



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-0187
Response to FDA Call for Comments
FDA draft guidance – Premarketing Risk Assessment

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2004 Federal Register notice (Volume 69, Number 87, Pages 25130 – 25132) announcing the request for comments on the FDA draft guidance – Premarketing Risk Assessment.

AstraZeneca has reviewed this draft guidance and our comments are attached.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

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**Comments from AstraZeneca on the
FDA Draft Guidance – Premarketing Risk Assessment
(Docket Number: 2004D-0187)**

General Comments

AstraZeneca welcomes this draft guidance as a much needed step in providing greater structure and consistency between Centers and across Divisions, especially in situations where FDA reviewers mandate conditions for product approval greater than those historically required by FDA regulation and guidance. Since requirements for additional studies and increased amounts of data will result in delays in drug development, the added value of identifying as many risks as possible prior to approval must be balanced against the decreased benefit to patients who are waiting for needed medicines.

AstraZeneca appreciates and concurs with FDA’s statement in this draft guidance that many recommendations are not applicable to all products, and indeed should only be employed in cases with particularized safety issues. At the same time, there are a number of concepts in the draft guidance that are areas of concern to AstraZeneca regardless of how frequently applied:

- Expectations for additional safety data from products when “an acceptable alternative” treatment exists, even if not all patients benefit from the acceptable alternative. This reflects an under-appreciation of patient-to-patient variability and the need for multiple treatment options within a therapeutic class, and would seem to unfairly penalize products that are not first in class or a first-line therapy.
- Expectations for a substantial increase in the number and variety of patients to be included in the pre-approval safety database without adequate consideration of the practical difficulties and unintended consequences associated with this expansion.
- Recommendations for delaying final dose selection until Phase III, which will not only significantly increase the size, complexity, and time to complete these trials, but will also increase the likelihood that patients will receive either a sub-therapeutic or toxic dose.
- Emphasis on large simple safety studies (LSSS) as a prior-approval requirement or as a Phase IV condition of approval without clear recognition of the limited value and significant burden of such studies and without clear guidance as to when these are appropriate.
- Proposals for sponsors to assess the potential for medication errors prior to approval, although a clear regulatory definition of medication errors has not been established and methodology to conduct such assessments has not been validated.

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Section	Line Number	Comment or proposed replacement text
IV.A.	183	We welcome the additional guidance the Agency has provided regarding the kinds of patients who should be included in a premarketing safety database. However, we request that FDA further define the terms “relevant doses” and “reasonable representation,” since this could be interpreted in many different ways. Specific examples would be helpful to better understand FDA’s expectations. We also request that the Agency clarifies whether the recommended size of exposure could include patients exposed to dose levels lower than the intended levels, especially in situations where higher doses may put some patients at increased risk.
IV.A.	194-195	This concern does not seem to be addressed by larger studies; rather, it would need to be addressed by longer studies.
IV.A.	203-206	Since many of the most rare and severe adverse reactions only occur at a rate of one event per ten thousand patient exposures (or even less in many instances), a 1500 patient pre-marketing safety database (as suggested by ICH E1A) will never definitively estimate the frequency of rare events, even if the size is increased tenfold. AstraZeneca is not aware of any recent examples where low-frequency adverse events observed in similar products have been successfully quantified prospectively (e.g., prior to postmarketing surveillance), and requests that FDA provide further guidance as to how this might be accomplished.
IV.A.	215-218	The sample size necessary to provide adequate statistical power to detect pre-specified increases over the baseline morbidity or mortality can be very high if the increase is small. The benefit of any additional knowledge about patient safety gained by exponentially increasing the size of the premarketing safety database should be considered in the context of the benefit to patients that may be lost due to longer development times and delay in patient access to improved therapies. AstraZeneca requests further guidance on what pre-specified increases are acceptable in various settings.
IV.A.	220-234	AstraZeneca is concerned that the two additional situations mentioned in the draft guidance when safety databases should be larger than described under ICH E1A essentially establishes a new standard for drug approval. Under the Federal Food, Drug, and Cosmetic Act, FDA must evaluate safety and effectiveness solely with respect to the drug under review, and has no authority to consider the safety and/or

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		<p>effectiveness of other drug products either on the market or in development when making this assessment unless the applicant itself intends to make comparative safety or efficacy claims. In the absence of such comparative claims, the existence of a “safe alternative” should make no difference in determining whether a larger database is necessary, since any drug requires an FDA determination of safety and efficacy to be approved. Therefore, if a drug is not the first in class or is the second treatment for a specific disease, this language would essentially mean that FDA might require a larger safety database than required under ICH E1A regardless of whether this will improve patient safety. Without clear criteria for determination of a concern and a “gold standard” via therapeutic guideline, arbitrary determinations motivated by a variety of factors besides safety will be possible. The new drug might have a better efficacy and/or safety profile than the "safe and effective alternative," or may provide patient compliance advantages, which means that the delay in approval while a larger safety database is collected will actually have an adverse impact on patients, especially for those patients who do not respond well to the older drug. AstraZeneca requests that FDA explain the rationale for requiring a larger database if studies of a new therapy demonstrate efficacy, an acceptable safety profile, and there is no specific safety signal that is being examined.</p>
IV.B.	253-277	<p>In the first sentence under Section 1, “Long-term Controlled Safety Studies,” the word “uncontrolled” should be replaced with “observational” since, presumably, some control over the conduct of a study always exists. “Uncontrolled” also conflicts with the title of this section.</p> <p>Additionally, AstraZeneca suggests that the weaknesses of long-term controlled safety studies should be discussed in more detail in this section.</p>
IV.B.	279-292	<p>Inclusion of diverse populations requires sufficient numbers of those patients to allow the data to be meaningful. This will have the cumulative effect of significantly increasing the number of studies and study subjects needed for drug approval. Additionally, it may not be feasible to recruit and retain such numbers in all situations. While AstraZeneca agrees with the need to broaden inclusion/exclusion criteria, since this will make it easier to find an adequate study patient population and will provide a more accurate picture of usage in the real world, it should be recognized that this will result in an increased number of confounding factors that will make the assessment of both</p>

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		efficacy and safety more difficult. Additionally, it may not be desirable or feasible to expose some populations, such as those that are high-risk or difficult to recruit. It would be helpful if FDA would align the recommendations in this draft guidance more closely to the current guidance in effect for gender, race, and age diversity in a pre-registration database, and add clarification as to how deal with efficacy and safety issues in small subgroups.
IV.B.	307-318	<p>AstraZeneca believes that dose ranging in Phase III should be considered on a case-by-case basis. Using a range of doses in Phase III will result in less data on the dose that is ultimately marketed unless the trials are significantly larger. It would be worthwhile to consider flexible dosing as a possibility for some drugs. Although flexible dosing does not allow for a formal comparison between doses, it does allow patients and their doctors to find the dose that works the best for the patient.</p> <p>Lines 316-318 state that demonstrating a dose-response relationship in late phase clinical trials could add important information to the assessment of efficacy. AstraZeneca believes that late phase clinical trials are generally too late in the development process to examine dose-response relationship. By this time, adequate dose-response examination should have been performed and the final dose(s) selected for commercial marketing.</p>
IV.C.	338-340	We request that FDA provide guidance to industry as to which population groups they want to see reflected in the demographic relationships (beyond gender, age and race), since that will affect collection forms and database data fields.
IV.C.	345	Due to the myriad of unregulated dietary supplements that exist in a multitude of different formulations, combinations, and strengths in many different countries, AstraZeneca requests that FDA provide additional guidance as to how to ascertain what products are “commonly used” by prospective patients, or “likely to be co-administered” especially in the context of cultural differences in medical practices and availability of such compounds through the Internet.
V.A.	443-463	On line 450, FDA indicates that a large simple safety study (LSSS) is most commonly performed as a Phase IV commitment, but then goes on to describe possible reasons for conducting a pre-approval LSSS (lines 454 to 463). No examples of when a post-approval LSSS might be considered are outlined. AstraZeneca suggests that circumstances

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		<p>that warrant an LSSS be described for both the pre-approval and post-approval situations, and that the Agency articulate specific examples of when a sponsor might consider conducting a pre-approval versus a post-approval LSSS. AstraZeneca’s general suggested approach follows:</p> <p>Conducting an LSSS is a significant commitment at any stage of the product life cycle. Not only does a pre-approval requirement for LSSS represent a <i>de facto</i> fourth phase to development, it is extremely difficult to design an ethical and effective LSSS study until evidence of efficacy in Phase III has been obtained. Due to the significance of this burden, AstraZeneca believes that a pre-approval requirement of a LSSS should be reserved for only those cases when a signal suggests a possible serious adverse event that, if confirmed, would result in an unfavorable benefit-risk profile, potentially representing a potential public health risk of sufficient magnitude that would prevent product approval.</p> <p>In addition, AstraZeneca requests that FDA provides references that describe considerations for LSSS design that are consistent with FDA expectations.</p>
V.B.	475-495	<p>AstraZeneca submitted extensive comments to FDA on medication errors in response to the March 2003 proposed rule for Safety Reporting Requirements for Human Drug And Biological Products safety reporting regulations (the “Safety Tome”). Until the FDA has responded to the comments of AstraZeneca and others and issued the final rule, AstraZeneca believes it is inappropriate for FDA to attempt to effect changes in existing regulatory standards via draft guidance documents.</p> <p>The draft guidance is requesting an extensive pre-marketing risk assessment regarding possible medication errors. It has been shown repeatedly that the majority of medication errors result from multifactorial issues in the healthcare delivery system rather than because of a single factor such as the drug itself. Creating artificial situations to simulate the real-world environment before the drug has been approved is problematic, especially when indications, dosages, trademarks, and even packaging have not yet been finalized. Therefore, we believe the reference to “clinical trials” should be deleted from the list of techniques that can be employed to assess the potential for medication errors.</p> <p>The draft guidance discusses attributes of a well-planned medication error prevention analysis (MEPA). The examples on lines 482 to 488</p>

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		appear to reflect situations when a post-marketing problem has been reported. Such a discussion seems out of place in a pre-marketing risk assessment document. AstraZeneca also respectfully notes that the usefulness of a MEPA in preventing medication errors is currently speculative and that additional research and study is needed to determine its value (as recommended at the December 4, 2003 meeting of the Drug Safety and Risk Management Advisory Committee) before FDA establishes any requirement or expectation for such analyses.
VI.A.	627-630	AstraZeneca suggests using a different example of coding consistency than the one given (e.g., weakness/asthenia and dizziness/vertigo.) Although some degree of consistency is important, it can be overemphasized. To attempt to achieve consistency between weakness and asthenia is not practical, and indeed is not useful—a sound analysis of results would combine weakness and asthenia, otherwise one would risk obscuring the overall finding (see bullet point on line 653). Of interest is that CTC grading is commonly used in oncology trials, and in the current CTC version (version 3), dizziness is specifically stated as including vertigo.
VI.A.	640-675	The advantages and disadvantages of “splitting” versus “lumping” coding practices are well known. Even when searchable pre-specified groups of certain adverse events exist, in order to make these useful and interpretable, uniformity is needed for drugs in the same class and perhaps, for drugs across classes. AstraZeneca suggests that this is something that can be built into MedDRA, and recommends that FDA establish and make publicly available groupings of MedDRA terms that would serve as case definitions for commonly reviewed signals and adverse events. Additionally, since prescribers often rely on package inserts to compare products for similar pharmacologic effects, it will be useful to have similar types of groupings in the prescribing information to facilitate such comparisons.
VI.F.	864-870	While AstraZeneca agrees with the importance of capturing the reasons for withdrawal from studies, it is important to note that study sponsors frequently cannot obtain such information without the patient’s cooperation (for example, in cases of threatened litigation, further requests for information may be denied). It is reasonable to expect that follow-up information should be diligently pursued and that the sponsor’s efforts should be documented, but it is not realistic to expect that all such efforts will be successful.

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VI.G.	878-881	AstraZeneca requests that FDA provide guidance on the criteria that will be considered to define the duration of post-therapy follow-up that will be needed to detect late safety events.
VI.H.	897-898 and footnote 12 (referenced in line 887)	<p>AstraZeneca suggests that reference to the 1988 guidance should be replaced by reference to the 2001 CTD guidance, as FDA has indicated that an integrated summary of safety (ISS) will not be routinely required, since the information previously contained there may now be addressed within the Summary of Clinical Safety in Module 2.</p> <p>Since it may not be possible for a sponsor to "fully characterize" the adverse event profile of other drugs in that class, it would be more appropriate to present a discussion of the known adverse event profile of the class and how this knowledge was used to enhance the development of the new compound.</p>
VI.H.	897-899	In addition to reference to the ISS, the draft guidance should also refer to the appropriate section within Module 2 of the CTD when such an application does not contain an ISS.