AstraZeneca

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

Re: Docket Number Docket No. 00N-1484, CDER 199665
Response to FDA Call for Comments
Safety Reporting Requirements for Human Drug and Biological Products;
Proposed Rule

Dear Sir or Madam:

Reference is made to the Friday, March 14, 2003 (Vol. 68, No. 50) Federal Register announcing the request for comments on Safety Reporting Requirements for Human Drug and Biological Products.

AstraZeneca has reviewed this regulation, and our comments are attached.

Please direct any questions or requests for additional information to Janet Steiner, Senior Director, Safety Compliance, US Drug Safety, AstraZeneca LP, at 302 885 1265.

Sincerely,

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Enclosure

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00N-1484

AZ-119

10/13/2003

Proposed Rule:

Safety Reporting Requirements for Human Drug And Biological Products

General Comments

The FDA has stated that the purpose of the proposed rule is to make it easier for them to identify potential problems during clinical trials and post-marketing, to strengthen its role in managing risks of medical product use, and to harmonize with ICH. The following general comments describe our concerns that these new regulatory requirements will not only fail to accomplish these objectives, but may, in fact, add major obstacles to achieving these goals.

Comment 1: The proposed definition of Suspected Adverse Drug Reaction (SADR) is inconsistent with ICH guidelines and will negate the value of distinguishing between adverse events and adverse drug reactions.

Given that the FDA was a signatory of the ICH E2A guideline, the definition of an adverse reaction should, wherever possible, be a complete match of that presented within the ICH E2A guideline unless, of course, the post-marketing situation warrants specific variation. Therefore, we would like to see the definition of an adverse reaction encompass all of the concepts presented within ICH E2A.

As presented, the emphasis is such that an adverse event (AE) would be considered as an adverse drug reaction (ADR) unless the relationship "cannot be ruled out". This is not a balanced representation of the ICH concept in this regard, in that there is no mention of the other key ICH E2A concept, namely that the expression "reasonable causal relationship" is meant to convey that there are facts (evidence) or arguments to suggest a causal relationship.

This is a critical issue, especially if the FDA is serious in its intent to harmonize its requirements with other ICH regions. For example, within the EU, the Clinical Trials Directive ADR Reporting guidance document clearly indicates that that the expression "reasonable causal relationship" means that there are facts (evidence) or arguments to suggest a causal relationship.

If the safety rule does eventually support the notion that a causal relationship exists simply if "*the relationship cannot be ruled out*", then the consequence would be that any adverse event that has a temporal relationship to administration of a drug should then be regarded as a suspected adverse reaction, given that a temporal relationship inevitably means that the role of the investigational product in the causation of an adverse event cannot be totally excluded. In practice, this would mean that virtually all reported adverse events would then be regarded as suspected adverse reactions, thereby completely negating any value in the distinction drawn between an adverse event and an adverse reaction.

It is more appropriate that the rule supports the concept that there is a reasonable possibility of a causal relationship if there are positive reasons for such a judgment rather than on the basis of simply being unable to totally exclude a drug's role.

Comment 2: The proposed definition of SADR will make it harder, not easier, to identify potential safety signals.

The FDA has indicated that it intends to use the additional information generated by these new reporting requirements to identify safety signals that will allow them to recommend/require labeling changes, request issuance of Dear HCP letters, or in certain cases, request/require the withdrawal of a drug. However, the proposed lower threshold for reporting AEs (SADRs) will result in a significant increase in the number of reports that the FDA will need to review and interpret. The phrase used in the proposed rule ("cannot be ruled out") is overly broad and will include cases where disease progression was the true cause of the AE. This will be of particular concern in the oncology area, where it is already difficult to differentiate between "SADRs" possibly caused by the drug and those that occur as a result of the disease. In short, this initiative is counter to FDA's initiatives around risk management (real and verifiable signals) and will "de-sensitize" (eg, make it difficult to determine what is real and what is artifact) and may result in inappropriate actions, or labels that provide no value to the physician.

It is quite possible that this initiative will have the opposite of its intended impact, and certain legitimate safety signals will be lost in the large number of additional reports that will be received as a result of the lower threshold for reporting extraneous data. It is not clear why the current regulation (that allows the investigator treating the patient and the sponsor who has the most in-depth knowledge about the drug to make a judgment as to whether the SADR is reasonably related to the drug) is not still a valid approach.

The increase in amount and type of reporting (eg, expanding the number and type of data sources used) is likely to add considerable noise to the identification of possible SADRs. In the proposed rule there is no discussion surrounding the additional time that will be required to investigate this increase in false positive associations, where a drug appears to be causing an adverse event, even

though, in fact, it does not. This is especially true for rare events. Even if a test has 99% sensitivity and specificity, a "positive" test will only amount to nine occurrences out of every one hundred events for those occurring at the rate of one in a thousand in the population, so there is still little chance of actually seeing the event. The lengthy in-depth investigations needed to rule out the increased number of false positive associations will take away resources from other safety surveillance efforts and potentially lead to a delay in identification of real signals. How will FDA address the high false positive rate that will be generated by these proposals?

Comment 3: The proposed changes in causality assessment will result in an increased volume of reports but these will have decreased informational value.

For example, in an investigational trial, a serious adverse event (SAE) is reportable as an expedited report when the event satisfies one of the serious criteria, is unexpected and is at least possibly causally related. If the causality assessment rules are changed so that an event is related unless the investigator can rule out any relationship with certainty, all events that an investigator would have previously considered unlikely related, will now be reported as possibly related, and thus be reportable as expedited reports. One could argue that the number of times that an investigator could rule out a causal relationship with absolute certainty may approach zero. The number of expedited reports will now have to increase. Not only will the volume of reports increase, but also their intrinsic value as a source of information for investigators/clinicians, as well as their value for the protection of patient safety, will decrease. Presently, the reader can at least obtain from the report the investigator's opinion regarding the causal relationship between the investigational product and the event and thus assign a ballpark probability regarding the likelihood of the suspect agent to cause such an event again in the future. If the proposed change occurs, then the reader will no longer be able to make this assessment because ALL reports will be listed as possibly related, both those that the investigator suspects are related and those that the investigator suspects are unrelated. The impact of each report on other investigators will decrease because the reports will all be listed in the same fashion. Ultimately patient safety may suffer, as the investigators' sensitivity with respect to linking the investigational agent to a potential adverse effect will decrease.

Another example of the proposed increased expedited reporting requirement that may result in decreased patient safety is the Always Expedited Report. If certain events are always reported regardless of the investigator's assessment of the relationship, then the sense of urgency associated with the report is diminished, ultimately leading to a decreased sensitivity as noted above.

Comment 4: Increasing the volume of information received will be ineffective without ensuring timely and appropriate responses to the information.

One could argue that the issues that resulted in the recent withdrawal of several drugs were not due to a lack of knowledge of certain "signals", but the lack of a rapid, focused response to this knowledge by FDA and sponsors. While it is clear that these proposals will result in an increase in the number of expedited reports submitted to FDA, it is not clear how this will promote appropriate and timely action. Increasing the size of the haystack requires qualitative improvements in the search for the needle. To understand fully the benefit/cost and optimize the data collection process, we think that it is extremely important for FDA to share detailed and comprehensive analysis strategies in addition to the new data collection strategy. What plans does the FDA have for improving review processes so that the Agency can better identify safety signals from the increased number of safety reports?

Comment 5: The new proposals are not appropriate for mature marketed products whose safety profile is already well characterized.

While we generally agree that adverse event (AE) reporting should be consistent regardless of whether a particular drug product is subject to the NDA, ANDA or other regulations (grandfathered drug products, etc), some of the new proposals, such as those requiring aggressive follow-up through active query and always expedited reporting of certain events, should not be applied to all drugs because these would result in little or no appreciable additional benefit to the health and safety of the public. While some of these actions may be appropriate to a newly marketed drug, or an established drug that has just received a new indication that could substantially change the population exposed to it, imposing these same rules for AE reporting for drugs that have well-characterized safety profiles based on extensive usage over many years does not seem to be an efficient use of resources.

Comment 6: While this proposal will increase the reporting burden for in vitro studies, this will not necessarily improve the quality of safety assessment, and may, in fact, make it worse.

The results of in vitro tests are often not interpretable when they are generated in terms of their clinical significance or value for benefit-risk assessment. Under the current regulations, we have always reported certain in vitro findings, e.g., those related to mutagenicity or carcinogenicity, which are known to be associated with increased risks.

Expanding the type of in vitro test results that qualify for expedited reporting will result in many reports of findings for which there is no knowledge of clinical significance or risk. If the Agency and investigators are deluged with expedited reports that seem to have little apparent relevance to clinical safety, then the net effect will be to add burden to the reporting organization without benefit to FDA, the clinical investigators, or, ultimately, to the patients. Additionally, it will dampen the impact of a truly significant non-clinical in vitro finding.

For example, when comparing in vivo versus in vitro studies, one has to consider their relative contributions towards assessing mechanism of action and biological or clinical significance. Studies in animals are considered as a "blunt instrument" to detect overt toxic changes (e.g., death, noticeable effects such as a hole in the heart in a teratology study, etc.), with results implying it is a "bad thing." By way of contrast, in vitro studies represent a significant portion of non-clinical studies and are much more finely tuned with respect to demonstrating toxic endpoints. With increasing complexity of the model (progressing from in vitro/subcellular systems to whole conscious animals), there is a decrease in informational content relating to mechanism of action. On the other hand, the amount of information obtained in regard to clinical significance will increase as one progresses from in vitro/subcellular systems to whole conscious animals. Therefore, for in vitro results, analyzing the information over time will lead to a linkage of observations with clinical significance. Reporting of in vitro test results in an expedited fashion (eg, 15 calendar days, as proposed) would not be useful for this purpose.

Comment 7: The new reporting requirements for epidemiological studies and databases will add considerable noise to the system without providing any real value in discovering drug-related adverse events.

In the past, associations between drugs and adverse events discovered in aggregate data have not been reportable because they did not meet the criteria of an identifiable patient or an identifiable reporter who has made a causal connection. When we look at large numbers of individuals in the aggregate, we find a wide array of events that can occur, the vast majority of which have nothing to do with the drug. Unless there is some reason to connect the drug to the event (previous suspicion, biologic plausibility, increased relative risk, etc), reporting these associations will just add considerable noise to the system without providing any real value in discovering drug-related adverse events.

The requirement for post-marketing safety reports to include reports created by epidemiological data bases would imply that we would actually have to explore thoroughly each database that we have access to for any associations between SADRs and the drug in question. This would be extremely burdensome as these data sets don't conform to any fixed standard and they usually were not designed for this type of investigation. The alternative is that companies would shun access to the database and thereby shut down legitimate research.

Further, the requirement that manufacturers submit any information that would suggest changes in product administration implies that if a sponsor has access to aggregate or epidemiological studies there would be a requirement to analyze these data. Obviously, data quantity increases as time from launch increases and so this requirement would result in providing more information on older products, whose safety concerns are already on their way to being well understood.

Additionally, it is unclear from the proposal as to the exact criteria for determining what studies or databases would need to be reported: health economics and patient outcomes-type database studies, managed care databases, etc. The agency estimates that about 300 reports would be received per year but this will be much higher if the inclusion requirements for epidemiologic studies and databases are taken at their most liberal. This increase in reporting burden to the industry is not reflected in the agency's analysis of burden.

Comment 8: By deviating from the globally accepted ICH E2C guideline for production of Periodic Safety Update Reports, the proposal jeopardizes the consistency of safety information relayed to worldwide regulators.

AZ currently produces one global PSUR document for each product, and handles US specific requirements with the addition of a small number of appendices. This ensures consistency of safety information relayed to worldwide regulators. This approach has previously been acceptable to FDA, a stance that is reiterated on page 12412 of this proposal where it is stated that "The PSUR recommended for post-marketing periodic safety reporting in the ICH E2C guidance provides regulatory authorities with a comprehensive overview of the safety profile of a product along with other relevant information such as estimates of worldwide patient exposure and worldwide marketing status of the product." If the information is comprehensive, then why is the FDA requiring so many additional appendices that are not required by other regulators?

The new appendices and new reports represent a duplication of current work, with dubious benefit, as most of the information is already provided in the current global PSUR document. The new requirements will result in the irregular generation of PSRs (i.e., PSURs, IPSRs and Semiannual Submissions of ICSRs) at varying times that are not harmonized with the rest of the world. Additionally, consistency of data interpretation as well as global compliance will be compromised by the fluidity of frequently resetting reporting frequencies.

We also request that this proposed rule be amended to include the recent recommendations of the ICH E2C guidance addendum intended to improve the PSUR process. FDA was an active participant in the ICH expert working group that authored this addendum, and FDA also agreed that the addendum could proceed to the final approval phase in the ICH process. We would also suggest that, in the spirit of global harmonization, it would be more appropriate for the FDA, as a member of the ICH E2C working group who approved the existing format, to work through this international group to harmonize collection of the additional data (information on medication errors, resistance to antimicrobial drug products, etc.) it believes would add value rather than just impose unilateral requirements through this proposed rule.

Comment 9: This proposal will force sponsors to establish Data Monitoring Committees for the majority of clinical studies, imposing an additional burden and cost to the drug development process that may result in higher costs for marketed drugs.

The lower threshold for AE reporting in clinical trials will greatly expand the number of events that require unblinding for regulatory reporting purposes. This will have a number of statistical and clinical implications and may result in a trial that does not have the power to meet its objectives.

To avoid unnecessary unblinding, it would be necessary to have data monitoring committees (DMCs) for studies that are expected to have large number of SADRs. They would perform the unblinded review and make the determination of what should be sent to the FDA for review. This would help preserve the integrity of blinded studies, but at an additional cost and burden to the drug development process. Without DMCs, sponsors could be forced to unblind a majority of patients experiencing SADRs for regulatory reporting purposes, thus compromising the statistical integrity of blinded trials. Unblinding a majority of patients will require an increase in sample size to compensate for this and lengthen the timeline for new product development. Not only will this delay delivery of new products to patients, but this will also affect a patient's eligibility to continue in trial, once they have been unblinded for regulatory reporting purposes, as regulations currently require that investigators receive copies of the unblinded expedited reports sent to FDA. This will also impact the number of patients required to prove hypotheses in order to control for potential impact to bias, since a sponsor would have to plan for a large number of patients to be withdrawn from the study due to unblinding for regulatory reporting purposes. This could be especially problematic when the available patient population is limited.

Comment 10: The proposed active query requirement will result in additional burden and cost to the healthcare delivery system with relatively little added benefit to patient safety.

We do not believe that active query as defined in this proposal (eg, a phone call to the reporter by a healthcare professional) is necessary for every SADR (suspected adverse drug reaction). This would result in thousands of phone calls to physicians, pharmacists, nurses, and other healthcare professionals (HCPs) who have reported non-serious and/or expected SADRs with very little added value. We feel it is more appropriate and less burdensome to reserve this effort for serious unexpected SADRs (since these are the ones subject to expedited reporting), and for some expected serious SADRs where there are medically valid reasons for aggressive methods of follow-up.

We are concerned that the active query proposal will result in a decreased willingness of HCPs to report adverse events to industry. According to our sales force, HCPs are already hesitant to report adverse events due to the current follow-up practices by the industry (e.g. letters and telephone calls) in exercising their due diligence obligations, and view this as a burden they can ill afford in the current practice environment. The requirements for active query phone calls for every SADR (including non-serious and labeled events) will wreak havoc with busy physician offices and healthcare institutions.

Active query will also be difficult to accomplish on a global level due to language and logistical differences, as well as cultural differences related to medical treatment and diagnosis. In addition, adverse event reporting is not exempt under data privacy laws in Europe as it is in the US, which will make active query there extremely difficult to achieve.

Comment 11: The proposals are inconsistent in describing the roles of licensed physicians and other healthcare professionals in protecting patient safety.

FDA stresses the value and importance of health care professionals in several of the new proposals, such as requiring a licensed physician to review cases, requiring that this physician is identified on every submitted report, and requiring that health care professionals conduct active queries. However, this would seem to be in conflict with an apparent distrust of medical judgment as evidenced in other proposals, such as not allowing investigators to rule out a possible causal relationship with the drug even if, in their judgment, the event was due to disease progression, not allowing medical judgment of expectedness by requiring reporting of certain labeled events to be always expedited. Additionally, if the FDA believes, as stated on page 12413, that "licensed physicians would ensure submission of high quality reports to FDA that articulately conveys all clinically relevant information associated with an SADR" why has the Agency imposed the new requirement that hospital discharge records, autopsy reports, and death certificates must be submitted for all reports of SADRs that result in hospitalization or death? The implication is that the Agency needs to confirm the quality of the licensed physician's reports, which seems to contradict the quote provided. These documents have always been sought and actively collected by companies, and made available to FDA upon request. The administrative burden of providing these as attachments to reports would seem to add little value.

Comment 12: The proposed changes will increase, not decrease, the reporting burden on industry.

The FDA also states that one rationale for the proposed changes is "to eliminate unnecessary reporting burdens on industry so that companies can focus on the safety profiles of their products and not on the different reporting requirements of different regions." However, the proposal adds several new types of expedited reports (potential medication errors, actual medication errors, always expedited events), several new types of reports at other various intervals (30 calendar day follow-up reports, 45-day reports for cases with unknown outcome, TPSRs at 5, 7.5, 10, 12.5, and 15-years post US approval, IPSRs 7.5 and 12.5 years post- US approval) that have no counterpart in regulatory requirements for other regions. Additionally, by lowering the causality threshold of "reasonable possibility" to "cannot be ruled out," the proportion of reports from clinical studies that will require expedited reporting will increase significantly, in our estimation, from 20% of cases in a clinical study to 80 to 90% or more. It is not clear how these new measures will decrease the reporting burden on industry.

Comment 13: FDA's proposed mechanism for amending the list of SADRs subject to always expedited reports is contrary to the Administrative Procedures Act (APA) and FDA's own regulations.

FDA proposes to require always expedited reporting for "[a]ny other medically significant SADR that FDA determines to be the subject of an always expedited report." 68 Fed.Reg. at 12474 (Proposed 21 C.F.R. §310.305(c)(2)(iv)(19)). FDA states that "[n]ew SADRS that become the subject of always expedited reports would be included in the agency's current guidance for industry on post marketing safety reporting for human drugs and licensed biological products." 68 Fed.Reg. at 12432. This proposed mechanism is entirely improper and contrary to both the Administrative Procedures Act (APA) and FDA's own regulations. A rule requiring always expedited reporting for a SADR not previously subject to always expedited reporting would create new legal obligations for companies subject to FDA's reporting requirements and thereby constitute a legislative rule, not an interpretative rule. *See Chemical Waste Management v. EPA*, 809 F.2d 1526, 1534 (D.C. Cir. 1989). As a legislative rule, notice-and-comment rulemaking is necessary. Additionally, FDA's proposal to identify additional SADRs in a guidance document is contrary to the Agency's regulations regarding the non-binding nature of guidance documents. FDA's good guidance practice rules specifically state that "[g]uidance documents do not establish legally enforceable rights or responsibilities." 21 C.F.R. §10.115(d)(1). Thus, it is impermissible under both the APA and the Agency's own rules to amend the list of SADRs subject to always expedited reporting through guidance on postmarketing safety. Proposed 21 C.F.R. §310.305(c)(2)(iv)(19) should be amended to make it clear that FDA will only impose always expedited reporting for additional SADRs after conducting notice-and-comment rulemaking.

Specific Comments

Page Number	Section Number	Specific Comment Number	Comment or proposed replacement text
12409	Preamble	1	The Addendum to ICH E2C (now designated as ICH-A), currently at Step 4 of the ICH process, should be implemented in the final rule. All of the recommendations included in the Addendum, such as use of summary bridging reports, including an executive summary, use of the version of the reference safety information in effect at the end of the reporting interval and other concepts not previously addressed by E2C, should be adopted. This would improve the PSUR process and will be consistent with FDA's stated goals for global harmonization.
12412	II.B.1	2	The agency is requesting appendices to PSURs, including "US labeling, information on medication errors, resistance to antimicrobial drug products and class action law suits." Please clarify whether appendices other than the US labeling appendix should come from all sources, or if all of these appendices should come from US sources only.
12412, 12413	II.B.1	3	An unintended potential impact of this ruling would be the additional administrative burden on all clinical trial investigators to manage the increase in written IND safety reports resulting from the change in reporting requirements. The logistical challenges of interpreting the increased volume of safety data would likely compromise the ability of investigators

			and IRBs to protect the safety of human subjects in clinical trials.
12413	II.B.2	4	The FDA states that "many of the post-marketing safety reports that FDA receives are complete and of very high quality. Others are incomplete, of mediocre or poor quality or both." We would like to suggest that, rather that addressing this problem by amending safety reporting requirements that impact all companies, even those who submit good quality reports, FDA address this issue with the individual problem manufacturers through its robust inspection process and powers of enforcement.
12413	II.B.2	5	The FDA proposes to require that a licensed physician at the company be responsible for the content of post-marketing safety reports submitted to the FDA, and indicates that having clerical personnel with no healthcare training prepare and submit reports is an unacceptable practice. <u>Question 1:</u> If only a physician can be responsible for the content, does that mean the manufacturer cannot use clerical staff to prepare cases? As a global company with a large volume of reports, we have found that better quality and efficiency is often achieved with case data entry performed by skilled clerical personnel. While a physician typically performs review of serious cases, in our experience other healthcare professionals are quite capable of this task. For example, a dentist is probably even better able to assess issues with dental products than a physician. <u>Question 2:</u> Please clarify the requirement for "licensed" physician. Are foreign

			licenses acceptable? Must the license remain current at all times? <u>Question 3:</u> Does this requirement only apply to post marketed reports, and does it apply to non-serious as well as serious cases? We would question the added value of having a licensed physician review individual non-serious and expected reports. We currently have a licensed physician conduct a medical review of all individual serious reports, but physician review of non-serious cases is done via a summary format, such as a monthly line listing. <u>Question 4:</u> We request clarification regarding the requirement to have the name of the licensed physician responsible for the content and medical interpretation of the data identified within each individual report. This is logistically difficult for large global companies, where different physicians in different countries may review the initial and subsequent follow-up reports. • In that situation, who is the responsible physician? • Should the contact name be changed with each follow-up report? • If the physician leaves the company, who assumes responsibility for the content? • What are the consequences, both from a regulatory and legal standpoint, of that responsibility for content?
12414	II.B.3.b	6	"Unexpected SADR with unknown outcome" is defined as an SADR for which a determination of serious or non-serious cannot be made. The use of the word "outcome" in this context is confusing and is not consistently applied to mean serious versus non-serious. The use of the word "outcome" may also refer to patient outcomes other than the regulatory serious criteria

			(improving, recovered, etc.). We suggest that an alternative word be used other than outcome since this could be confused with clinical outcome of the patient. FDA states that it intends to compare information on the unexpected SADR with unknown outcome with information on other similar unexpected SADRs with known serious outcomes that are on file with the agency. Will the FDA provide the results of their analysis back to the manufacturer? We would like to be included on this comparison of data and given the opportunity to comment.
12418	III.A.1	7	Defining 'reasonable possibility' as "relationship to the drug cannot be ruled out" removes any scientific or medical assessment based on relevant factors such as knowledge of the patient, knowledge of the drug, knowledge of the disease, biologic plausibility, alternate cause, temporal relationship, or class effects, among others, which might support a causal relationship between the adverse event and the drug. This is a deviation from the ICH guidance on Clinical Safety Data Management: Definitions and Standards for Expedited reporting, which states in section III: "reasonable causal relationship is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship." This will also increase the number of false positives that will require active investigation in order to make an accurate causality assessment. Sensitivity will be increased, but specificity will be decreased, increasing the noise to signal ratio.
12418	III.A.1	8	The proposal that SADRs are subject to expedited reporting if the causal relationship cannot be ruled out (with the example given that even disease progression cannot be ruled out) will result in an exponential increase in

			expedited clinical trial reports (in our estimation, from approximately 20% to 80 or 90% or more of all reported SAEs in a clinical trial). Asking investigators to "prove a negative" on a drug still under investigation will lead to a default "everything is related" assessment, since the investigator will be forced to disregard his own medical judgment. Causality assessment has always been an imperfect science, but, in the pre-approval environment, while much of the information regarding the safety profile of the drug is still unknown, it has previously been an acceptable practice to prioritize SAEs for expedited reporting, since all SAEs will be analyzed and reported in IND annual reports as well as in the clinical study report. If the FDA is determined to make this change, we would suggest that the standard for expedited reporting be harmonized with that of the spontaneous SAE – that there is an automatic implied causality; so all serious unexpected events are subject to expedited reporting. The end result will be nearly the same, and this will relieve the investigators and the study sponsors from collecting a data point (eg, causality) that FDA apparently feels does not add value.
12419	III.A.1	9	The "disclaimer" provided in the current regulations is of little value in protecting manufacturers against the misuse of SADR Reports in product liability suits. Such statements are insufficient to describe FDA's position that SADR Reports should not be misused in product liability suits, and thus FDA should adopt a new rule clarifying its position and prohibiting the misuse of SADR Reports.
12419	III.A.1	10	Requiring licensing partners to exchange safety information within 5 calendar days, especially in situations where multiple partners have complex multinational agreements across many countries and time zones, may result in poor quality reports, since this will only allow sufficient time

			for forwarding raw source data, with no time for active query or translation. Please confirm whether the 15-day regulatory reporting timeframe does or does not includes the 5 calendar days allowed for exchange of safety information with contractors.
12420	III.A.1	11	Could the FDA please clarify and expand on the definition of "full data set?" We feel that a "full data set" should be identifiable by specific data elements outside of any form structure. Otherwise, how does one determine the "applicable elements" of a MedWatch or CIOMs reporting form? Obviously this can vary widely according to the nature of the case. Is it acceptable for the reviewing company physician to determine the applicable elements? Additionally, having multiple full data set standards for data collection (such as using the MedWatch as the standard for domestic reports, and the CIOMs form as the standard for foreign reports) will cause much confusion. For example, which standard should be followed for expatriates or visitors? This will also potentially lead to gaps and discrepancies in the safety databases of global companies, since the fields of these two forms are not the same. Using two different paper forms as standards for data collection based on the geographic location of the patient will also be problematic for electronic reporting, which is based on ICH E2b data standards intended to promote global harmonization and consistency, regardless of the origin of the report.
12420	III.A.1	12	Currently, like many companies, we have a call center staffed by healthcare professionals who are trained in adverse event identification and collection. Every effort is made to collect as much information regarding adverse

			events at the time of the initial report. We utilize written requests as well as telephone contacts to obtain additional information that is needed. However, we do not believe that active query as defined in this proposal (eg, a phone call by a healthcare professional) is necessary for every SADR (suspected adverse drug reaction). This would result in thousands of phone calls to HCPs who have reported non-serious and/or expected SADRs with very little added value. 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 HCPs 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 HCP 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. We would also ask for clarification around whether active query must be performed with consumer reporters who will be unable, in most instances, to provide a full data set. We typically contact consumers to ask for authorization to contact their treating physician. If the consumer refuses permission, we honor their request. We always maintain full records of our due diligence attempts; we see little added value in having to send an expedited report to the FDA to report this. We would also request clarification of the definition of HCPs who are supposed to perform active queries. What does "some form of health care training" (especially in a global context) include? If a truly focused line of questioning is utilized, as proposed, is it really necessary for the person to be a healthcare professional? In our experience, we have not found this to be necessary to produce high quality reports.

			Additionally, the Agency has overlooked a very important exception for cases where the filing of a lawsuit or the receipt of a demand from an attorney is the initial report of an SADR, in which case it would neither be practical nor feasible for a company HCP to contact the reporter for additional information associated with the drug product and the SADR. We propose that an exception for cases where the initial report is a lawsuit or the receipt of a demand from an attorney should be added to this section of the proposed new rule.
12421	III.A.1	13	We welcome the differentiation between spontaneous and solicited reports. However, since solicited reports require causality to determine reportability, we would point out that, due to the nature of many of these programs (e.g. patient support programs, disease management programs, patient registries), it is extremely difficult to get causality from the treating physician. Currently, the reviewing company physician will determine causality, in the absence of the treating physician assessment, until additional information is received, although, in our experience, it is often very difficult to get additional information from the treating physician. In addition, many programs will purposefully keep the consumer or patient anonymous, making follow-up impossible. Often the AE information is an 'incidental' finding and not the focus of the program, therefore, follow-up is even more difficult. For example, when the company attempts to contact a patient, via letter, to renew their participation in a Patient Assistance Program, the company may receive a letter indicating the patient has died. The data set is thus limited to patient, drug, and death cause unknown. This is common for our company due to our oncology products. The outcome of this will be a default of a positive causal relationship because we will not have adequate information to rule it out. When we sent such cases as expedited reports in the past, we were asked by the FDA not to send these reports in an expedited manner, because they did not add value, but rather to report them via the periodic safety update report instead. The new proposal would seem

			to reverse FDA's previous guidance.
12421	III.A.1	14	We agree that "spontaneous report' should not be defined to include information compiled in support of class action lawsuits and accordingly, support the exception for class actions proposed by FDA, i.e., that manufacturers and applicants should not submit SADRs from class action lawsuits in an expedited report. We see no reason to limit the exception to class action lawsuits, however, as the same rationale for allowing class action lawsuit SADRs to be filed on a periodic basis applies to all lawsuits alleging personal injury from exposure to a drug. We recommend that FDA permit periodic reporting of any SADR that arises from a "legal" origin, i.e., any SADR that is reported to the company via a lawsuit or contact from an attorney representing a patient who was allegedly exposed to a drug.
12421 12472 12487	III.A.8 310.305a 600.8a	15	We would like guidance/clarification of medication errors versus variations in standards of practice and off-label usage: For example: • A medication is labeled for use on a monthly basis. An individual physician intentionally decides to administer the medication again in 2 weeks (as a loading dose) rather than wait 4 weeks. Is this a medication error? • The correct medication is administered via an IM injection (the correct route of administration) to an appropriate but obese diabetic patient, resulting in a subcutaneous injection with resulting necrosis at the injection site. While this would be reportable as an SADR, can FDA comment on whether this example would also be considered a medication error?

12422 12472 12487	III.A.8 310.305a 600.80a	16	We would like clarification about the classification of medication errors, as the proposed rule appears to contain multiple definitions. • Actual medication error (proposed rule): A medication error that involves an identifiable patient whether the error was prevented prior to administration of the product or, if the product was administered, whether the error results in a serious SADR, non serious SADR, or no SADR. • Potential medication error (proposed rule): "An individual case safety report of information or complaint about product name, labeling or packaging similarities that does not involve a patient." • Page 12422, III.A.8, 1st column of the proposed rule also states: "Potential medication errors do not involve a patient, but rather describe information or complaint about product name, labeling, or packaging similarities that could result in a medication error in the future." We have concerns that these variances in definitions may cause confusion, especially as FDA has previously recommended to industry on a number of occasions that the Taxonomy provided by the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP), is used for classification of medication errors, as listed below: **31 NO ERROR** **31.1 Category A** Circumstances or events that have the capacity to cause error **32 ERROR, NO HARM** [Note: Harm is defined as temporary or permanent impairment of the physical, emotional, or psychological function or structure of the body

			and/or pain resulting therefrom requiring intervention.] **32.1 Category B** An error occurred but the error did not reach the patient (An "error of omission" does reach the patient.) **32.2 Category C** An error occurred that reached the patient, but did not cause patient harm 32.2.1 Medication reaches the patient and is administered 32.2.2 Medication reaches the patient but not administered **32.3 Category D** An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm **33 ERROR, HARM** **33.1 Category E** An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention **33.2 Category F** An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization **33.3 Category G** An error occurred that may have contributed to or resulted in permanent patient harm **33.4 Category H** An error occurred that required intervention necessary to sustain life **34 ERROR, DEATH** **34.1 Category I** An error occurred that may have contributed to or resulted in the patient's death.

			Several companies are currently reporting medication errors according to these categories either at the specific request of FDA or as part of a Phase 4 commitment to FDA. We would like to request that FDA please align the medication error definitions in the proposal with the NCC MERP definitions so that these previously established reporting requirements may continue without interruption and confusion, with a resulting potential for non-compliance. With regard to medication errors reported in the medical and scientific literature, we request guidance on reporting requirements for lists of "confusing name pairs" compiled by authors to illustrate look-alike or sound-alike drug names. Extensive tables of similar looking or sounding drug names have been compiled, and these lists are frequently published in the literature. Does FDA consider these to be reportable as NCC MERP Category A medication error reports? Sponsors are interested in knowing whether FDA has plans to educate health care providers on the importance of providing more complete information for both medication errors and SADRs. Regarding reporting of medication errors, please clarify reporting of domestic (US) medication errors only as opposed to those from international sources. The term domestic is used in some instances but not in others in the document. For trademark-trademark confusion in particular, all reports should be for the US only given the complexity of global language and pronunciation differences and different marketed products. We request that reported medication errors should be verifiable as to specific circumstances surrounding the error, including an identified health care professional to whom sponsors can speak. Such verification will assure that unsupported or erroneous reports would not lead to a requested change

			to the trademark. Can FDA please comment on medication error verification? When medication errors are reported directly to FDA, as is often the case, sponsors need access to this information quickly in order to take appropriate action to protect patient safety. The current mechanisms available to sponsors, eg, the FDA's MedWatch to Manufacturer Program and the FDA's Freedom of Information database, lag months behind the time the reports are received. However, there is no alternative provision stated in this proposal. Can FDA please comment on its plans to provide sponsors with copies of MedWatch reports of medication errors in an expedited fashion to help us in our assessment to ensure patient safety?
12422	III.A.9	17	It is unclear whether a separate document called the Company Core Safety Information (CCSI) will be required to be submitted to FDA, or whether the current core data sheet (CDS) format, which contains this information, will fulfill the requirement.
12424	II.B.2	18	Regarding the proposal that a chronological history of all active query efforts must be documented in detail in the report narrative, records of due diligence efforts have always been maintained by companies and made available upon request. Listing efforts in the narratives adds no value and may lead to inconsistencies that could create legal risk in the event of lawsuits. For example, there may be subtle differences in how due diligence is described in the narrative (since the person performing data entry will seek to keep the description as brief as possible) and the full record of the effort may differ enough to allow a plaintiff's lawyer to challenge the record. Although the FDA has stated that this history does not need to be included

			in IND reports sent to investigators (since the history of these effort will likely be quite lengthy) this creates a conflict with the regulatory requirement that a study sponsor must tell investigators the same information that is reported to FDA.
12425	III.B.2	19	We request clarification of 'an animal finding suggestive of a significant human safety risk'. Can FDA please provide examples other than those that would be classified as mutagenicity, carcinogenicity, and/or teratogenicity? Does the finding need to originate from a reproducible validated controlled model?
12425	III.B.2	20	FDA has proposed a requirement to submit expedited IND safety reports for information "sufficient to *consider* changes in either product administration or in the overall conduct of a clinical investigation." We suggest that "consider" is too vague a term, since many of these considerations take place as part of routine, ongoing review sessions and safety surveillance activities, and the outcome may be that no change is needed. We would suggest that it would be more appropriate to require expedited reporting for information that ***will result*** in a change to medicinal product administration or in the overall conduct of a clinical investigation.
12432	III.D.4	21	We question the value of always reporting some SADRs in a 15-day timeframe ("Always Expedited" Reports) even if the event is described in the product label as a known effect of the drug. If there is a qualitative or quantitative difference in the reported event from that described in the product label, it will, as required by regulation, be subject to expedited reporting as unexpected. If not, it will still be reported to the Agency within 6 months in the PSUR. "Always expedited" reporting of these events would seem to negate much of the purpose of an accurate product label, and

			to conflict with the Agency's own guidance in this regard. Additionally, for many products, this will exponentially increase the number of expedited reports required. For example, some of the events may be the indication for the drug, such as an anti-seizure medication for severe epileptics. This greatly increased reporting burden would decrease the available resource at both the company as well as the Agency to focus on more important safety surveillance and risk management activities. Although the FDA offers some relief in terms of waivers, in our experience tracking and adhering to regulatory reporting exceptions in a global environment leads to error and jeopardizes compliance. To have to do so on a product-by-product basis (and potentially on an indication by indication basis) would be a huge burden. As an alternative, we would propose requiring expedited reporting for this list of "Always Expedited" events in the absence of serious outcome only if the event is not consistent with the event described in the product label or is not the approved indication for the drug. We currently practice this approach, although we use an even longer list of events that we have assessed as having sufficient medical gravity to warrant expedited reporting.
12432	III.D.4	22	We object to the proposal that the Agency could make a new SADR the subject of an always-expedited report simply by adding it to the Agency's current guidance for industry on post-marketing safety reporting. We feel that this is, in effect, allowing regulatory reporting requirements to be codified without going through the required formal rule-making process, and question the authority of the Agency to do this.

12433	III.D.6	23	We question the value of requiring that, in addition to 15-day expedited follow-up reports, manufacturers must now also submit a 30-day follow-up for expedited reports (even if there is no new information) to document specific efforts taken to obtain new information and the reason for the inability to obtain complete information. It has always been standard practice that new information is submitted when it is received, and companies are held accountable for due diligence as well as for documentation of their due diligence efforts. Requiring additional individual reports to reiterate what is already required and available upon request does not seem to be a good use of resource at both the company as well as the Agency. For example, under this proposal, a company could submit a 15-day follow-up on Day 29 and still have to submit another report on Day 30, even though no new information was available. In many of these instances, we know when we receive the initial report that no additional information is obtainable (for example, when access to contact information for the reporter and/or patient is denied due to European privacy laws). If this is stated in the initial report, what is the value of sending another report in 30 days to reiterate this statement?
12433 12474 12479	III.D.5 310.305.c.2.v 314.80.c.2.v	24	The proposed rule indicates that potential medication errors must be submitted to FDA within 15 calendar days. Currently AZ is reporting potential medication errors for selected products quarterly, not within 15 calendar days. This reporting schedule has not compromised patient safety. Can FDA comment on the value of receiving all potential medication errors (NCC-MERP categories A and B) on an expedited basis? • What turn around time can industry expect FDA to take on root cause analysis of potential and actual medication errors?

12489	600.80.c.2.v		• Will FDA be able to receive all medication errors under ICH Guidance E2B?
12434	III.D.7	25	We routinely seek copies of hospital discharge records and autopsy reports for serious unexpected SADRs. However, requiring companies to obtain copies of hospital discharge records in every instance where the patient was hospitalized will result in significant additional costs for increased clerical work for HCPs and healthcare institutions. Has FDA surveyed doctors and hospitals as to whether they are willing and/or able to respond to the increased number of requests they will receive for these documents? We feel that requiring submission of source documents such as hospital discharge summaries as attachments to every report and requiring full translation of these documents will not add value, since all *clinically relevant* information is currently required to be translated, extracted, and reported in English on the MedWatch form. These source documents have always been available for inspection upon request. Compliance with this will be especially difficult outside of the US due to data privacy laws. This requirement will also severely impede industry's efforts to comply with the Agency's mandate for electronic submission of expedited reports. Although a methodology exists for electronic submission of attachments, it requires significant expense and resource to implement, especially if this is required for every report While we understand that there have been instances where companies have not provided full and complete information from source documents, we would assert that this is an exception rather than the rule, and that this is best addressed by regulatory inspections and the FDA's powers of enforcement rather than through penalizing compliant sponsors with additional requirements.

12434	III.D.7	26	We question the value of listing in the narrative all available source documents for each case. Source documents are maintained and readily available upon request. As this is not something that other regulators wish to have in report narratives, this US-only requirement will make it even more difficult for manufacturers to report consistently on a global basis. Additionally, this is in conflict with the proposed rule for electronic report submission, which requires a separate field (eg, not the narrative field) for listing additional documents.
12437	III.E.1	27	Guidance is needed on what criteria should be used for the assessment of increased frequency of serious expected SADRs.
12437	III.E.1	28	Please define 'meaningful change in SADR occurrence'. Please specify reporting frequency and format of serious, expected SADR via TPSRs. Please specify reporting frequency and format of lack of efficacy reports.
12438	III.E.1	29	Can FDA please verify whether "History of safety-related actions taken" should include information on changes to the packaging, etc., in response to medication error concerns?

12439	III.E.2	30	Please clarify the term "Lack of approval." Is this 'not yet approved' or 'not approved'?
12439	III.E.2	31	Can FDA please advise the purpose of its request for providing a listing of trademarks in use outside the United States as part of PSURs?
12439	III.E.2	32	We question the value of attaching communications to health care professionals to the PSUR, since any safety actions will be described in the PSUR, and in most instances this communication is also sent to regulators. We also request clarification of 'Any correspondence.'
12439	III.E.2	33	The requirement for providing worldwide patient exposure appears to add a significant burden without any apparent added benefit. Why does FDA believe that distribution data are a poor alternative?
12439	III.E.2	34	For worldwide patient exposure it is proposed that, when possible, data should be provided broken down by gender and age. If these data are not available, an explanation for the lack of such information should be provided. The proposal for worldwide patient exposure should reflect the ICH E2C requirements, which does not include the requirement to provide an explanation "for the lack of such information." Applicants should be able to determine the most appropriate source of exposure data for a product and use a consistent approach in the analysis. Therefore, applicants should not be required to provide an explanation "for the lack of such information".

12439 12440	III.E.2	35	There should be an option to use the company core safety information (CCSI) in effect at the end of the reporting interval as the reference information. When listedness is assessed at the time of PSUR preparation after the data lock point, it is generally considered appropriate to use the current version of the CCSI as the reference document, as long as that choice is made clear in the PSUR text. This is consistent with the recommendations in the Addendum to E2C guidance (step 4), which recognizes the current existing pragmatic approaches to this process in the industry setting. The changes to the CCSI will be described in the PSUR section "Changes to the Reference Safety Information."
12441	II.E.2	36	The proposal to require expedited reporting of information on the resistance to antimicrobial drug products will result in many reports of changes in susceptibility within a small area or hospital because of the large number of organisms tested and the large number of antibiotics included in the testing and the multiple centers that routinely do and report such testing (ie, hospital antibiograms). It is not clear what information this will add. What is needed is more large and rigorous studies on drug use and susceptibility changes that can include looking at interactions, etc, not more reports flooding the system that do not suggest a means of providing adequate treatment and decreasing or delaying onset of resistance.
12441	III.E.2	37	We seek clarification for "specific errors" in the following: "For potential medication errors, the number of reports for specific errors would be provided." It is unclear as to whether "specific errors" refers to NCC MERP categories.

12442	III.E.3	38	Regarding the proposal for semi-annual submission of ICSRs , we believe that the reporting intervals should be consistent with the reporting intervals of the periodic reports (PSURs) that are required in the final rule, and not semi-annual reporting interval in perpetuity. There should be an option to base the submission of these ICSRs on the US labeling (expectedness), for consistency with the submission of expedited ICSRs. FDA is proposing to receive serious unexpected (per the US label) adverse reactions on an expedited submission basis and serious listed (per the CDS) adverse reactions on a periodic submission basis. This proposal ignores the situation that frequently occurs where a serious adverse reaction may be expected per the US label, but unlisted according to the CDS.
12443	III.E.4	39	Does the FDA want multiple PSURs for each indication or patient population, or a streamlined approach where all information for an active moiety is contained in one single report, with pediatric information broken out if needed? Although it is unlikely that a sponsor would base a decision to conduct (or not conduct) pediatric studies based on periodic safety reporting requirements, it appears that the requirement to submit separate periodic reports for pediatric supplements runs counter to FDA's initiatives to encourage the study of drugs in the pediatric population. Couldn't this information be included in the existing periodic reports for the product based on the international birthday for the original approval? What about multiple pediatric supplements? Would they require separate reports?

12443	III.E.5	40	Receipt of an approved application supplement for use in pediatric populations should not always require restarting the PSUR reporting schedule ("restarting the clock"). This is inconsistent with harmonizing worldwide PSUR schedules. The decision to restart the clock should be made on an individual product basis with the Agency.
12449	V.A	41	FDA has stated that the proposed changes will result in a "2% reduction in hospital-related SADRs." We would like to ask how this number was derived since these metrics will drive process and content change. FDA has stated at recent public forums that this reduction is expected from implementation of bar-coding of pharmaceutical products and minimization of medication errors through proprietary name evaluations early in the drug development process. However, as these initiatives are not the focus of this proposed rule, we believe that the benefit from them should not be used as justification for imposing additional requirements, especially when the FDA's estimate of burden also seems to be extremely low in terms of the associated costs of these additional requirements.
12454	V.D	42	We fully support the proposal that MedDRA is used as the medical dictionary for coding each SADR in a post-marketing individual case safety report for human drugs and biologics, as this is consistent with our current practice. However, we request clarification of the requirement that the "latest version" of MedDRA is used. We recommend that the Agency define "latest version" of MedDRA to mean *only* the major yearly updates of the MedDRA dictionary, since we believe that requiring the use of the quarterly MedDRA updates will be logistically difficult and will provide little added value.

12482	F.3	43	We request that the statement: "The applicant must conclude this section with a brief discussion of the data concerning the individual case safety reports in the PSUR (e.g., discussion of medical significance or mechanism)" is clarified to be consistent with page 12440 section III.E.2.f.ii, column 2, which follows the E2C guidance: "This section of the PSUR would also contain a brief discussion of the individual case data in the summary tabulations (e.g., discussion of medical significance or mechanism). This section of the PSUR should be used to comment on specific cases rather than to provide an overall assessment of the cases."