



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-0189  
Response to FDA Call for Comments  
FDA draft guidance – Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment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2004 Federal Register notice (Volume 69, Number 87, Pages 25130 – 25132) announcing the request for comments on the FDA draft guidance - Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment.

AstraZeneca has reviewed this draft guidance and our comments are attached.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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**Comments from AstraZeneca on the  
FDA Draft Guidance – Good Pharmacovigilance Practices and  
Pharmacoepidemiologic Assessment  
(Docket Number: 2004D-0189)**

**General Comments**

AstraZeneca is happy to note that the draft guidance evidences many improvements from its predecessor concept paper. However, we would like to highlight several areas where further expansion and clarification are needed.

AstraZeneca suggests that the definition of pharmacovigilance in the draft guidance (line 115) be harmonized with the broadly accepted WHO definition, “the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug related problem.” The FDA definition is specific to post-approval activities, whereas the WHO definition does not include this limitation. AstraZeneca believes that pharmacovigilance is a necessary activity throughout the product life cycle. Additionally, the WHO definition encompasses all pharmacoepidemiologic studies, while the FDA definition limits this to pharmacoepidemiologic *safety* studies. We would point out that the information gathered by non-safety pharmacoepidemiologic studies, such as those focused on patient characteristics, patterns of drug use, and the natural history of disease, can also add value to pharmacovigilance efforts.

An additional benefit to harmonizing with the WHO definition is that this would also ensure consistency with the definition contained in the ICH E2E draft guidance on Pharmacovigilance Planning. We believe that a global approach to pharmacovigilance and risk management is very important, and we strongly encourage FDA to harmonize with international consensus initiatives. Since both the ICH E2E document and the FDA guidance document are in draft, we strongly urge FDA, as a member of ICH and the E2E Expert Working Group, to harmonize the terminology used in these documents. The final FDA guidance document should incorporate the terminology and definitions used in the final ICH E2E guidance document.

Due to the amount of effort that companies will be expected to expend on investigation of “signals,” AstraZeneca requests that a clear definition of “signal” be provided and used consistently in the final guidance. In the current version of the guidance, this term is used frequently but with apparently different meanings. For example, in line 121, there is an implied definition that a signal is “an excess...of adverse events associated with a product’s use.” Lines 361-384 refer to a wide-ranging list of “safety signals that warrant further investigation” that potentially encompass more than just a simple excess of events, while line 327 in the section on data mining defines a “signal” as “any product-event combination with a score exceeding the specified threshold.” AstraZeneca requests that FDA work with industry to develop an appropriate definition.

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We are concerned that the guidance document appears to place more emphasis on data mining rather than on validated methods of signal detection. We believe that data mining should be used only as a supplement to, not as a substitute for, traditional methods of signal detection that utilize clinical and pharmacological judgment. Limitations of the underlying data as well as the limitations of various data mining techniques must be fully appreciated to avoid false positive causality conclusions. Until the systematic performance characteristics of data mining techniques are more fully established, we do not believe that use of data mining techniques should be a mandated part of signal identification and evaluation.

While the draft guidance addresses population risks, we believe that an individual’s risks *and* benefits should also be addressed. It should be recognized that many sub-groups and individuals are willing to accept more risk for more benefit, depending on personal preferences, quality of life, stage of disease, aggressiveness of the progression of the disease, or other considerations. The goal of pharmacovigilance should be not only to *minimize* risks, but also to clearly *describe* the risks so that patients and physicians can make informed decisions.

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<b>Section</b>	<b>Line Number</b>	<b>Comment or proposed replacement text</b>
II.B.	97	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.
IV.A	145-153	<p>The FDA’s Proposed Rule for Safety Reporting Requirements for Human Drug And Biological Products, issued in March 2003, also proposed a requirement for trained healthcare practitioners (HCPs) to query initial reporters. As we indicated in our response to the proposed rule, if a truly focused line of questioning is utilized, as proposed, in our experience it is not necessary for the person to be a healthcare professional to produce high quality reports. If FDA nonetheless retains this approach, we would request clarification of the definition of HCPs who are supposed to perform active queries, since this can vary widely in a global context.</p> <p>We also feel that, in some instances, written follow-up requests are more appropriate, especially if a large amount of detailed information is being requested. If the reporters are contacted via written request, it allows them to choose the time when they can sit down with the patient’s chart and provide the current valid data to the industry. Telephone solicitation can result in a reporter attempting to remember the details of a patient’s event without the support of the patient’s chart. In our experience, information obtained in this manner often conflicts with the written record obtained later.</p>

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		Furthermore, since the new regulations are unlikely to be issued before this guidance is finalized, we believe that this section should be revised to conform to current regulations and guidances, which do not specifically mandate the qualifications of internal company personnel who perform this activity. Once there is a clear and agreed regulatory requirement, the guidance can be revised accordingly. To proceed otherwise will lead to unnecessary confusion and conflict between the Agency and industry.
IV.A.	156-157	We propose to delete the phrase “other factors.” This is a very non-informative, aspecific term, which does not provide any guidance. Alternatively, please clarify this vague terminology.
IV.B.	161-205	Currently, the elements of a “good case report” that are listed for medication errors are difficult to obtain. For example, recent testing using actual data for a 4-month period showed that it is extremely rare for reporters to provide the sequence of events leading up to an error or the causes of an error. Before imposing any requirement or expectation in this area, FDA should research with relevant stakeholder groups what sort of outreach efforts would be required to motivate reporters to provide the kind of detailed information on medication errors suggested in this guideline.
IV.B.	188-205	The FDA’s Proposed Rule for Safety Reporting Requirements for Human Drug And Biological Products, issued in March 2003, included quite specific regulatory requirements concerning medication errors. However, since the new regulations are unlikely to be issued before this guidance is finalized, we believe that this section should be revised to conform to the current regulations, which require reporting of medication errors only when they also involve an adverse event. Once there is a clear and agreed regulatory definition, the guidance can be revised accordingly. To proceed otherwise will lead to unnecessary confusion and conflict between the Agency and industry.
IV.C.	255-257	Case-control studies cannot be used to determine causality. We recommend that this sentence be revised accordingly.
IV.C.	256	“Long-term” should be changed to “appropriate length of....” Not all AEs occur with consistent risk over time or with risk accrued with exposure to a product. Some AEs may occur with a short period of exposure, after which the patient is no longer at risk for the AE in question. Moreover, some products have a short half-life and are used in acute settings (e.g., surgery). The likelihood of these having a long-term effect is negligible.

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IV.C.	273-279	The draft guidance states “FDA recommends that sponsors seek to identify possible failure points in the medication use system.” Research has shown that identification of such system failures is most successful when analysis occurs within the institution (hospital, pharmacy, etc.) in which the error occurred, as soon after the event as possible, by someone familiar with the institution’s system of medication distribution. A pharmaceutical company’s ability to fulfil this function would seem to be quite limited, especially in multi-national environments where such systems vary widely. AstraZeneca believes that root cause analysis of medication errors by sponsors should address those limited causes over which the sponsor has control (e.g., brand name, labelling and packaging).
IV.E.	313	Please expand on what is meant by “characteristics” of a signal. The disproportionality method can only show that a disproportionality exists or does not exist and to what degree. Further analysis (i.e., case review) is required to ascertain any other “characteristics”.
IV.E.	312-317	In view of the limitations and uncertainties of data mining methodology, the sentence “...using statistical or mathematical tools, or so-called data mining, <i>can</i> provide additional information about the existence or characteristics of a signal.” should be changed to “...using statistical or mathematical tools, or so-called data mining, <i>may</i> provide additional information about the existence or characteristics of a signal.” Additionally, the last sentence of the paragraph, “Data mining <i>is not the only technique used</i> to make causal attributions between products and adverse events,” should be changed to “Data mining <i>should not be used</i> to make causal attributions between products and adverse events.” The original statements imply that data mining can make causal attributions, which is not true.
IV.E.	325-327	The phrase “statistic (or score)” should be changed to “score” only. The term “statistic” implies that the AERS data are more methodologically meaningful than they are. For the available data mining tools, statistical validity has not yet been established. The functionality of these tools has been overstated as to what their current capabilities are (e.g., thresholds, sensitivity and specificity). More developmental work is needed on these tools.
IV.E.	329-331	The statement “The lower the threshold, the more likely it is that signals of true effects will be detected, but these lower thresholds will also result in more false positive signals” is misleading and too strong. We suggest that

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		this sentence be changed to “True positives are less likely to be screened out as the signal threshold is lowered, but this will also lead to more false positive signals.”
IV.E.	333	The FDA provides references for the data mining techniques suggested in IV.E, including a note that no evidence is apparent that any of these techniques had proved valuable in the past. Applying sophisticated statistical techniques to data of, at best, uneven quality does not make sense, particularly if no successes have been seen while using these approaches.
IV.F.	357-358	We request clarification of the phrase “preliminarily characterize.” We suggest that the statement “FDA believes that the methods described above will permit a sponsor to identify and preliminarily characterize safety signals” be changed to “FDA believes that the methods described above are additional tools which may assist a sponsor to identify safety signals for further investigation.”
IV.G.	389-434	<p>The FDA provides references for the data mining techniques suggested in IV.E., including a note that no evidence is apparent that any of these techniques has proved valuable in the past. Applying sophisticated statistical techniques to data of, at best, uneven quality does not make sense, particularly if no successes have been seen while using these approaches.</p> <p>The data suggested by the FDA is often not available: e.g., prevalence of statin use in Asian-Americans (the sample in the NHANES is too small for this estimate), or the outcomes associated with statin use in patients with low body mass (height and weight are usually not available in claims data sets and outcome data are not available in NHANES). Thus, no readily available data set for analysis may exist.</p> <p>The lack of clarity in the guidance leads to the suggestion that more detail is needed to determine which approach should be used to assess a safety signal. Surveys can be quickly conducted but the validity of subject responses may be questionable, and sufficient response rates can be difficult to achieve. Registries can be very expensive, take much time to develop, and are usually of very limited use. The FDA should include some discussion about, or point to a document that discusses, the strengths and weaknesses of each method of data collection that is suggested for consideration.</p>
IV.G.1.	399-400	Add “...or may be at best gross estimates, with significant imprecision” to the statement.

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IV.G.	408-423	There is a wide difference between reporting rates during the product’s life cycle. FDA should clarify how these crude reporting rates impact the risk-benefit and how the variation in reporting rates over the product’s life cycle should be taken into account.
IV.G.	410-415	<p>Sponsors usually perform safety analyses using fully integrated global data sets. Performing region-specific (e.g., US only) analyses adds a layer of complexity to these analyses and opens up the possibility for inconsistent results. In addition to complicating the preparation of regulatory reports, there is the possibility of different regulatory agencies receiving different views of the product’s safety.</p> <p>The guidance document should follow the same approach for estimating exposure as outlined in the CIOMS V document, namely:</p> <ul style="list-style-type: none"> <li>• total quantity sold (e.g., kg, liters)</li> <li>• # of packages sold (e.g., boxes, bottles)</li> <li>• # of units sold (e.g. tablets, vials)</li> <li>• # of prescriptions or treatments</li> <li>• # of patients</li> <li>• person-time: treatment-months, person-months, person-years (incidence density)</li> <li>• Defined Daily Dose (DDD)</li> </ul> <p>The unit for reporting rates should be determined on a case-by-case basis. For example, person-years are commonly used to describe exposures for chronic diseases. The # of prescriptions may be more appropriate for infectious diseases. The DDD, as suggested as a standard unit by the WHO, is used for assessing market penetration of a drug and for making comparisons between countries.</p> <p>In non-US countries, the patient-level estimates are seldom available. Often, it is not feasible to provide an estimate of national patient exposure. We do not collect patient-level data, the best we have is prescription data.</p>
IV.G.	412	<ol style="list-style-type: none"> <li>1. We propose to add patient exposure time in addition to the number of patients exposed to the product. In many situations we are unable to estimate the number of patients; therefore adding patient exposure time (e.g. treatment days/months/years) could be valid.</li> <li>2. Please specify what methods are implied in the phrase “whenever possible.”</li> </ol>
IV.G	417-423	We request that the inadvisability of using information from spontaneous

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		reporting systems for comparisons of drugs is stated more strongly in the guidance. Comparisons of drugs or drug classes based solely on data mining computations carried out using data from these databases are scientifically invalid and should not be performed regardless of the caveats that might accompany such analyses.
V.A.	490	<ol style="list-style-type: none"> <li>1. We suggest substituting “virtually always” for “may,” since it is a virtual certainty that pharmacoepidemiologic studies are more difficult to interpret given the inherent biases, etc.</li> <li>2. The value of observational studies that do not have huge sample sizes should also be acknowledged.</li> <li>3. Because of inclusion/exclusion criteria that may affect size, clinical trials can also be biased and confounded.</li> <li>4. The difference between confounding and effect modification should be explained.</li> </ol>
V.A.	491-493	<p>The last sentence of the paragraph should be entirely deleted.</p> <p>While a large sample might overcome some of the problems associated with pharmacoepidemiologic studies, other problems of confounding and bias might in fact be made worse, as the larger sample might imply significance and give greater credence to the flawed results (e.g. HRT studies).</p>
V.A.	511	Although it may be ideal to conduct more than one study, this is often not feasible. In the instance of a rare or very rare event, and when medical records are needed to validate the data, the options for conducting even a single safety study are very limited.
V.A.	554	<p>“Highly recommended for most” should be replaced by “recommended for some.”</p> <p>The medical record abstract is only needed if the diagnosis is ambiguous. Requiring that the patient have two or more diagnostic codes or other supportive diagnosis or procedures codes may also be an effective approach to classifying a patient correctly. This argument is particularly valid given the option offered in the guidance to use surveys (which may have problematic validity given errors in memory) to assess safety signals from either patients or physicians.</p>
V.C.	564	The CIOMS V Working Group recommended that the term “registry” be reserved for inventories of case information collected without an <i>a priori</i> research hypothesis, but held in reserve for future possible study and analysis. If this recommendation were included in the definition of a

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		registry, it would help to clarify the difference between a registry, an observational study, and a survey.
VI.		We agree that FDA should receive findings from pharmacoepidemiology studies. However, the FDA should recognize that, in most instances, findings from these types of studies are not available until a year after the product is marketed. Enough patients must be prescribed the product and the data have to be available in an accessible data set before an analysis occurs. Also, patients may have to be followed over the course of many months to determine whether an adverse event has occurred. The penetration of the product into the market, the identification/negotiation for the data, and the follow-up itself delays the initiation of the analysis plan.
VI.	637	Use of causality algorithms in interpreting a single case is likely to lead to misinterpretation because of the inadequacy of spontaneous report data. It becomes almost impossible to rule out the possibility that the suspect drug may have contributed to an adverse experience. Thus, most adverse experiences at the individual case report level end up with a possible association. Except for cases involving a positive rechallenge, there is little benefit in performing causality assessment on individual case reports. Although a number of cases could form a hypothesis in the association between an adverse experience and drug exposure, there is no reliable and reproducible methodology determined for individual causality assessment. Thus, causality assessment of the individual case is likely to be misinterpreted.
VI.	638	After a signal has been identified, what does data mining add to further characterize the signal? We suggest explaining or deleting this statement.
VI	645	We request that the phrase "...all available safety information and analyses performed" is qualified by the word "relevant."
VI.	663	The statement "General marketing experience with similar products in the class" is too vague. Please define what is meant here – an assessment of the label of similar products, published literature on similar products, or something else.
VII.5.	724	This sentence could be expanded by making reference not only to the range of population but their overall health and medical need (lower threshold to implement a pharmacovigilance plan in primary prevention population than in population at high risk with substantial need).
VII.	727-728	The footnote is inconsistent with the text. We suggest using consistent language (i.e., either performance linked systems or controlled access

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		systems throughout the documents).
VII.	756-761	The examples listed are databases, and are not designed or intended to be adverse event collection mechanisms. We currently do not have the type of access to these systems that would be needed to use the data for surveillance purposes.