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Date: JUL 01 2004

Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket Number 2004D-0188
Response to FDA Call for Comments
FDA draft guidance - Development and Use of Risk Minimization Action Plans

Dear Sir or Madam:

Reference is made to the May 5, 2004 Federal Register notice (Volume 69, Number 87, Pages 25130 – 25132) announcing the request for comments on the FDA draft guidance - Development and Use of Risk Minimization Action Plans.

AstraZeneca has reviewed this draft guidance and our comments are attached.

Please direct any questions or requests for additional information to me, or in my absence, to Debra N. Shiozawa, Associate Director, at (302) 886-3137.

Sincerely,

Gary Horowitz, Executive Director
Regulatory Affairs
Telephone: (302) 885-1008
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DNS

Enclosure

2004P-0188

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**Comments from AstraZeneca on the
FDA Draft Guidance – Development and Use of Risk Minimization Action
Plans
(Docket Number: 2004D-0188)**

General Comments

AstraZeneca appreciates and agrees with FDA’s statement that risk minimization action plans (RiskMAPs) need not and should not be employed routinely and in the absence of an identifiable heightened safety concern. Even where such a particularized safety concern can be identified, however, there are important legal limits on FDA’s authority under the law to require the adoption of RiskMAPs, particularly for risk management tools that involve distribution restrictions or otherwise impinge on the practice of medicine. These comments focus on the substance of the draft guidance, and not on these legal points. However, the legal limitations on FDA’s jurisdiction are significant, and FDA must respect those limitations as it implements the draft guidance in particular cases.

Legal considerations aside, it is not clear if risk minimization action plans need to be written prior to embarking on a registration program for launch. It would seem that in earlier stages of development routine measures such as educating investigators how to report SAEs, attention to inclusion/exclusion criteria and design of case report forms and specified investigations to capture efficacy and safety data would suffice to assess, minimize and manage patient risk. If this is correct, it should be stated.

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Section	Line Number	Comment or proposed replacement text
II.B.	95	Nurses represent a significant portion of medical health professionals, especially with drug products administered in the hospital and physician office settings. Nurses should be included in the list of stakeholders.
III.B	151	Please add specifics and examples about when a RiskMAP is needed. The statement that “a RiskMAP need not be considered” for most products is appreciated, but the criteria on which a RiskMAP is needed are not clear despite section III.D.
III.C.	179-181	In the proposed objectives, there is not a clear distinction between the role of pharmaceutical companies and the role of health care providers. While AstraZeneca agrees that the role of pharmaceutical companies is to attempt to minimize risk to patients as much as possible through communication and possibly other efforts, it is not the sponsor’s responsibility to “police” health care providers. It is both unrealistic

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		and unwise to direct sponsors to impose and enforce undue constraints on health care providers, who can and should exercise discretion together with their patients based on available scientific and medical information, their sound professional judgment, and individualized risk-benefit determinations.
III.D.		<p>Additional information on how to identify issues that may need RiskMAPs is needed. Areas for consideration should include:</p> <ul style="list-style-type: none"> • The mechanism of the event (e.g., pharmacologic or idiosyncratic, dose-related or not-dose-related) • Incidence and prevalence (e.g., predispositions for event in the target population) • Potential for misuse or abuse • Similarity to other available therapies, and whether these have RiskMAPs • Medication errors • Patient compliance <p>The role that pharmacogenomics can play in identifying when a patient is at risk or when a patient is unlikely to benefit should also be considered.</p>
III.D.	193 (footnote 6)	This footnote states that a generic product "...may have the same or similar benefit-risk balance as the innovator." Other than the possibility of brand name confusion, generic products should have an identical benefit-risk balance as the innovator, except in special cases. FDA should either clarify other situations where a generic would not be identical to the innovator product, or modify this statement accordingly.
III.D.	195-201	<p>The draft guidance does not specify the nature of adverse events that may warrant a RiskMAP. In addition to the information presented on lines 206 to 228, this section should state that consideration of a RiskMAP requires certain activities that can reasonably be expected to result in appropriate product use. If the desired behaviors of prescribers, other health care providers, or patients can be assured, the overall benefit-risk balance can be enhanced. An acceptable benefit-risk balance depends on the following attributes:</p> <ul style="list-style-type: none"> • The risks are in some way preventable, • Benefits of the drug can be enhanced (e.g. identifying who is most likely to benefit via assessment of a biomarker), or

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		<ul style="list-style-type: none"> Given the potential severity of possible rare risks, informed decision making by patients and prescribers must be assured.
IV.A.	217	<p>Please define “prespecified increases”.</p> <p>Examples of prespecified increases would be appreciated.</p>
IV.B.		<p>Please consider using a standard step-wise approach with the first step always being a Letter to Health professionals, introduction of patient package inserts and prominent public notification. The step-wise approach is consistent with the philosophy of using least burdensome strategy possible.</p>
IV.B.2.	308	<p>Patient agreement or acknowledgment forms are impractical in many standard clinical settings.</p>
IV.B.2.	310-311	<p>It can be problematic for manufacturers to certify practitioners from a liability viewpoint. Successful completion of Continuing Education may be an alternative way to meet this objective.</p> <p>The distinction between a certification program for practitioners (as a reminder system) and training programs for health care practitioners (as targeted education and outreach) should be clarified.</p>
IV.B.2.	313	<p>Clarification should be provided regarding the distinction between special educational programs that reinforce appropriate product use (as a reminder system) and training programs for health care practitioners and patients or continuing education for health care practitioners (as targeted education and outreach).</p>
IV.B.2. & 3.		<p>It is important to take into account the cost to healthcare providers and institutions of administering certification programs and special product dispensing programs. Input on these issues should be sought from professional organizations (pharmacists, physicians, etc.).</p>
IV.C.		<p>Tools that have been used or are being used should be available on the web site unless proprietary (e.g., trademarked, copyrighted, or otherwise confidential commercial information). If possible, there should also be a description of effectiveness of the program, within the limitations of FDA’s public disclosure rules.</p> <p>Sponsors can learn from one another.</p>
IV.C.	345-354	<p>An FDA web site that summarizes recent experience with risk tools would be a very useful resource for sponsors. The web site should also contain FDA’s analyses of previous plans and the tools used, including overall feasibility assessments, as well as the known advantages, disadvantages, and limitations associated with a given tool.</p>

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		All of this information could only be disclosed if it is not trade secret or confidential commercial information.
IV.D.	377	Nurses are another key group of health care professionals that have the ability to minimize risks.
IV.D.	389	A statement should be included about making tools available to each market and tailoring as necessary based on available technology, culture of medical practice, etc.
IV.D.	409-421	Text should be added to reflect that, like FDA, pharmaceutical manufacturers could not control the actions of prescribers. Tools applied as part of RiskMAPS are intended to facilitate safe use of the product in accordance with its labelling, not to supplant the practice of medicine. We suggest that FDA consider modifying this statement to indicate that health care practitioners are "...one of the most important managers of product risk". For some products and events, patients may be the primary targets for risk communication.
IV.D.	415-421	It should be recognized that 100% achievement of specific objectives might not be attainable given the appropriate autonomy of the health care practitioner in making prescribing decisions with patients.
V.B.	482-508	RiskMAPs should seek continuous improvement until an acceptable risk-benefit balance is maintained. Specific quantitative reporting goals are problematic as are <i>a priori</i> thresholds for action. An assessment of the quantity and quality of reports, nature and severity of events that occur after the interventions have had time to make an impact should be performed prior to refining a RiskMAP. The decision to add, modify or remove tools requires a comprehensive assessment of all available information rather than focus on an isolated metric.
V.B.1.	485	Whenever possible, knowledge by itself should not be used to measure the effectiveness of the tool. Surveys and testing of knowledge are inadequate measures of success without corresponding changes in patient outcome and prescriber behavior.
V.B.1.	487-488	Proposed new text: "...a sample outcome measure could be complication rate, and a target or objective for that measure could be to have no more than a specified number or rate of that complication." In the original example, this is not a sample outcome measure, but rather a threshold objective for the outcome measure. The actual outcome measure in this example is a <u>complication rate</u> .

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V.B.1.	488-508	The draft guidance states that if health outcomes cannot be practically or accurately measured, closely related measures can be used. How often can health outcomes be practically or accurately measured and at what cost? We ask that FDA acknowledge that it might take a significant time for enough data to become available to prove that rates of an event have gone down and by how much. Additional discussion on the decision-making process for monitoring an actual patient outcome versus a closely related measure should occur between FDA and the sponsor.
V.C.	611-613	We ask that FDA share the results of its assessment of the RiskMAP effectiveness with the sponsor and discuss any differences of interpretation (reference line 652).
V.D.	620-621	This is a reasonable objective, but it is not realistic to postulate that components of a risk management program could be described without disclosing product and sponsor. This would only be the case if RiskMAPs become ubiquitous, something that this document suggests the FDA opposes.
VI.		Please consider using an assessment of risk to determine how information will be communicated to Regulatory Authorities. If it is high risk, communicate as needed. If it is not high risk or a program has been in place for some time, the communication could be incorporated into the PSUR.
VI.	666-668	Clarification should be provided as to whether a pre-approval RiskMAP should be submitted to both the IND and the pending NDA/BLA, or to only one of these files.
VI.	669-670	FDA recommends that RiskMAPS proposed during postmarketing should be submitted as a supplement to the NDA or BLA. FDA should also confirm that sponsors would not be required to pay additional user fees with submission of these applications.
VI.A.	706	Mentioning that a Cox proportional hazards model might be used instead of or in conjunction with a Kaplan-Meier seems appropriate. Most of the time, adjusting for potentially confounding variables in a time-to-event analysis makes sense. This adjustment can be accomplished with a Cox proportional hazards approach.
VII.A.	728-730	It should be made clear what success or failure experiences should be discussed here (e.g., for the specific product under discussion or for all RiskMAP experience).

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VII.A.	747-751	The guidance should include clarification regarding the type of evidence that should be provided. There are very few examples in the public domain of successes for any tools. If the tools are recommended in the guidance, what other evidence needs to be provided?
VII.A.	764	The problem of multiple comparisons should be discussed more fully or include a reference. The issue of multiple comparisons is not insignificant. These guidances should provide some additional insight about this problem.
VII.A.4.	770	General discussion and guidance should be included on how the sponsor should establish ‘targeted values’ for each measure.
VII.B.2.	817-818	The guidance should clarify what measurement errors, sensitivity, etc. are being discussed in this paragraph.
VII.B.3.	821-830	These sections seem to overlap. Why not have a single “Results section” that contains primary data and analyses?
VII.B.5.	838-839	The guidance should also include situations when it might be possible to modify a RiskMAP if the goals are achieved. A RiskMAP should not necessarily be a never-ending activity, and the guidance should make clear that there is a potential for modification based on success.