

**Meeting Background**

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## **Petition Overview**

Bayer HealthCare's Petition submitted on February 11, 2003 seeks approval for the use of aspirin in individuals at moderate risk or greater of coronary heart disease (CHD) who have not experienced a previous MI. The following was provided to support the requested indication:

- There is clear evidence from 5 adequate and well-controlled clinical trials, involving over 55,000 apparently healthy subjects, demonstrating the benefits of low dose aspirin (75-325 mg) in reducing the risk of MI (32%).
- The long-term safety of aspirin in the management of cardiovascular disease is well-studied (over 150 studies involving more than 150,000 individuals). The adverse event profile for the proposed indication is reflected in the current labeling of approved aspirin indications.
- Conservative labeling has been proposed to further enhance the benefit-to-risk relationship by restricting the use of aspirin to individuals whose 10-year risk exceeds 10% (moderate risk). This is in spite of evidence from the 5 primary prevention studies showing aspirin's effectiveness in reducing the risk of MI in even low risk patients (as well as moderate and high risk individuals).
- Government bodies such as the United States Preventive Services Task Force (USPSTF), as well as all major professional scientific and medical organizations, including the American College of Cardiology, American Diabetes Association, The American Heart Association, and many others, support the use of aspirin in individuals of at least moderate risk (greater than 10% 10-year risk) of CHD.

In summary, Bayer's position on the key questions is as follows:

- Sufficient evidence exists to support the use of aspirin (75 – 325 mg) in individuals at moderate risk or greater of coronary heart disease (CHD) who have not experienced a previous MI.
- A shift from event-based to risk-based labeling (i.e., 10% risk or greater based on standard, available risk assessment tools (e.g. Framingham)), similar to that used in the labeling of statin drugs, will add needed clarity to healthcare professionals regarding appropriate use of aspirin for primary prevention.
- Since there is no biological difference between men and women in terms of the cardiovascular benefits of aspirin, and adequate numbers of women have been studied, as with secondary prevention, the use of aspirin for primary prevention is appropriate in both male and female, moderate-to-high risk individuals.
- Bayer shares the belief expressed by a majority of the Cardio-Renal Advisory Committee members that the existing body of data supports the use of aspirin in preventing a first non-fatal MI, particularly in men, and that this was statistically significant in the key primary prevention studies.
- It is clear that the Committee recognized the public health importance of the Petition as reflected by their personal use and recommendation of aspirin for the proposed indication, but may require additional data for broader labeling beyond non-fatal MI.

## **Questions for Discussion**

To assist the Agency in providing meaningful feedback, the Bayer position and relevant data to support it are provided below for each of the questions posed to the Agency in our meeting request of January 16, 2004. As a number of questions relate to the same topic, they have been grouped for discussion. As a link to the meeting request document, the question numbers are included; complete questions are included in Tab 2: Questions for the Agency.

## **Risk-Based Labeling (Questions 1, 4, 5)**

### ***Bayer Position with Respect to the Appropriateness of Risk-Based Labeling for Aspirin***

A shift from event-based to risk-based labeling is not only appropriate for primary prevention, but also reflects how the Agency labels other conditions such as the use of aspirin in patients with stable and unstable angina, and the use of statins for cardiovascular risk management. Therefore, the Petition requests the Agency to consider approval of the use of aspirin in individuals deemed to be at appropriate risk of first MI.

### ***Supporting Points***

- The current labeling paradigm for aspirin requires the presence of a previous cardiovascular event before aspirin is indicated. This labeling approach resulted from the fact that the initial studies with aspirin were secondary prevention studies.
- Now, there are a number of studies in apparently healthy subjects which confirm that the risk reduction benefits of aspirin relate more to the level of underlying risk than the presence or absence of a previous event.
- There is no evidence that the underlying disease process (plaque rupture and coronary thrombosis) differs as a result of the presence or absence of a previous event. There is considerable support for the utility of risk-based labeling to guide therapeutic interventions in cardiovascular risk reductions. Current treatment guidelines for a wide array of cardiovascular risk interventions recognize the importance of risk stratification in patient selection.
- Recently published National Cholesterol Education (NCEP) Adult Treatment Panel (ATP III) guidelines define candidates for cholesterol reduction based on a comprehensive risk assessment.
- Current FDA-approved labeling for cardiovascular risk management with statins is based on individual patient risk assessment (see recently approved statin labeling below).

**Table 5. NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories**

Risk Category	LDL Goal	LDL Level at which to initiate TLC	LDL level at which to consider drug therapy
CHD <sup>a</sup> or CHD Risk Equivalent (10-year risk > 20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100-129 mg dL drug optional) <sup>b</sup>
2+ Risk Factors (10-year risk ≤20%)	<130 mg/dL	≥130 mg/dL	≥130 mg dL 10-year risk 10-30%
			≥160 mg dL 10-year risk <10%
0-1 Risk Factor <sup>c</sup>	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL LDL lowering drug optional)

<sup>a</sup> CHD= coronary heart disease.

<sup>b</sup> Some authorities recommend use of LDL-lowering drugs to this category if an LDL-C <100 mg/dL cannot be achieved by TLC. Others prefer use of drugs that primarily modify triglycerides and HDL-C e.g. nicotinic acid or fibrates. Clinical judgment also may call for deferring drug therapy in this subcategory.

<sup>c</sup> Almost all people with 0-1 risk factor have 10-year risk <10%, thus 10-year risk assessment in people with 0-1 risk factor is not necessary.

- While the Advisory Committee discussed the level of underlying risk where the benefit of treatment with aspirin would be expected to exceed the risk of injury, there was agreement regarding the use of risk stratification for patient selection. There was significant agreement among Committee members that individuals without a previous event can be at substantial risk of MI, in many cases with risk greater than that of patients who have had a previous event.
- Standard risk assessment tools can be used effectively in clinical practice to identify CHD risk and guide therapy.
- Based on the overwhelming support of the major professional and scientific organizations involved in cardiovascular risk management, it is clear that a risk-based approval can be actualized in practice. These independent bodies, who have carefully reviewed the data, have concluded that risk assessment is the ideal approach for guiding appropriate aspirin utilization.
- While the FDA has clearly articulated that it does not regulate the practice of medicine, it has sought to ensure that its approvals and label indications reflect real world utilization paradigms. The labeling adjustment proposed in the Petition would more closely align aspirin use with current medical practices and be expected to translate into significant public health impact.

**Evidence of Effectiveness in Moderate Risk  
 (Question 2)**

***Bayer Position on Demonstration of Effectiveness of Aspirin in Intended Population***

There is substantial evidence of safety and efficacy in the intended moderate-risk population. In fact, over 36,000 patient years of evaluation are included in the primary prevention database, including patients from a large study (Thrombosis Prevention Trial (TPT)) that had as its specific aim inclusion of patients at baseline moderate risk.

***Supporting Points***

- Over 55,000 patients who had not suffered a previous event and had various underlying CHD risk levels were studied, providing substantial evidence of safety and effectiveness for aspirin in preventing MI. Evidence from four studies evaluating low-risk patients (British Doctors Study (BDS), Physician’s Health Study (PHS), Hypertension Optimization Treatment Trial (HOT), and Primary Prevention Project (PPP), and one study evaluating *moderate risk* patients (TPT), along with the secondary prevention database, confirms that aspirin reduces the risk of MI at all risk levels. This is driven largely by reductions in the more common form – non fatal MI (2/3 of all MIs).
- While the patients’ average risk level in four of the five studies was deemed to be low, all five studies included patients at various levels of risk (see table below).

**Patient Enrollment by Underlying CHD Risk Per Year**

	<u>&lt;1%</u>	<u>1-2%</u>	<u>&gt;2%</u>	<u>TOTAL</u>		<u>&lt;1%</u>	<u>1-2%</u>	<u>&gt;2%</u>	<u>TOTAL</u>
<b>BDS</b>	3,584	1,136	419	5,139		70%	22%	8%	100%
<b>HOT</b>	15,179	2,870	741	18,790		81%	15%	4%	100%
<b>PPP</b>	3,230	935	330	4,495		72%	21%	7%	100%
<b>TPT</b>	4,028	981	76	5,085		79%	19%	2%	100%
<b>PHS</b>	19,828	1,846	397	22,071		90%	8%	2%	100%
<b>TOTAL</b>	<b>45,849</b>	<b>7,768</b>	<b>1,963</b>	<b>55,580</b>		<b>82%</b>	<b>14%</b>	<b>4%</b>	<b>100%</b>

- The major professional and scientific organizations who have reviewed these data agree the evidence is clear that even patients at the lowest risk level (low risk (<10% 10-year risk)) achieve a statistically (and clinically) meaningful reduction in CHD risk as a result of aspirin use.

- The Petition request for an indicated use in patients whose CHD risk is at least moderate is based on the desire to enhance the benefit-to-risk relationship, by restricting use to those where this relationship is appropriately favorable. It is not based on lack of effectiveness in the low-risk study population as defined by the 5 primary prevention studies.
- Over 36,000 moderate risk patient years are included in the current Petition (patient years by entry risk level are summarized in the table below).
- Both intra- and inter- study analyses confirm that equivalent benefits (e.g., risk reductions) are seen regardless of baseline global risk.

Global Risk	Aspirin		Placebo		RR
	Events	Patient Years	Events	Patient Years	
<10%	280	110,360	368	110,085	27% (7)
10% - 20%	97	18,056	145	18,139	35% (11)
>20%	31	4,385	53	4,203	43% (18)

- Specific evaluation of moderate risk patients confirms a reduced risk of non-fatal MI of 35%.
- The TPT trial, which specifically included patients deemed to be at moderate risk (>10%), demonstrates non-fatal MI risk reductions equivalent to the other four primary prevention studies (32%).
  - Based on its size and design, TPT should be viewed as pivotal and supported by the other four studies for the use of aspirin to prevent MI in moderate risk patients.
  - The statistical review of TPT undertaken by the FDA appears to contain a number of inaccuracies, which has led to an apparent erroneous conclusion regarding the benefit-to-risk findings of this study. A more thorough review of this study appears to be warranted.
  - A single study has been used to support other approved aspirin indications. Most recently, the Swedish Angina Pectoris Aspirin Trial (SAPAT) formed the basis of the FDA approval of aspirin for chronic stable angina in 1998.

### ***Bayer's Position on the Handling of Silent MI***

Due to the difficulty in assessing time and presence of silent MIs, these events have been appropriately excluded from most cardiovascular studies and should not be retrospectively re-evaluated on an *ad-hoc* basis. This includes analyses by the Antithrombotic Trialists (ATT), which have not included silent MI for more than 10 years, and is consistent with previous FDA approvals based on studies that specifically excluded silent MI.

### ***Supporting Points***

- Silent MIs are associated with a risk of classification error (due to difficulty in assessing time and presence of silent event) and are thus appropriately excluded from most studies.
- Only two of the five primary prevention studies actually recorded silent MIs, and only one (HOT) specifically evaluated these findings. It is important to note that the timing of silent MI could not be adequately assessed in these trials.
  - As is the case with most studies evaluating effects on cardiovascular events, silent MIs were not prospectively evaluated across the five primary prevention studies. As a result, the meta-analysis of the studies conducted by the ATT specifically excluded these events. It is important to note that this decision was made prospectively and follows the protocol implemented by the ATT for more than 10 years.
- It appears that the FDA statistical review retrospectively re-evaluated silent MIs, adding them back in its analysis of the submitted studies, and suggested that no effect on MI was achieved. Based on the *post-hoc* nature of these analyses, their relevance requires discussion.
- It is recommended that a detailed analysis of the study protocols be undertaken to provide insight as to how silent MIs were treated in the individual studies and therefore validate the appropriateness/inappropriateness of the *post-hoc* analyses.
- It is important to note that the design features of the primary prevention studies closely mimic those deemed to be appropriate by the Agency in their approval of the use of aspirin in secondary prevention as well as other approved treatments (S-NDA for Altace in heart failure).
- Several large studies have specifically excluded silent MI from the primary endpoint (e.g., HOPE and HERS) and have been deemed supportive of an MI indication by the Agency.

## Establishing a Favorable Benefit-To-Risk Relationship (Questions 2, 8)

### *Bayer's Position on Demonstration of a Favorable Benefit-to-Risk Relationship*

The benefit-to-risk relationship can be enhanced by limiting aspirin use to individuals of at least moderate risk, where the benefits of treatment significantly exceed the potential for harm.

### *Supporting Points*

- The safety profile of chronic low dose (50 –325 mg/day) aspirin has been established in numerous studies.
- Overview analyses of the primary and secondary prevention study database provide meaningful estimates of the risk of treatment.
- Individual primary prevention studies provide estimates of risk that are consistent with those from previous analyses of the total aspirin database.
- Primary prevention patients would not be expected, based on being relatively healthier, to be at greater absolute risk of injury compared to secondary prevention patients.
- The available evidence demonstrates that the risk of CHD can be reduced by about one third, regardless of the level of baseline risk.
  - The Petition request to limit the use of aspirin to physician-identified individuals at 10-year risk equal to or greater than 10% reflects the view that while lower risk individuals also benefit, the benefit-to-risk relationship is more favorable at this moderate risk level.
  - This position is supported by the independent reviews of the data by major professional and scientific bodies (including United States Preventive Services Task Force, which recognizes a lower risk level of >6%).
- As highlighted in the table below, in moderate risk patients, 14 MIs will be prevented for every 5 major bleeds and 1 hemorrhagic stroke caused, for every 1,000 patients treated for 5 years, representing the importance of access to aspirin for these patients. The benefit-to-risk relationship would be even more favorable for individuals at high risk, who have not had a previous event and are not currently included in the labeling for aspirin.

<b>Annual risk of CHD event</b>	<b>CHD event</b>	<b>Ischemic stroke</b>	<b>Hemorrhagic stroke</b>	<b>Major bleed</b>
<10%	5	0	1	5
10-20%	14	0	1	5
Secondary	25-50	25-50	1	5

- It is important to note that major intracranial and extracranial bleeding, while serious, are often resolved more favorably and are associated with less morbidity and mortality than the non-fatal MI prevented.
- Furthermore, it is believed that through appropriate labeling, many of the individuals at increased risk of these adverse events can be excluded.

***Bayer Position Regarding Benefit Restricted to Non-Fatal MI***

The existing body of data clearly supports the use of aspirin in preventing first non-fatal MI, in that this was statistically significant in the key primary prevention studies. This finding represents a clinically meaning benefit since non-fatal MI is the most common form of MI.

***Supporting Points***

- Non-fatal MI is the most common form of MI, making up 2/3 of all MIs.
- MI is the most common outcome in the primary prevention studies and occurs at a rate high enough to allow meaningful comparisons to placebo.
- Stroke and death are more rare in this population and therefore do not occur at sufficiently high rates to allow meaningful comparisons.
- The absence of a mortality or stroke benefit in the relatively low-risk population as defined by the five primary prevention studies is not surprising based on the number of events observed, nor does it minimize the importance of the MI findings.
- Preventing non-fatal MIs is clinically important; this benefit alone is an important reason for amending the labeling for aspirin.
- While the existing primary prevention trial database clearly supports the use of aspirin in preventing first non-fatal MI, it is possible that trials, such as the soon-to-be-completed Women's Health Study (WHS), may allow for an evaluation of the possible benefits of aspirin in preventing stroke and death, as well as provide additional data with respect to the benefits in women. Nonetheless, such additional findings should not be required for approval of the current Petition, as the benefit-to-risk relationship is highly favorable based on the non-fatal MI findings alone, and the dosing pattern in the WHS is significantly lower than in the currently available studies (100 mg Q.O.D):
  - New data may allow the labeling to be broadened to include even lower-risk patients in the future.
  - This study will double the person years of evaluation for low-risk populations from the current level to approximately 350,000 patient years.
  - New findings with respect to a benefit on stroke and death would be expected to only strengthen the benefit-to-risk relationship and allow aspirin to be appropriately indicated for patients at 10-year risk of less than 10%.

### The Appropriateness of Including Women in the Labeling (Question 3)

#### ***Bayer's Position Regarding the Utility of Aspirin in Women***

Since there is no biological difference between men and women in terms of the cardiovascular benefits of aspirin, and 11,466 women (21% of subjects) have been studied, as with secondary prevention, the use of aspirin for primary prevention is appropriate in both male and female individuals whose risk of CHD is at least moderate.

#### ***Supporting Points***

- There is no evidence to suggest that aspirin differs in its efficacy or safety profile in moderate risk women as compared to moderate risk men, suggesting that it would be inappropriate to exclude women from the labeling of aspirin based on the available data.
- Numerous *in vitro* studies confirm that female and male platelets are equivalently inhibited by aspirin.
- There is agreement that the proximal cause of MI is the same in men and women.
- While women are, by definition, at lower overall risk of MI than men, their inclusion in labeling defined by underlying risk predisposes them to a favorable benefit-to-risk relationship.
- The benefits of aspirin accrue equally to men and women in all currently approved indications for aspirin.
  - The ATT study published in the *British Medical Journal* in 2002 demonstrates benefits are the same irrespective of gender.
- Historical failure to recognize the importance of including women in the labeling of effective drugs has, in part, led to the dramatic underutilization of important therapeutic options in this population. The increased MI fatalities of women versus men may reflect this phenomenon.
- While the Advisory Committee suggested that too few women were evaluated in the intended population, it should be noted that 11,466 women were actually studied across the five primary prevention trials, accounting for 21% of the subjects studied.
  - This number exceeds those included in the NDAs of a range of approved drugs used in the prevention of cardiovascular events or treatment of heart failure.

DRUG	NUMBER OF WOMEN
Plavix (clopidogrel)	3,453
Aggrenox (dipyridamole + aspirin)	2,773
Diovan (valsartan)	1,003

- While the numbers of patients within each study do not provide sufficient power to evaluate gender effects, no trends or differences were seen in any of the studies.
- Meta-analyses of the overall primary prevention database confirm an absence of a gender effect (same finding as in larger secondary prevention database).
  - ATT Primary Prevention gender analysis of the five primary prevention trials demonstrated a proportional risk reduction of CHD of about one quarter that is unaffected by gender.
  - Findings do not differ from the larger secondary prevention database where no gender differences were observed.
- Previous errors that have excluded women from aspirin labeling should be avoided.
  - TIA labeling in 1980 parallels the current situation with primary prevention, in that women were excluded from the labeling based on small numbers of female subjects and a failure to acknowledge the absence of differences in pathophysiology by gender. This was not remedied until the 1998 monograph amendment.
  - The current under-treatment of women may reflect physician perception that aspirin is ineffective in this population based on these previous FDA rulings.
- The current guidelines of professional organizations, including the recently published American Heart Association guidelines, recommend risk assessment and consideration of the use of aspirin in female patients of at least moderate risk of CHD.

## **Due Diligence (Question 6)**

### ***Bayer's Position Regarding FDA Review of Trial-Related Materials***

A full review of the protocols, final reports and study documentation for all primary prevention trials could assist the Agency in addressing any further outstanding questions.

### ***Supporting Points***

- Trial designs have been published in peer reviewed journals, results have been published in high quality journals, and data are available for FDA audit and review.
- Bayer is interested in assisting the Agency as necessary in obtaining study-related materials for the primary prevention trials.
- Investigators are available and interested in being of assistance to the Agency in its review of the studies.
- Without adequate review, it is unclear how the Agency can reach meaningful conclusions regarding the quality and findings of the trials (including the handling of the silent MI findings).

## **The Path Forward in the Service of Public Health (Questions 7, 9, 10)**

### ***Bayer Position Regarding Public Health Implications***

Underutilization of aspirin remains a significant public health concern. Risk-based labeling and education can ensure appropriate aspirin utilization (allowing the right people to be treated and discouraging the wrong ones). Further, additional studies to evaluate the benefits and risks of aspirin in moderate-risk patients are unlikely to be conducted in the current scientific environment.

### ***Supporting Points***

- Data presented at the Advisory Committee hearing suggests that as little as 25% of high risk patients are compliant with physician-directed aspirin recommendations. The numbers are even worse in moderate-risk patients.
- Risk-based labeling will guide physician patient assessments and ensure that the appropriate people have access to aspirin.
- Physicians and patients are looking for more guidance, suggesting that improved aspirin labeling would be expected to improve public health.
- Appropriate education that can result from expanding the professional labeling for aspirin can have significant impact in remedying this situation.
- While some have suggested that additional data is needed to evaluate the benefits and risk of aspirin in moderate risk patients, such studies are unlikely to be conducted for several reasons:
  - Ironically, in spite of a lack of FDA recognition, for scientific and ethical reasons, a number of IND authorized primary prevention studies are underway that require all participants to receive aspirin as baseline therapy due to Institutional Review Board requirements.
  - This reality will serve to limit the likelihood of future placebo-controlled studies in this area.