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

RE: DOCKET NO. 00N-1484

Dear Sir or Madame:

Thank you for the opportunity to comment on the Proposed Rule on Safety Reporting Requirements for Human Drugs and Biological Products. Amersham Health would like to provide the following comments:

II.B. Rational for This Proposal

II.B.1. International Standards

Fifth paragraph, sentence 3: "International harmonization efforts … is essential 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."

FDA's intent is highly appreciated; nevertheless, especially by introducing new reporting timelines (II.B.3.) and term definitions (III.A.1.) the pharmaceutical industry will have to focus mainly on the additional bureaucratic burden.

All in all it can be said that many of the proposed changes would be devastating in cost and resources to pharmaceutical companies, would distract resources from safety signal surveillance to regulatory processing, and would therefore probably not achieve the desired goals.

Tenth paragraph, sentences 2, 3, and 4: "These third parties may employ clinical terminology standards that differ from those proposed here. Therefore, the agency invites comment on the unintended potential impact of this proposed rule on those parties not subject to FDA's safety reporting requirements. The agency also invites comment on the potential strategies and approaches for facilitating seamless cross-standard communications, such as mapping between alternative terminologies and MedDRA."

It is felt that MedDRA offers a sufficient terminology repertory and updating processes to reflect the information reported by third parties.

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II.B.2. Quality of Postmarketing Safety Reports

Third paragraph: "Another amendment would require direct contact with the initial reporter of an SADR by a health care professional at the company for collection of certain postmarketing safety information (*e.g.*, collection of followup information for a serious SADR) (see section III.A.6 of this document). Currently, some companies use this approach for collecting information, whereas others send the initial reporter a letter. The latter case is a passive approach which, in FDA's experience, results in limited acquisition of new information. In most cases, the initial reporter simply does not respond to the letter. Instead, using an active approach, as proposed by FDA, companies would more likely obtain the additional information needed for an SADR. Thus, use of this approach should result in submission of higher quality reports to FDA for review."
Direct contact with the initial and additional professional sources via "health care professionals" or experienced pharmacovigilance staff members is certainly desirable, but sometimes impossible to obtain. A reporter may not be willing to receive any additional call or in retrospect case reporting might have left the facility. As imperfect a passive approach might be, sometimes it is the sole choice, and might even result sooner into attaining the requested information than an 'active' approach.
It could be supportive though, if the FDA would approach the mentioned third parties with an appeal to report adverse experiences as comprehensive as possible.

Fourth paragraph: "Another amendment would require that a licensed physician at the company be responsible for the content of postmarketing safety reports submitted to FDA (see sections III.E.1.h, III.E.2.k.xi, and II.F.4 of this document). As in the previous examples, some companies currently use licensed physicians for this purpose, whereas others have their postmarketing safety reports prepared and submitted by clerical personnel with no health care training. The medical significance of postmarketing safety reports warrants review by a licensed physician. The agency believes that licensed physicians would ensure submission of high quality reports to FDA that articulately conveys all clinically relevant information associated with an SADR."
Licensed physicians are indeed essential to ensure reports of higher quality. In many instances physicians in pharmaceutical industry's pharmacovigilance are not licensed in the United States, but in other countries. The FDA's proposed "licensed physician" is understood as a physician with completed training and license.

II.B.3. New Postmarketing Expedited Safety Reports

II.B.3.a. Medication errors

Fourth paragraph, sentences 1, 2, and 3: "FDA is therefore proposing to require that these companies submit to the agency expeditiously all domestic reports of actual and potential medication errors (see section III.D.5 of this document). FDA would review information about suspected medication errors to determine an appropriate risk management plan (*e.g.*, changes to the proprietary name, labels, labeling or packaging of the drug or biological product or educational initiatives to protect public health). This proposal, which is consistent with one of the Department of Health and Human Services' major health initiatives, would allow FDA to form the framework for building a comprehensive risk assessment and management system for preventable SADRs."

FDA's goal to provide the public with a higher level of protection is worth all support. However it is believed that blindfolded reporting of all actual medication errors and potential medication errors will lead to complex accumulation of reports. A pre-sorting and profound evaluation at company side seems preferable. In cases of either increased frequency of non-serious medication errors or verified medication errors with serious consequences expeditiously reporting and proposal of preventive measures should be mandatory.

II.B.3.c. Always expedited reports
Sentence 4: "For example, even though the labeling for a product indicates that ventricular fibrillation may be associated with use of the product and thus not subject to expedited reporting to FDA (*i.e.*, SADR is expected), the agency needs to review each new report of ventricular fibrillation for this product as quickly as possible to ascertain if there is a qualitative or quantitative change in the nature of the SADR."
The current regulation to submit unexpected adverse experiences in an expedited report includes the industries liability to analyse their data for any qualitative or quantitative change. The proposed regulation will result in substantially increased reporting rates, thereby increasing administration efforts on both sides.
Nevertheless, the listed events should always be considered serious.

III.A. Definitions
III.A.1. Suspected Adverse Drug Reaction (SADR)
FDA's existing definition of "associated with the use of the drug" as "there is a reasonable possibility that the experience may have been caused by the drug" is sufficient. ICH's definition of "a reasonable possibility" as "the relationship cannot be ruled out" basically excludes reasoning and will lead to over-reporting of premarketing adverse experiences.

III.A.4. Contractor
Last sentence: "Persons under contract to manufacture, pack, sell, distribute, or develop the drug or licensed biological product, or to maintain, create, or submit records regarding SADRs or medication errors (whether or not the medication error results in an SADR; see section III.A.8 of this document) would have postmarketing safety reporting responsibilities."
It is assumed that the proposed requirement is aimed at nationally contracted sales forces. Clarification is kindly requested.

III.A.5. Minimum Data Set and Full Data Set for an Individual Case Safety Report
Paragraph three, sentences 2, 3, and 6: "The proposed rule would, as described below, require at least a minimum data set for all individual case safety reports, except for certain reports of medication errors (see sections III.B.2.a and III.C.5 of this document). In addition, a full data set would be required for postmarketing individual case safety reports of serious SADRs, always expedited reports, and medication error reports (see sections III.C.5, III.D.1, III.D.4, III.D.5, and III.E.4 of this document). Reports of nonserious SADRs with a minimum data set would include all safety information received or otherwise obtained by the manufacturer or applicant for the SADR."...

"Manufacturers and applicants would be required to submit a full data set for reports of nonserious SADRs resulting from a medication error (see sections III.C.5 and III.D.5 of this document)."
This reads as if a "full data set" has to be obtained for the listed reports at any price. Although this is aimed by any pharmacovigilance department, it is impossible to achieve in many cases. It would be appreciated if instead of making a "full data set" mandatory, it could be stressed that obtaining a "full data set" has to be the objective of any reporter contact.

Paragraph four, sentences 2 and 3: "Reports from blinded clinical studies (*i.e.*, the sponsor and investigator are blinded to individual patient treatment) should be submitted to FDA only after the code is broken for the patient or subject that experiences an SADR. The blind should be broken for each patient or subject who experiences a serious, unexpected SADR unless arrangements have been made otherwise with the FDA review division that has responsibility for review of the IND (*e.g.*, the protocol or other documentation clearly defines specific alternative arrangements for maintaining the blind)."
Like the SADR definition will lead to over-reporting of clinical adverse experiences in general, the specifically required breaking of the blind for all serious and unexpected SADRs (basically all serious and unexpected AEs) will compromise the integrity of otherwise well-regulated clinical investigations.

III.A.6. Active Query
Second paragraph, fourth bullet point: "Obtain supporting documentation for a report of a death or hospitalization (*e.g.*, autopsy report, hospital discharge summary) (see section III.D.7 of this document)."
The introduction of HIPAA resulted in enormous difficulties to obtain patient identity. In order to attain e.g. an autopsy report the patient's ID would be a pre-requisite. As mentioned in the comment on the "full dataset", instead of making the obtainment of the listed reports mandatory, it could be stressed that attaining them has to be the objective of any reporter contact in cases of death or hospitalization.

III.E. Postmarketing Periodic Safety Reporting
III.E.1.g.and 2.k.x. Location of safety records.
"Proposed §§ 314.80(c)(3)(i)(D) and 600.80(c)(3)(i)(D) would require another new section in TPSRs that would contain a list of the current address(es) where all safety reports and other safety-related records for the drug product or licensed biological product are maintained. FDA is proposing to require a list of these addresses to provide rapid access to safety-related records for FDA inspections and for requests by FDA for additional information concerning safety issues."
Certainly it is of interest for FDA to get rapid access to safety-related records for inspections and for request for additional information. As with previous occasions the pharmaceutical industry will be happy to provide FDA with all required information and/or source documents. Yet providing FDA with all current addresses, national and

international, (and to keep them current) would entail an administration effort for the companies not justifying the result.

Please feel free in contacting me at (609) 514-6752 should you have any questions.

Sincerely,

Bernhard Heiles, MD, Ph.D
Director, Pharmacovigilance