Comments to FDA Proposed Rule "Safety Reporting Requirements for Human Drug and Biological Products"
Docket No. 00N-1484

Section III.A.1 Suspected Adverse Drug Reaction

FDA proposes in §§ 310.305(a) and 314.80(a) to equate "adverse experience" with "suspected adverse drug reaction" is likely to lead to confusion where these two terms historically have had separate and distinct meanings. As stated in ICH E2A:

> "Definitions for the terms adverse event (or experience), adverse reaction, and unexpected adverse reaction have previously been agreed to by consensus of the more than 30 Collaborating Centres of the WHO International Drug Monitoring Centre (Uppsala, Sweden). [Edwards, I.R., et al, Harmonisation in Pharmacovigilance. *Drug Safety* 10(2): 93-102, 1994.] Although those definitions can pertain to situations involving clinical investigations, some minor modifications are necessary, especially to accommodate the pre-approval, development environment." The introduction of the term "drug" was used to indicated that a causal association to a drug existed. The following definitions, with input from the WHO Collaborative Centre, have been agreed:
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> **Adverse Event (or Adverse Experience)**
> *Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.* An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
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> **Adverse Drug Reaction (ADR)**
> In the *pre-approval clinical experience* with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: *all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.* The phrase "responses to a medicinal products" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out."

The distinction between an "adverse experience" and an "adverse drug experience" is useful in the pre-marketing environment, where causality is assessed, compared to the post-marketing environment where causality is assumed. In the former case, the reported event is an "adverse experience" until the causality assessment determines there is a reasonable relationship to the

drug. In the post-marketing case, since causality is assumed when the case is reported, the term "adverse drug experience" is appropriate.

The FDA's proposal to equate "adverse experience" with "suspected adverse drug reaction" as well as "adverse drug experience" is inconsistent with definitions put forth by ICH E2A. Such a change would lead to substantial confusion between events for which a causal association to a drug has not been made — "adverse experience/adverse event" — and an event for which a causal relationship has either been stated (pre-marketing) or implied (post-marketing) — "adverse drug experience/adverse drug reaction". The use of the phrase "suspected adverse drug reaction" is appropriate, and consistent with ICH E2A, to the extent that it is understood that there exists a causal association between the drug and the event.

The proposed changes to § 312.32(a) appear to leave the section without a definition of an adverse experience; that is, an untoward event without a causal association to the suspect drug.

Section III.A.1 Causality Assessment

In the analysis of causality, FDA proposes to equate the phrase "reasonable possibility" with "the relationship cannot be ruled out". This is consistent with ICH E2A. However, FDA appears to be further restricting the definition to effectively mean "the relationship cannot be ruled out with certainty." This interpretation is implied by the example given where the "adverse event may most probably have occurred as a result of a patient's underlying disease and not as a result of a drug..." but would be considered an adverse drug reaction "because there would be at least a 'reasonable possibility' that the drug ...may have caused the event" since "it cannot usually be said ***with certainty*** that the product did not cause the adverse event.

During the clinical development of a drug, clinical trials are conducted in part to explore the safety profile of the compound. Not all of the properties of the drug are known with certainty. Considering all adverse events drug-related unless the contribution by the drug can be ruled out with certainty effectively negates the ability to perform a causality assessment since by definition nothing is known with certainty during clinical development.

Indeed, few clinicians acting as study investigators would ever consider an adverse event not drug related if they had to state with certainty the lack of a possible contribution by the study drug. The goal of asking the study investigator to render an assessment of causality is to be able to benefit from his/her consideration all available data – knowledge of the drug, knowledge of the disease state and familiarity with the study subject. On the basis of consideration of all this information, s/he is asked to determine the most reasonable factor responsible for eliciting the adverse event. A signal may emerge when the investigator (or sponsor) believe that the drug may have been responsible for an adverse event. However, when the question is asked in the context of first ruling out with certainty any contribution by the drug, all the other sources of

information become irrelevant. Lacking complete knowledge about the drug, a drug-related effect cannot be entirely excluded with certainty and the assessment process ends. The result is over-attribution of the association to the study drug.

FDA appears to be offering contradictory language when it states that a causal relationship would not include instances where adverse experiences were "considered to be unlikely or remotely related to the product" (p. 56) and yet would consider as causally related instances where "the relationship between a product and a response to the product cannot be ruled out" (p. 57). If the event is only remotely related to the product, it cannot be ruled out; hence, by this definition it should be considered causally related.

FDA correctly surmises that this proposed definition will significantly increase the number of reports from clinical studies (p. 55). Study investigators will rarely be able to completely rule out the effect of the drug with certainty. The result will be that most all events will be considered drug-related. When these events are also "serious" and "unexpected", the result will be a greater number of expedited alert reports submitted to FDA. Recognizing that the increased volume of reporting will contain cases of limited clinical value in signal detection, the Agency has proposed that company may request that certain known, disease-related events be exempted from this reporting rule. However, citing the Agency's example of wishing to avoid another FIAU scenario, if the FIAU investigators had exempted instances of hepatotoxicity from reporting, the same outcome would likely have transpired.

This proposed approach to causality assessment may have several unintended consequences:

1. The increased number of expedited reports submitted to FDA will result in a corresponding increase in the number of reports sent to study investigators and Institutional Review Boards. If study investigators feel that they are being overwhelmed by the number of alert reports that, to their assessment, do not represent potential signals and do not add substantially to the safety knowledge of the compound, they may opt to cease participation in the study or limit reporting of SAEs. Personal experience with expanded alert reporting requirements has shown this to be the case. Faced with such situations, FDA indicates that companies "are invited to propose any such alternative(s) report method to the agency"; however, to do this for each study sponsored by the company would be a burden on both the company and the Agency.

2. Some companies may wish to expand what are considered "expected" adverse events so as to mitigate the effect of a high proportion of events reported as "related". This would effectively reduce what is submitted on an expedited basis to regulatory authorities – negating the intent of the Agency to increase the number of expedited reports for review.

   This unintended effect also undermines the concept of rationally developing the Core Safety Information document for the product. For some time FDA has been encouraging

companies to more diligently evaluate safety information, an stance echoed by the CIOMS Working Group when they issued their recommendations for creating and maintaining the Developmental Core Safety Information document (CIOMS Working Group report III/V). The Developmental Core Safety Information document contains those adverse events that, after careful analysis, are believed by the company to be likely related to the drug. Such a document provides a more useful safety reference to the study investigator, and also establishes a clear list of adverse events considered "expected" for reporting purposes. If companies discard the concept of the Core Safety document to expand the "expected" events list merely to limit the extent of expedited reporting, a disservice will have been done to the movement to more rationally evaluate the safety profile of drugs.

3. The higher threshold proposed by the FDA to exclude a causal association with a drug appears to be inconsistent with the interpretation of causality exercised by other countries. This may lead some companies to create different expedited reporting frameworks for different countries, a development which would be contrary to the efforts toward international harmonization.

4. In order to reduce "over reporting", FDA proposes sponsors devise alternative reporting methods. However well thought out, each sponsor is likely to develop different methodologies. The result will be a tremendous degree of discordance with reporting requirements for pre-marketing products. FDA will need to develop analytical tools specific to individual trials or programs with specific reporting requirements, which will increase the burden on FDA staff. Sponsors will need to develop specific reporting criteria for their own trials and programs which internally may be inconsistent between trials and programs, increasing the burden on Drug Safety staff. In keeping with the concept of international harmonization, a preferred approach would be to implement a consistent system by which the reportability of a pre-marketing adverse event can be determined.

One difficulty with this increased level of reporting is separating a signal from the increased amount of "noise". FDA states that the purpose for the new definition is to "minimize situations in which an adverse event that proves ultimately to be due to a drug ... is not reported as soon as possible to the agency because the etiology of the adverse event is attributed to the patient's underlying disease by the sponsor, manufacturer or applicant." For this system to realize a benefit assumes that systems are available to reliably identify an adverse event signal and be able to act upon it. The present system effectively identifies adverse event signals that occur with a frequency that allows a reasonable ability to detect them. The more rare events that generally require post-marketing experience to identify may or may not be present during clinical development. When they are present during clinical development, their infrequent nature hinders their identification as important signals. The proposed rules would appear to add to the system

more cases ultimately not related to drug exposure than it would add truly drug-related cases. The net effect would seem to make it more difficult to detect a safety signal than to facilitate the process.

To help justify these proposed changes, it would be helpful if there were quantifiable examples where increased reporting would be useful. For example, the Agency has available submitted expedited reports for various drugs as well as the full safety database submitted for the NDA. An analysis could be performed on probably a large number of drugs to determine the extent to which serious adverse events, not considered related to study drug and not reported on an expedited basis, later were identified during post-marketing experience to represent bona fide safety signals. This analysis would not only be useful to quantify the extent of the "problem", but also perhaps provide guidance as to types of adverse events, or types of underlying disease states, where the misidentifications were occurring.

The purpose of an expedited reporting system is to bring to regulatory agency attention those clinically significant adverse events that are likely caused by the drug and which could impact study subject safety. This "early warning" system allows prompt education of investigators and study subjects, and may warrant changes to the study protocol or methods of monitoring. In order to improve the ability to identify these safety signals, an argument could be made that changes to the "expectedness" criteria would be more valuable than changes to the method by which causality is assessed. As noted above, unintended consequences of making causality assessment overly strict may undermine the stated goal. However, requiring a thoughtful and thorough analysis of safety information to construct a list of adverse events believed to be related to the study drug ("expected" adverse events), a list not padded with extraneous events, would provide regulators with more, and more meaningful, expedited alert reports. Raising the bar on what constitutes an "expected" adverse event would likely do more to improve the quality of data for signal analysis than would effectively making all events "related". Criteria could be stated such that lists of all adverse events observed in a trial could not be considered "expected". Arbitrary rates of occurrence – 3 times or 5 times, for example – would not be acceptable to define an "expected" adverse event. This would be consistent with the approach espoused by the CIOMS Working Group's concept of the Developmental Safety Information document and further promote a common international approach. FDA has already supported the concept of the Company Core Safety Information document. The natural extension of this philosophy would be to publicly support its predecessor, the Developmental Core Safety Information document, and the philosophy of what constitutes an "expected" adverse event.

III.A.2 Definition of a Life-Threatening SADR

The FDA's proposal to allow the sponsor to also consider whether an adverse drug experience placed the patient or subject at immediate risk of death from the reaction as it occurred is a positive one. Unlike an outcome of death or hospitalization, "life-threatening" is a subjective

assessment. However, it is most accurately made by the clinician caring for the patient at the time of the adverse event. The number of opportunities for the sponsor to assess the outcome of an event as immediately life-threatening is likely to be small.

FDA may also consider expanding the role of the sponsor in determining the seriousness of adverse events by also expressly allowing the sponsor to determine if an adverse event is serious due to the criteria that it was an important medical event that may not have resulted in death, have been life-threatening or required hospitalization but did jeopardize the patient and may have required medical or surgical intervention to prevent one of the above outcomes. Many sponsors already may upgrade an event to being considered "serious" by the "other" criteria in the absence of a reporter's assessment of seriousness. But as long as the Agency is allowing sponsors to explicitly make an assessment of the life-threatening nature of an adverse event, it would be consistent to also explicitly state the ability of the sponsor to consider an adverse event to be "serious" on the basis of the "other" criteria.

However, the rationale FDA gives for expanding this role of the sponsor is not supported by the quote from ICH E2A: "Causality assessment is required for clinical investigation cases. All cases judged by either the reporting health care professional or the sponsor as having a reasonable suspected causal relationship to the medicinal product qualify as ADR's [adverse drug reactions]." This state refers to an assessment of causality, not an assessment of seriousness, which is the topic of the FDA proposal. It is important to recognize the distinction between what classifies an adverse event as "serious" from what classifies the event as causally related to the drug.

III.A.3 SADR with Unknown Outcome

In addition to the categories of nonserious and serious adverse experiences, FDA proposes to create a third category "suspected adverse drug reaction with unknown outcome" in order to accommodate the situation where outcome is not known. The purpose for creating this third category is unclear. This classification is not supported by ICH. The Agency has not indicated how reportability should be assessed for an adverse event in which the outcome is unknown. For example, if the adverse event occurs that is unexpected and related to drug is reported, but the outcome is not known so as to establish whether it meets the criteria for seriousness, should it be considered subject to expedited reporting or not? The proposed rule only states that it would not default to "non-serious". It is not until Table 6 and section III.D.3 that there is reference to requiring SADRs with unknown outcome to be submitted on an expedited basis. The requirement to submit these within 45 days of receipt is odd and not consistent with the 15-day requirement for serious, unexpected SADRs. Creation of a new and different reporting timeframe is likely to introduce confusion.

For SADRs of unknown outcome submitted on an expedited basis, it is not clear how section B2 on the 3500A form would be completed. And for consistency, how would the corresponding section 8-12 on the CIOMS I form be completed?

This section makes reference to the post-marketing environment; would the "unknown outcome" category also apply to pre-marketing events?

Rather than make SADRs of unknown outcome a different report type with a different reporting timeframe, it may be preferable to have an unknown outcome default to being "serious" until proven otherwise. Then it would fall into the reporting framework for other "serious" expedited reports. The outcome in section B2 on the MedWatch form would be marked "Other – unknown outcome".

III.A.5 Minimum Data Set and Full Data Set for an Individual Case Safety Report

The proposal to define a minimum data set is laudable.

FDA proposes that for reports from blinded clinical studies, the blind should be broken for each patient or subject who experiences a serious, unexpected suspected adverse drug reaction. The concern that submitting a report with the suspect drug clearly identified from a blinded trial would unblind and potentially bias both internal sponsor personnel reviewing the report as well as study investigators and staff who would be notified of the report. Management of the subject who experiences the serious adverse event does not always require unblinding the treatment assignment as the medical management may not be determined by the knowledge of the treatment assignment.

An elegant method to meet both the reporting requirements and maintain the blind at the sponsor and investigator's site has apparently been in use in Europe for some time. The process involves unblinding only limited sponsor personnel (e.g., drug safety staff) involved with the report. The actual report form (3500A or CIOMS I) is submitted with the suspect drug listed as "blinded therapy". A separate submission coincides with the report form that provides the unblinding information. Thus, concern over needlessly unblinding sponsor and study site personnel is avoided while regulatory authorities receive knowledge of the actual suspect drug.

III.A.6 Active Query

FDA proposes to define "active query" as direct verbal contact. The requirement to employ direct verbal contact to the exclusion of written contact appears to make process take precedence over the product. The desired product is a high quality description of the clinical course of events. The sponsor should be left some discretion regarding how to best achieve this desired

product. Often direct verbal contact is the most efficient manner to obtain these data. On the other hand, email queries often work equally well and are often responded to more rapidly than attempts at making phone contact. A sponsor may leave a phone message, but then receive a thoughtful written reply (e.g., by mail, fax or email). Email is actually an extremely useful tool to communicate with the busy clinician who has many competing priorities. Email allows the sponsor to clearly file the contents of the follow-up information with potentially more accuracy than a hand-written telephone log, and the correspondence receives an automatic date and time stamp. While direct verbal contact is useful, other means of communication should not be excluded.

III.A.7 Spontaneous Report

The proposed definition is useful and would help clarify the current variety of sources of safety information.

III.A.9 Company Core Data Sheet, Company Core Safety Information (CCSI)

The proposal to codify the use of the CCSI to determine "listedness" ("expectedness") is a welcome development. The CIOMS Working Group efforts that established the concept of the CCSI also developed the idea of a Developmental Core Safety Information document to serve in the pre-marketing development of a drug (See Guidelines for Preparing Core Clinical-Safety Information on Drugs, Second Edition, Report of the CIOMS Working Groups III and V). In order to establish consistency in the determination of "listedness" across pre-marketing and post-marketing realms, it would be useful to expand this section to include the definition and role of the Developmental Core Safety Information document. (see also the discussion pertaining to section III.A.1)

III.A.10 Data Lock Point and International Birth Date

The definition of the International Birth Date as the date the first regulatory authority in the world approved the marketing application is a helpful development.

The dates used in the example of lock dates over a 6 month reporting period would more accurately be 1 April to 30 September since the definition of the lock date is inclusive.

III.B.1 Review of Safety Information

The proposal to add "*in vitro* studies" to the list of sources of information that may be relevant to an investigational drug is valid.

The proposal to replace the phrase "commercial marketing experience" with "and reports of foreign commercial marketing experience for drugs that are not marketed in the United States" implies that in cases where a drug is both marketed in the US and the subject of an active IND, that expedited reports arising from a post-marketing source will no longer be required to be submitted to both the NDA and IND. If this interpretation is correct, it would be useful to specifically state that post-marketing expedited reports are no longer required to be submitted to the IND as long as the drug is approved in the US.

III.B.2.b Serious and Unexpected SADRs

Clarifying the requirement to submit to FDA safety reports within 15 days of receipt of a minimum data set for serious, unexpected SADRs is useful. However, the debate over whether the day of receipt of the minimum data set by the sponsor represents Day 1 or Day 0 in the 15-day timeframe is likely to persist. It would be worth clarifying this point to put this issue to rest.

III.C.2 Review of Safety Information

FDA proposes to change the current language "applicants are not required to resubmit to FDA safety reports forwarded to the applicant by FDA; however, applicants must submit all followup information on such reports" to "individual case safety reports forwarded to the applicant by FDA must not be resubmitted to the agency by applicants." It would be useful in the new language to include the stipulation that followup information must still be submitted to FDA.

III.D.4 Always Expedited Reports

It is unclear whether the 'always expedited' rule applies only to post-marketing reports or to both pre-marketing and post-marketing reports. Audrey Thomas stated at one point during her presentation at the 30-Apr-2003 FDA/DIA meeting that the rule only applies to post-marketing reports, but she later contradicted herself by stating that it applies to both pre-marketing and post-marketing reports. Clarification on this point would be appreciated. It is important to note, however, that if an 'always expedited' event is listed on an adverse event case report form, but not considered by the site to meet the criteria for 'serious', it will not be brought to the sponsor's attention in an immediate manner. The sponsor is not likely to know of this event until the adverse event case report forms are collected from the site and processed.

Among the list of conditions that would always be subject expedited reported is "acute renal failure". Although the intent is understandable, in practice clinicians often use the term "acute renal failure" to describe a condition of renal insufficiency that is of less severity or clinical

significance than is probably what is intended by this rule. The diagnosis of acute renal failure is made on the basis of a clinical impression rather than based on standard quantifiable criteria (e.g., serum creatinine). In order to bring to the Agency's attention those instance of acute renal failure that truly warrant examination, the condition might better be expressed as "acute renal failure requiring dialysis support".

III.D.6 Followup Reports

FDA is proposing a 30-day follow-up report that would be required even in the absence of follow-up information. Although the apparent intent is to prompt the sponsor to obtain follow-up information for expedited reports, the actual effect is likely to be one of increased administrative burden without a beneficial impact on safety knowledge. The requirement may frequently lead to duplicate reports. If follow-up information is quickly obtained, then the first 15-day follow-up report will be due at the same time as the 30-day follow-up report. There seems to be little advantage to submitting multiple reports with the same information in the same timeframe. This proposal also seems to be focused more on process than product. FDA has made the point that active follow-up is expected to be performed, with appropriate documentation of efforts made. Safety departments should be allowed to implement procedures to ensure this activity without having to be burdened by additional reporting requirements that do little to advance the follow-up process and penalize Safety departments with effective systems in place.

Clarification of what constitutes "new information" subject to expedited followup reporting would be helpful. Advice from FDA inspectors has indicated that new information subject to followup include 1) new information that corrects previously reported information, and 2) new information not previously reported that advances the understanding of the case. It would be helpful if this local guidance was verified by FDA.

The use of the phrase '30-day report' is somewhat misleading as all other reporting timeframes are based on the clock starting with the receipt of information that qualifies for expedited reporting: 7-day alert reports, 15-day expedited reports, 15-day follow-up reports, for example. However, the '30-day report' timeframe is not based on the day of receipt of information, rather it is based on the submission due date for the 15-day expedited report. To use the usual nomenclature, this would effectively be a 45-day report. Introducing a new definition as to when a reporting clock starts is likely to cause confusion.

III.D.7 Supporting Documentation

The proposed rule requires that a copy of the autopsy report be submitted to FDA if available. The proposed rule then stipulates that in the absence of an available autopsy report the death

certificate be submitted; however, there is no statement concerning the availability of the death certificate. In some cases, neither a death certificate or autopsy report is available from the reporter. The requirement to submit either an autopsy report or a death certificate should be contingent upon the document's availability.

III.E.1.h Contact Person

FDA is proposing that the contact person for the TPSR be a licensed physician. Other healthcare professionals, including non-licensed physicians, pharmacists and nurses, can provide equivalent knowledge of the medical significance of the information provided in the TPSR. In cases of particular safety signals, it is not uncommon to consult with a physician specialist, which would still be the case if the contact person was a licensed physician whose specialty area was different from that of the safety signal. The quality of safety information can be maintained by simply requiring that the contact person be an appropriately trained healthcare professional.

III.K Safety Reporting for In Vivo Bioavailability and Bioequivalence Studies

FDA is proposing to require submission of expedited safety reports for qualifying SADRs that arise in human bioavailability and bioequivalence studies that do not require an IND. Further, FDA would not require submission of an IND for these studies. It is not clear from the proposed rule how these reports should be submitted to the Agency. Since there is no IND, it would appear that the expedited safety reports should be submitted to the NDA, yet this would not necessarily acknowledge the investigational source of the SADR. Further clarification on submission of an expedited safety report from an investigational study in the absence of an IND would be helpful.

V. Analysis of Impacts

The Agency estimates that the impacts of the proposed rule would provide a net benefit in terms of reductions in hospitalizations and hospital durations. The analyses substantiating this presumed benefit appear to focus on the contribution of medication errors and post-marketing experiences.

The assumption that the proposed rule would result in avoidance of 2 percent of the annual hospitalizations due to SADRs does not appear to be supported by quantitative evidence. The proposed rule deals only with the reporting component of the system of SADR handling. Other factors beyond the scope of this rule impact significantly on the ultimate incidence of SADRs and their social and economic consequences, e.g., regulatory and medical analysis, communication pathways and educational efforts. While some of the components of the proposed rule are positive steps toward improving good safety practices, caution is warranted in

statements that quantify the magnitude of the benefit, particularly since the premise upon which these conclusions are made have not been validated. It would be laudable if the Agency performed a study to examine the extent of benefits afforded by the various components of the proposed rule.