425 Market Street, 32nd Floor
San Francisco, CA 94105

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Writer's Direct Contact
415/268-7469
RReinhar@mofo.com

Via E-Mail FDADockets@oc.fda.gov
And hardcopy followup by U.S. Mail

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

Re: Comments on FDA's Proposed Rule -- Safety Reporting Requirements for Human Drug and Biological Products (68 Fed. Reg. 12406, March 14, 2003) – **Docket No. 00N-1484** ("Safety Reporting Rule" or "SRR")

To the Food and Drug Administration:

I. INTRODUCTION AND SUMMARY.

The signators to this letter appreciate the opportunity to comment on FDA's proposed Safety Reporting Rule (or "SRR").[1] We comment as individuals or on behalf of consumer oriented organizations devoted to accelerate ethical research and global delivery of AIDS vaccines. We serve in volunteer and advisory capacities working with vaccine advocacy or AIDS service organizations or government sponsored clinical trial unit community advisory boards. Many of us or those we represent have participated as human subjects in clinical trials. The point of contact for these comments is provided in the conclusion if you would like us to provide further information, and we welcome any feedback you may have.

Our principal focus is on premarketing and postmarketing safety reporting for biologics. We support a thoughtful population approach to the AIDS pandemic that integrates immunization, therapeutics for those who become infected with HIV (the virus that causes AIDS), rational behavioral prevention methods and/or the development of other products such as microbiocides. For those reasons, our comments may apply to all drugs and biologics within the scope of the SRR and are not confined to vaccines.

[1] In these comments, references to the Federal Register will be to the pages of the proposed SRR unless otherwise noted.

For the most part, we are supportive of the FDA's proposed revisions, especially adjustments to conform FDA's safety reporting program to guidelines issued by the International Conference on Harmonisation ("ICH")[2] and to broaden the scope of reportable data. FDA's explanation of market failures resulting from conflicting international requirements is especially welcome.[3] We encourage efforts to pursue harmonization in areas necessary for commencement of multisite international clinical trials, product regulatory approval and safety reporting.

Our comments show that the proposed SRR can be improved to guarantee adequate and timely consideration of safety data. To that end, valuable lessons in safety reporting are available from similar reporting requirements issued by other federal agencies with which FDA maintains important interagency liaisons -- such as the U.S. Environmental Protection Agency ("EPA") and the Consumer Product Safety Commission ("CPSC"). Like FDA, these agencies are charged with protecting public health and safety from exposure to commercially distributed chemical and biological substances. We will make reference to the relevant approaches in these comments.[4] We request that FDA consult with these other agencies during the promulgation of the SRR to coordinate and compare bases for federal safety reporting requirements. Our detailed comments below track as nearly as possible the order in which FDA discusses issues in the proposed rule.

II. DETAILED COMMENTS ON PROPOSED SRR.

We support several of FDA's proposals to increase the quality and timeliness of safety reporting.

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[2] The full organization name is the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (http://www.ich.org). ICH documents will be referred to in these comments as "ICH Guidelines."

[3] p. 12450.

[4] Specifically, EPA has issued regulations and guidance to implement the Toxic Substances Control Act ("TSCA;" 15 U.S.C. § 2601, et seq.) and the Federal Insecticide Fungicide and Rodenticide Act ("FIFRA;" 7 U.S.C. § 136, et seq.) Sections of TSCA for safety reporting and documentation include the TSCA §8(c) rule (40 C.F. Part 717) to require receiving and recording of significant adverse reaction allegations from employees and consumers – much like FDA's "spontaneous reports" – and guidance to implement TSCA §8(e) (15 U.S.C. §2608(e)) – requiring notification to EPA of information that reasonably supports the conclusion that a substance poses a substantial risk of injury to health (http://www.epa.gov/opptintr/tsca8e/doc/rguide.htm). FIFRA regulations (40 C.F.R. Part 159) require submittal of equivalent "postmarketing" information to EPA regarding unreasonable adverse effects of pesticides. The CPSC requires reporting of substantial hazard product reports or product liability information at 16 C.F.R. Parts 1115 and 1116.

A. Definition of SADR and Related Terms

The proposal to include reactions that "cannot be ruled out" being caused by the product in the definition of reportable "suspected adverse drug reactions" (SADR)[5] would bring FDA's reporting regulations in line with those of EPA and the CPSC. EPA and CPSC rules also direct chemical manufacturers and processors to report significant adverse event observations without waiting to determine causation conclusively.[6] Years of experience have shown those programs to be workable and without undue burden. Unwarranted reporting delays would hinder appropriate regulatory evaluation and response. Because consumers look to FDA to exercise its public health oversight function and weigh factors of attribution independently of the assessments made by investigators or sponsors, we request that FDA adopt the proposal as written. This oversight function is particularly important in the neutral evaluation of novel therapeutics, vaccines or adjuvants for which there is little experience in humans. To assist investigators or sponsors, FDA may issue further guidance for industry to discuss the judgments involved when meeting this standard of reporting.

We request that FDA broaden or at least clarify the definitions of life threatening or other SADR, spontaneous reports and reports from clinical trials. The SRR proposes to include life threatening SADRs or reports as they become known only to or "in the opinion of" "investigators" or "sponsors."[7] However, clinical staff, agents or other persons qualified to appreciate the significance of safety observations or employed by sponsors or investigators may also have reason to record or observe adverse experiences

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[5] pp. 12417-8.

[6] For example, EPA's TSCA 8(e) Guidance states:
"The decision-making process for Section 8(e)-reportability should focus primarily on whether the toxicity or exposure information offers reasonable support for a conclusion of substantial risk under the criteria described above, but should not focus at all on whether the information is conclusive regarding the risk. A decision to report information to the Agency under Section 8(e) should not involve exhaustive health and/or environmental risk assessments of the subject chemical(s). Further, determining reasonable support for a conclusion of substantial risk should not include any evaluation of either the economic or social benefits of the use(s) of the subject chemical substance(s). .....The evidence that offers reasonable support for a conclusion of substantial risk need not be complete or definitive but should provide a plausible link..." TSCA Section 8(e) Reporting Guide," June 1991, pp. 2-3 and 7 and at http://www.epa.gov/opptintr/tsca8e/doc/rguide.htm. CPSC regulations state, "subject firms are urged to report if in doubt as to whether a defect could present a substantial product hazard" (16 C.F.R. §1115.4(e)). EPA's pesticide safety reporting guidance states: "Under the new regulations, neither an inference nor a pattern needs to be established before reporting an incident. If basic information is available – an effect, an exposure, the identity of the pesticide, location where the incident occurred and a person to contact -- the incident is reportable." (EPA, PR Notice 98-3, p. 7; http://www.epa.gov/opppmsd1/PR_Notices/pr98-3.pdf).

[7] pp. 12419, 12424 and 12430-1.

even if their opinions differ from those of principal investigators or sponsors.[8] The SRR would be improved if the definitions are clarified to mention that investigators or sponsors must evaluate information communicated to them or recorded by their qualified staff or agents; the investigators and sponsors would have responsibility to transmit reportable information to FDA. The clarification is consistent with ICH Guideline E2A.[9]

Sources of reportable information can come from a wide variety of media or outlets. For example, investigators or sponsors participating in private or public meetings or conferences can learn from colleagues or professionals of adverse experiences associated with their products that should be made known to FDA. EPA typically requires chemical manufacturers to be on the alert for such information.[10] We request these sources or outlets of information be added to the lists proposed in 21 C.F.R. §§ 312.32(b), 314.80(b) and 600.80(b).[11] The investigator or sponsor would retain the responsibility to determine if the information is reportable.

FDA asks if expanding the definition of SADR to apply to adverse experiences for which the product cannot be ruled out as the cause would result in over reporting because patients with underlying disease conditions may generate reports attributable to their illness rather than the product.[12] Over reporting would not occur for healthy populations chosen for inclusion in trials specifically because of the absence of confounding disease conditions. The "cannot be ruled out" standard can apply in the case of preventive vaccine clinical trials and postmarketing.

FDA asks for comment about liability concerns in product liability actions.[13] Unsubstantiated allegations, mere reporting of observations or those for which causation cannot be established do not give rise to liability. On the other hand, FDA's public

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[8] See EPA's TSCA 8(e) guideline.(http://www.epa.gov/opptintr/tsca8e/doc/rguide.htm) or pesticide reporting rules at 40 C.F.R.§159.158(a). Pesticide "registrants are responsible for information possessed by their employees or agents."(http://www.epa.gov/opppmsd1/PR_Notices/pr98-4.pdf p. 2).

[9] See also ICH Guideline E2D "Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting," http://www.fda.gov/cber/gdlns/ichexrep.pdf .

[10] EPA states, "TSCA Section 8(e)-reportable information can come from a variety of sources including, but not limited to draft, interim or final written reports (including study reports, letters, telegrams, telex reports) or verbal reports (received at meetings or by phone) that involve observations (including preliminary observations." TSCA Section 8(e) Reporting Guide," June 1991, p.7 and at http://www.epa.gov/opptintr/tsca8e/doc/rguide.htm .

[11] pp. 12424 and 12426.

[12] p. 12418.

[13] pp. 12418-9.

health responsibilities to investigate potential risks would be compromised if observations are withheld.

We request that FDA refrain from prohibiting use of SADR reports in product liability actions, as it has considered doing.[14] The prohibition would be contrary to FDA's longstanding policy going back at least to 1979 when the Agency stated: "It is not the intent of the FDA to influence the civil tort liability of the [drug] manufacturer."[15] Use of reports in litigation is already – and should be – guided by rules of evidence. Federal rules of evidence act to restrict the use of reports of adverse events that cannot be shown to be caused by a product on grounds of relevance, hearsay or other criteria.[16] Section 379v of The Food Drug and Cosmetic Act ("FDCA") proscribes FDA's authority in this area to permitting manufacturers, sponsors or applicants to add specific disclaimers. At the same time, Section 379v resolves litigation problems that could arise in misuse of reported data.[17]

FDA's proposal to require reporting of significant human risk sufficient to consider changes in product administration or in postmarketing is reasonable.[18] We request that examples of significant risk also be understood to include instances of significant impairment or dysfunction.

The SRR is unclear as to reporting of adverse events reflecting the safety of employees or health professionals who work with and are exposed to products they

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[14] p. 12419.

[15] 44 Fed. Reg. 37,437. Opposing sides of tort litigation may disagree on many uses of submitted data, but they agree on the need for FDA to be neutral in such litigation and have no effect on outcome (See for example contrasting letters from William Vodra to FDA, November 16, 2001; http://www.fda.gov/ohrms/dockets/dailys/01/Nov01/112601/sup0001.pdf and letter from Michael Fischbein to FDA dated September 28, 2001; http://www.fda.gov/ohrms/dockets/dailys/01/Oct01/100201/c000006.pdf).

[16] Federal Rules of Evidence, Rules 104, 401-403, 801-803.

[17] The FDCA states: "With respect to any entity that submits or is required to submit a safety report or other information in connection with the safety of a product (including a product that is a food, drug, device, dietary supplement, or cosmetic) under this Act (and any release by the Secretary of that report or information), such report or information shall not be construed to reflect necessarily a conclusion by the entity or the Secretary that the report or information constitutes an admission that the product involved malfunctioned, caused or contributed to an adverse experience, or otherwise caused or contributed to a death, serious injury, or serious illness. Such an entity need not admit, and may deny, that the report or information submitted by the entity constitutes an admission that the product involved malfunctioned, caused or contributed to an adverse experience, or caused or contributed to a death, serious injury, or serious illness."

[18] pp. 12432 and 12448.

administer. The SRR should clarify circumstances when such information would be provided.

B. Reporting Mechanisms

We agree with proposed changes to 21 C.F.R. §312.32(c) to expedite rapid communication to FDA of serious adverse events or reactions in clinical trials to harmonize with ICH guidance.[19] We request that the added regulatory language specify that such communications also be made to IRBs.

We disagree with FDA's proposal to deviate from ICH guidance by not requiring reports of an increase in the rate of occurrence of expected, serious SADRs until submittal of IND annual reports.[20] Expedited reporting of this information may alert FDA to situations of more widespread and serious risks than were previously known or in populations that had not been previously identified as at risk. Prompt increased frequency reporting is typically required by EPA in similar situations.[21]

We agree with FDA's proposals to revise procedures for postmarketing surveillance, receipt, and reporting.[22] The content of surveillance and evaluation should include procedures to monitor for adverse reactions that were mentioned during clinical trials in informed consents, perhaps on the basis of animal data, but not yet observed or conclusively known to occur in humans - such as potential long term chronic or reproductive effects that were unknown in the short period a trial was conducted. FDA has already recommended such surveillance in guidance to establish pregnancy registries connected with testing and marketing of preventive vaccines.[23] At a minimum, some degree of postmarketing surveillance should be required for reactions for which there is any known biological basis that were mentioned during informed consent.

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[19] p. 12425.

[20] p. 12425.

[21] See, for example, EPA's "Questions and Answers Concerning the TSCA Section 8(c) Rule," July, 1984, p. 45; "TSCA Section 8(e) Reporting Guide," June 1991, p. 8 and at http://www.epa.gov/opptintr/tsca8e/doc/rguide.htm ; or pesticide rules at 40 C.F.R. §159.195(a)(3).

[22] p. 12426.

[23] Establishing Pregnancy Exposure Registries (August, 2002) http://www.fda.gov/cder/guidance/3626fnl.pdf; Draft Guidance for Industry, "Considerations for Reproductive Toxicity Studies for Preventive Vaccines for Infectious Disease Indications, August, 2000. http://www.fda.gov/cber/gdlns/reprotox.pdf .

We agree with FDA's proposal to require lack of efficacy reports.[24] To carry out this directive, lack of efficacy should be understood to include information on lack of efficacy at different doses or periods of administration.

We agree with FDA's proposal to clarify reactions or situations that always require expedited reporting.[25] The list should be considered a list of examples and not an exclusive list. A good model to encourage sponsors or investigators to review the seriousness of reactions is found in ways EPA advises chemical manufacturers to determine whether exposures present a significant risk under TSCA §8(e). EPA collects all such reports in a database - using appropriate business confidentiality protection. Manufacturers are urged to consult the database to learn how other regulated entities have reported. We request that FDA adopt a similar mechanism.

FDA's proposal to direct "active query" followups after initial collection of adverse reaction data is also reasonable.[26] We request that FDA explain that active query procedures be conducted to maintain patient privacy under HIPAA or other requirements, especially if FDA allows followup queries by means that are subject to security breach such as email.

We disagree with FDA's direction that SADRs from class action lawsuits would not be included in expedited reports.[27] FDA speculates that this information may already be provided in other reports prior to initiating the lawsuit. However, the process of class certification may result in significant revisions to the description, severity, frequency and magnitude of the events noticed in other reports. If information sufficient to justify a class action lawsuit differs from earlier reports in any respect, it should be provided.

We support FDA's proposals for worldwide patient exposure reporting.[28] Reports should also be made if any drug or biologic is subject to foreign recall or safety warning letter for any reason. We support FDA's direction to have information broken down by gender and age when possible. Information should also be broken down by race or ethnicity if scientifically relevant.

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[24] p. 12431.
[25] p. 12432.
[26] p. 12434.
[27] p. 12435 and 12443.
[28] p. 12439.

III. CONCLUSION.

Thank you for consideration of these requests. Robert Reinhard has agreed to act as a contact person for any questions or response you may have in connection with this submittal. **Contact info**: Robert Reinhard, 425 Market Street, 32nd floor, San Francisco, CA 94105; telephone: 415/268-7469; fax: 415/268-7522; email: rreinhar@mofo.com. Please let us know if we can answer any questions you have about the comments.

Very truly yours,

Robert Reinhard

Robert J. Reinhard, on behalf of signators

Signators:
Organizations: AIDS Vaccine Advocacy Coalition (AVAC) (http://www.avac.org); San Francisco AIDS Foundation (http://www.sfaf.org); Project Inform (http://www.projectinform.org); Drug Development Committee of the AIDS Treatment Activists Coalition (http://www.atac-usa.org/DDC.html)

Individuals: Gail Broder, MPH; John Bunting (Member, Baltimore Commission on HIV/AIDS); Paul Williams, M.D. (St. Louis HIV Vaccine Trials Network (HVTN) Community Advisory Board); Steve Wakefield (Board Member, AVAC); Robert Reinhard (Board Member, AVAC)

cc: Miles Braun, CBER (HFM-220)