PHS showed that some of the study patients had a prior MI and aspirin is already known to reduce the risk of recurrent MI in such patients. • According to the PHS study protocol, subjects should not have had an MI before randomization, but the Agency's evaluation showed 8% of subjects who suffered a nonfatal MI during the study also had evidence of an old MI. • The PHS, in particular, did not show a statistically significant effect when all deaths as well as nonfatal MI and stroke were combined. • The BDT, despite its similarity to the PHS, does not support the use of aspirin to prevent an initial MI. • Currently approved indications: • Vascular: ischemic strokes and TIA, suspected acute MI, prevention of recurrent MI, unstable angina pectoris, chronic stable angina pectoris. • Revascularization Procedures in Selected Individuals: CABG, PTCA, carotid endarterectomy. • Rheumatologic Disease: rheumatoid arthritis, juvenile rheumatoid arthritis, spondyloarthropathies, osteoarthritis, arthritis and pleurisy of SLE.	TAB 9

Questions

aspirin

December 8, 2003

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Cardio-Renal Advisory Committee

The Cardio-Renal and OTC Advisory Committees are asked to opine on the use of aspirin for the primary prevention of myocardial infarction. This meeting is 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?

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?