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Dockets Management Branch (HFD-305)
Food and Drug Administration
Room 1061
5630 Fishers Lane,
Rockville, MD 20857

Ref: **Docket No. 01D-0056 - Draft Guidance for Industry on Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines; Availability**

Abbott Laboratories is pleased to have the opportunity to provide comments on the "Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines" Draft Guidance – Notice of Availability published in the Federal Register on March 12, 2001.

We thank the Agency for your consideration of our comments. Should you have any question, please contact Ivone Takenaka (Corporate Regulatory Affairs – Policy& Information Coordinator) at 847-935-9011 or by FAX at 847-938-3106.

Sincerely,

RPoka for Doug Sporn.

Douglas L. Sporn

01D-0056

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COMMENTS TO FDA
DRAFT GUIDANCE FOR INDUSTRY ON
"POSTMARKETING SAFETY REPORTING FOR HUMAN DRUG AND BIOLOGICAL PRODUCTS INCLUDING VACCINES".

(Docket No. 01D-0056)

COMMENTS

I. INTRODUCTION
B. What Does This Guidance Not Discuss?

Line 63

This guidance does not apply to product-manufacturing defects.
Further clarification is needed as to whether product-manufacturing defects would include medication error reports.

Line 75

"The use of mandatory language..." The guidance discusses language that differentiates between statements that are regulatory requirements and those that are Agency policy. Please clarify as to whether or not a regulatory requirement is equivalent to an Agency policy and whether or not a deviation from Agency policy is considered a violation of regulations.

II. BACKGROUND
A. Final Rules

Line 102-103

"... June 25, 1997., the FDA published a final rule revoking..."
Clarification is needed regarding the June 25, 1997 revocation of the requirement to submit postmarketing increased frequency reports to the Agency in an expedited manner as to whether or not this is equivalent to not requiring any submission or completion of such a report.

III. WHO MUST REPORT

Lines 163-165

Please clarify whether a contract manufacturer whose name appears on the label of a marketed product, but another company holds the application and has the sole market authorization, is required to submit postmarketing safety reports to FDA.

IV. WHAT DO I REPORT?
A. Type of Adverse Experiences

Lines 214-219

The guidance states that adverse experiences from postmarketing in vitro and animal investigations need to be submitted to the FDA if the applicant believes

there is "reasonable possibility that the product caused the adverse experience." Guidance is requested as to how to define "reasonable possibility." Clarification is requested whether this would include published/literature/manufacturer studies, and what sources are to be utilized. Please provide the rationale for the relevance of in vitro and animal adverse event reporting and how this differs from Annual Reports. This requirement would greatly increase the applicant's workload. Please clarify as to whether the applicant's determination of causality is to replace that of the author, as recommended in the 5/92 guidance.

Lines 246-249

The guidance states that one of the possible serious outcomes is an "important medical event based upon appropriate medical judgment that may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the definition of serious." Consideration should be given to bringing this statement into harmony with the ICH definition which states "or" rather than "and".

Lines 251-252

Guidance is requested regarding the application of serious outcome to reports of adverse experiences that involve 23-hour observation, overnight observation, or in which the patient visited the hospital, was treated, and released.

Lines 260-263

Clarification is requested regarding whether or not any report from an incarcerated individual would automatically be considered serious. This constitutes a change in the ICH definition of significant or persistent disability/incapacity. Guidance is requested as to how a report identifying the sponsor's drug as the interacting drug but not necessarily the drug reported as responsible for the behavior leading to incarceration, particularly if the latter is an illicit drug, is to be considered.

Lines 265-268

The section regarding important medical events implies that the events listed should be always/automatically considered medically important. This is inconsistent with the ICH Guidances which state that medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations of important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of these serious outcomes. These events should usually be considered serious. Consideration should be given to harmonization with the ICH definition.

Line 268-269

Completion of the "other" box and filling in the adjacent space requires more specific instruction consistent with the Medwatch form instructions.

Lines 271-278
The guidance implies that cases can never be closed if no outcome is obtained or no healthcare professional is identified/contacted for information. Documented attempts at obtaining outcome or contacting a healthcare professional, whether or not successful, should be considered due diligence.

Lines 288-294
The definition of spontaneous has been previously interpreted as equivalent to postmarketing. The guidance implies that spontaneous reports are a subset of postmarketing reports (lines 290-294). The term "spontaneous" needs to be clearly defined, due to potential implications for current validated processes.

This section also states that spontaneous reports should not include adverse experiences identified from information solicited... (e.g. any organized data collection scheme) requires clarification as to whether this pertains to manufacturer-sponsored surveys. Additionally, guidance is requested regarding the handling of regulatory agency initiated surveys, such as AFSSAPS' survey for protease inhibitor reports of myocardial infarction or bone disorders, if they are not to be considered spontaneous reports. Please clarify how Pregnancy Registry and Patient Named Programs reports should be reported on the periodic report and indicated on the Medwatch form (Should we check study?).

B. Data Elements to Include in a Postmarketing Individual Case Safety Report

Lines 316-321
The requirement for direct verbal contact with the reporter is overly restrictive, particularly outside of the U.S. where culturally acceptable ways of obtaining follow up are country-specific. If a letter results in the acquisition of information, phone call may be unnecessary. Some reporters may refuse or avoid phone follow up attempts, or specifically request written communications.

In response to the FDA's proposal that only healthcare professionals are to make contact with the initial reporters, we suggest that, with appropriate training to regulations and AE reporting, non-healthcare professionals can effectively investigate and prepare reports. Since a majority of consumer-only reports are nonserious and limited in information, using non-healthcare professionals eases the workload burden. Additionally, consumer-only reports are considered not medically confirmed internationally. Medical follow up is performed by a healthcare professional. This proposal eliminates the possibility of utilizing an allied medical professional or an individual with safety experience in this capacity.

Lines 326-330
Clarification is requested regarding "identifiable patient." Does provision of a specific number of patients mean that a patient is identifiable (e.g. 4 patients had a

rash), when no further information is available? If identified on the basis of the number of patients only, is this 1 case of 4 patients or 4 separate cases?

Line 330
Please clarify on confidentiality and the use of consumer reporter information in the case in which the consumer is the only reporter

Lines 337-342
Guidance is requested on the handling of reports of dispensing errors or medication errors in which no additional adverse events are identified.

V. TYPE OF REPORTS

A. 15-Day Reports of Serious, Unexpected Adverse Experiences

Lines 373-375
The exclusion of U.S. federal holidays in the 15 calendar day count is inconsistent with ICH guidelines and meeting report timelines, consideration should be given to harmonization with these.

Line 381
Inclusion of contact attempt documentation will create a longer narrative if added to the Medwatch 3500A. This is inconsistent with the FDA proposal later in the guidance to shorten the narrative due to AERS limitations. This information is already available upon Agency request, in the company's AE files, and does not need to be included in the 3500A. This proposal would require duplicate workload, as many companies track this systematically.

Lines 402-407
Including patient source documents routinely in report submissions will increase the amount of paperwork forwarded to the FDA that duplicates information on the Medwatch form. Also, confidentiality and informed consent of reporters will require a formalized process, and may potentially result in poor follow-up quality since reporters are hesitant to break patient confidentiality in a regulatory environment that does not mandate public reporting. Translation issues for ex-US reports puts added workload burden on affiliates. This also does not prepare for future E2B submissions. Consideration should be given to eliminating this proposed requirement.

Does the inclusion of attachments eliminate the need to add relevant medical information to the Medwatch form (if information is in the attachment)?

B. Periodic Reports

Line 455
It is not reasonable to require PSUR-like changes to the periodic report, while regulations are pending. This would result in current system changes to support these periodic changes followed by further changes when the PSUR regulations are published. Time frames for periodic reports are different from PSUR. Clinical data is not required by current regulations.

Line 465-468
It is noted that the proposed ordering of sections differs from the current regulation. The impact of this on the current computer system generation of the periodic needs to be further explored, as the system now prints and paginates in the order requested by the current regulation/guidelines.

Lines 486-495
Please clarify whether or not reports received from the FDA should be included in the summary tabulation by body system of the periodic report if additional information has not been received.

Lines 500-504
Current regulations request a summary of AE reports in which the drug or biological product was listed as one of the suspect products, but the report was filed to another NDA, ANDA, or BLA held by the applicant. The proposed regulations request a listing. Please clarify regarding this format.

Line 506
Guidance is requested regarding assessment of AE frequency changes.

Lines 579-581
Regarding Lack of Effect – should these reports be specifically identified under separate tabulation?

Line 583-587
Inclusion of source documents with FDA 3500A forms of serious, expected reports in Section 4 of the periodic should not be required. This increases the amount of paper forwarded to the FDA that includes the same medically relevant information that would already be on the Medwatch 3500. This additionally would require formalized confidentiality and information release agreements between company and reporter.

C. Follow up Reports

Lines 613-631
Re-writing the narrative in follow up reports should not be a requirement. FDA currently advises that follow-up should be identified. Current AE software systems cannot support rich text format, therefore, sequential follow-up identified by received dates is the clearest way to demonstrate follow-up information. Manual highlighting of reports would add to the workload burden, and be confusing in cases of multiple follow-ups. Manual highlighting would not be consistent with the spirit of electronic reporting (E2B).

Lines 633-635
Concise narratives in follow up reports should not be a requirement. It is an industry responsibility to provide all medically relevant AE information, and the length and quality of information needs to be handled on an individual case basis. Also, the history of reporting has seen increase in space for narratives, from the 7-line 1639 to the current multiple page 3500A format.

Definition for "concise" is required: medically relevant information is required to demonstrate a complete clinical picture. Additionally, we suggest the elimination of the previous FDA request for contact documentation in order to utilize the space for important medical data.

Lines 639-641
Please clarify whether or not follow-up is required for non-serious reports that contain the 4 basic elements. Does this pertain to both non-serious expected and unexpected reports?

There is significant potential to miss the collection of information that may lead to signals and impact a drug's safety profiles if follow-up is not required on cases that are nonserious by regulatory definition. Additionally, follow up may identify that a report is, in fact, serious.

Lines 656-658
Please clarify that a report that was initially received by the company as a non 15 day report, should be submitted as a follow-up 15 day report when follow-up information is received that changes the regulatory status and not submit as an initial 15 day report. Is the handling changed if the report was submitted in a periodic previously?

Lines 660-667
We request clarification on how to handle reports from clinical trials (IND) that meet NDA reporting requirements. E.g.: In the situation of the same patient in the same study on a drug with an NDA and the same events occurred with 2

hospitalizations separated by time, is this submitted as 1 case with follow-up, or 2 initial cases? If there are 2 different events, is this 1 case with follow-up, or 2 initial cases?

VI SPECIAL REPORTING SITUATIONS

A. Scientific Literature Reports

Lines 738- 745

Please provide clarification on submission of serious unexpected literature reports based on abstracts only, when the abstract provides sufficient information to identify the 4 basic components of a report. Should one wait for the article, even if it takes more than 15 days from awareness to obtain the full article? Does the prohibition against submitting abstracts apply to abstracts presented at meetings for which no full publication may ever be available?

Please clarify the role of a generic manufacturer in the submission of literature that does not specify the use of the generic product by its brand name. Special reporting situations section does not address the issues of literature reporting responsibilities of an innovator versus a generic manufacturer (specifically, when the literature doesn't indicate whether the drug was a generic or not).

Line 762-765

Should any report be generated if it is known that an applicant does not manufacture or hold any applicants for formulations of the product mentioned in the article? This cause potential confusion when the suspect drug is presented in generic name.

Recommended change: When the suspect drug is presented in generic name and the manufacturer source has not been identified for the suspect drug, the applicant(s) owning products with the same active ingredients and formulation, should submit reports described in the scientific literature.

B. Postmarketing, Clinical Trial, or Surveillance Studies

Line 775-776

The examples given in parenthesis as postmarketing studies are different from the description in section IV, A, line 214-216, where it stated that postmarketing studies include in-vitro, animal.... Please clarify.

Lines 793-799

Please provide detailed clarification and guidance for the handling of Private IND and IND Exempt studies on NDA approved products, when an investigator forwards blinded information to the company, but does not break blind.

C. Foreign Reports

Lines 811-813
Printing NDA number in C1 should not be a requirement as it already prints in the appropriate section G.

D. Death Reports

Lines 817-820
Will the previous guideline for "death only" reports still apply, i.e. "death only" as serious expected? (This is in reference to "death (nos)" rather than "sudden death").

F. Lack of Effect Reports

Lines 836-839
The statement emphasizing that "All ...lack of effect reports should be reported on a 3500A form and ...submitted in the periodic report...", seems to be inconsistent with the earlier statement (line 575) encouraging application for a waiver for non-serious lack of effect reports. Also, "all" implies lack of effect could be reported for non-indicated uses as well. The word "All" should be deleted.

G. Information on the Internet

Lines 848-855
We request consideration that Internet AE should be handled consistently like media report sources (hearsay). Reporters from the Internet should not necessarily be considered "identifiable". This form of anonymous reporting is more open to fraudulent and less verifiable reporting than more traditional means. We agree with the requirement that company sites should be monitored for AEs.

H. Pediatric Patients

Line 862
Placeholder initial/abbreviations for the actual words "day, month, year" should be considered.

Lines 864-870
Regarding congenital anomaly follow-up for events obtained through pregnancy registries, follow-up requests are regulated by the charter/SOPs of the registry. Please comment on the manufacturer responsibility for follow-up in these cases.

J. Another Applicant's Product

Lines 891-894
Please provide clarification on reporting responsibility. Routinely, other suspect company's products are listed as suspect on the Medwatch form. The guidance implies that it is the applicant's responsibility to report for the other company's suspect product if the company is not known or if the report is serious, unexpected occurring during the conduct of a study. This further implies that the applicant should have knowledge of another company's product labeling and send the non-applicant suspect drug under separate cover to the Agency. The requirement for reporting in a study is inconsistent with prior wording that "associatedness" was required in addition to seriousness and unexpectedness.

J. Another Applicant's Product and
K. Multiple Suspect Products

Lines 898-918
Please clarify that, when an applicant receives a copy of a 3500A from another company, that this information should not be resubmitted to the FDA, in the absence of any other information. The guidance contains contradictory statements regarding this.

It would be helpful if all scenarios where FDA does not want to receive information from the applicant are delineated, e.g. Medwatch Program, USP and related, if the reporter checks "also reported to the FDA", when one of the suspect applicants has already sent a report to FDA.

Also, we request clarification on FDA expectations for applicants to share follow-up information received in parallel, and the impact on the voluntary reporter who receives follow-up requests from more than one applicant.

O. Product Interaction

Lines 950-952
If a labeling change is made regarding a drug interaction, please clarify the manufacturer's responsibilities regarding notification of the manufacturer of the interacting medication.

P. Reports from the FDA

Lines 959-960
Please clarify the definition of initial reporter that goes on the Medwatch form if follow-up information is received from another report source. Is initial reporter always equivalent to the first reporter, or, in follow-up, may it be the healthcare professional or reporter that provided the most relevant information?

VIII. REPORTING FORMATS

Lines 1093 –1097
Certain of the FDA's proposed format changes (e.g. margins, including the company name at the top of each Medwatch page, adding "FDA Facsimile Approval," etc.) will necessitate investigation regarding current computer system reporting capabilities and vendor system validation issues.

Lines 1099-1100
Please clarify whether or not the company name should be both in the right hand corner and centered on the top of the first page of the Medwatch.

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- [x] FedEx Standard Overnight — Next business afternoon
- [ ] FedEx First Overnight — Earliest next business morning delivery to select locations
- [ ] FedEx 2Day* — Second business day
- [ ] FedEx Express Saver* — Third business day

*FedEx Envelope/Letter Rate not available. Minimum charge: One-pound rate

4b Express Freight Service *Packages over 150 lbs.* Delivery commitment may be later in some areas.

- [ ] FedEx 1Day Freight* — Next business day
- [ ] FedEx 2Day Freight — Second business day
- [ ] FedEx 3Day Freight — Third business day

* Call for Confirmation: * Declared value limit $500

5 Packaging

- [x] FedEx Envelope/Letter*
- [ ] FedEx Pak*
- [ ] Other Pkg. Includes FedEx Box, FedEx Tube, and customer pkg.

6 Special Handling Include FedEx address in Section 3.

- [ ] SATURDAY Delivery — Available for FedEx Priority Overnight and FedEx 2Day to select ZIP codes
- [ ] SUNDAY Delivery — Available for FedEx Priority Overnight to select ZIP codes
- [ ] HOLD Weekday at FedEx Location — Not available with FedEx First Overnight
- [ ] HOLD Saturday at FedEx Location — Available for FedEx Priority Overnight and FedEx 2Day to select locations

Does this shipment contain dangerous goods? One box must be checked.

- [x] No
- [ ] Yes — As per attached Shipper's Declaration
- [ ] Yes — Shipper's Declaration not required
- [ ] Dry Ice — Dry Ice, 9, UN 1845 ____ x ____ kg
- [ ] Cargo Aircraft Only

Dangerous Goods cannot be shipped in FedEx packaging.

7 Payment *Bill to:* Enter FedEx Acct. No. or Credit Card No. below. Obtain Recip. Acct. No

- [x] Sender — Acct. No. in Section 1 will be billed.
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- [ ] Third Party
- [ ] Credit Card
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Total Packages 1 Total Weight Total Charges Credit Card Auth.

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