

05/02 '02 JUN 20 12:40



January 21, 2002

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

**RE: Docket No. 01N-0464, Proposed "Vaccine Adverse Event Reporting System; Revised Form VAERS-2; Availability" – 66 Federal Register 58153: November 20, 2001**

Merck & Co., Inc. is a leading worldwide, human health product company. Merck's corporate strategy -- to discover new medicines through breakthrough research -- encourages us to spend more than \$3 billion annually on worldwide Research and Development (R & D). Through a combination of the best science and state-of-the-art medicine, Merck's R & D pipeline has produced many of the important pharmaceutical products on the market today.

As a leading human health care company responsible for providing health care professionals with full and complete prescribing information for its many marketed products, Merck is very interested in the proposed revision to the Vaccine Adverse Event Reporting System (Form VAERS-2). Since this revised form is intended to facilitate electronic reporting and Merck is currently submitting to FDA (CDER) all spontaneous 15-Day alert reports for pharmaceutical products in electronic format according to ICH E2B, "Data Elements for Transmission of Individual Case Safety Reports," Merck is especially well qualified to comment on this topic.

The comments below are divided into (1) general comments and recommendations regarding the proposed Form VAERS-2; (2) specific comments addressing individual data items on the Form VAERS-2, as proposed by FDA; (3) implementation of database and report changes; and (4) conclusions.

**1. General Comments**

We commend the FDA on its efforts to facilitate the electronic transmission of vaccine adverse experience reports. Merck supports Agency efforts to standardize the transmission of safety reports for vaccines along the same lines as those established for drugs. To achieve this goal, Merck recommends that the Agency concentrate its efforts on ensuring that the Form VAERS-2 is consistent with ICH E2B, rather than adding new fields that deviate from ICH standards. The addition of unique fields to the Form VAERS-2 is problematic for manufacturers who would need to add several new database fields and create new reporting

01N-0464

C3

forms to accommodate the FDA. In addition, Merck recommends that any revisions to the Form VAERS-1 be accompanied by instructions for completing the form; the instructions are helpful to the public when commenting on the significance of proposed changes.

## 2. Specific Comments

### 2.1 Organization of the Form

- The revised/reformatted form is more user-friendly for both naïve and experienced individuals who complete the form. However, the statement at the very top of the Form VAERS-1, “Patient Identity Kept Confidential,” has been deleted from Form VAERS-2.

**Recommendation:** This statement should be maintained to promote and facilitate reporting.

- The actual layout of the Form VAERS-2 has been revised logically and is aesthetically pleasing. Dividing the Form VAERS-2 logically into boxes, labeling each box alphabetically, and providing main descriptors for each box will facilitate the user’s ability to complete the form appropriately. However, the Form VAERS-2 does not consistently provide numbers within each box for data elements within the box, which could be a source of confusion. For example, Box E has only two numbered data fields within the box, namely “5. List results of relevant diagnostic procedures or lab testing,” and “6. Has the patient recovered to his/her original state of health?” Other data fields within the box have no numbering at all.

**Recommendation:** All data fields within lettered boxes should be consistently numbered.

- Date fields in Boxes A, C, D, and E on the Form VAERS-2 should identify the format for date reporting to eliminate any confusion.

**Recommendation:** “\_/\_/” should define the order of the fields by including “mm/dd/yy” in parentheses or below the lines, similar to the Form VAERS-1. Alternatively, to take up less room on an already crowded form, an explanation of the preferred format could be provided in the instructions for completing the form.

### 2.2 Content of the Form

- **Box A:** Several new fields have been added to Box A, namely, “Patient’s Occupation,” “Parent/Guardian Name,” and “Race/Ethnicity,” all of which are not consistent with ICH E2B data elements.

**Recommendation:** While providing additional and perhaps relevant information to an adverse experience report, any new data field should be consistent with ICH E2B.

- **Box A:** The data fields, "Date of birth," and "Age at vaccination," lack numbers within Box A.

**Recommendation:** These data fields should be numbered items within Box A.

- **Box B:** Item 7 now includes several additional choices that are not consistent with ICH E2B data elements. Additions to database reference tables will be required.

**Recommendation:** All data fields should be consistent with ICH E2B.

- **Box C:** Item 1 requests the reporter of the information be identified as "Reporter is the person listed: in Box A, in Box B or Below". The choice, "Below," for the reporter is confusing. It is unclear as to whether the latter refers to the "primary/original reporter," or a secondary reporter, such as the manufacturer.

**Recommendation:** If the intent is to capture the primary reporter's identity, it may be more appropriate to change the heading to "Primary Reporter Information" instead of indicating "Below". If the intent is to capture who completed the form, it may be more appropriate to change the heading to "Form completed by".

- **Box C:** Items 1, 4 and 8 are new data fields, and may provide important information, however, they are inconsistent with ICH E2B data elements. Item 7 is to be used for the date the form is completed. On the Form VAERS-1, this field reflects the date the form is completed by the individual/manufacturer, responsible for submitting the form to FDA. For Item 8, the check boxes for the relationship to patient list an incorrect title of "Physicians' Assistant."

**Recommendation:** All fields should be consistent with ICH E2B. If Item 7 is to be used in a manner consistent with the Form VAERS-1, this Item should not reside in Box C, but should appear as a separate field to be utilized by the reporter of an adverse experience, i.e., primary or secondary. For Item 8, the correct title is "Physician Assistant."

- **Box D:** Box D does not contain any numbered items, thereby appearing inconsistent with other boxes on the form. The "Dose number in series," is a new data field for use by manufacturers, but is inconsistent with ICH E2B data elements.

**Recommendation:** Box D should be consistent with other lettered boxes on the form and contain numbers for various items within the box. All new data fields should be consistent with ICH E2B. Additionally, rather than having two separate lines for the time of vaccination, it may be more appropriate to have one line with a checkbox for AM or PM, as found on the Form VAERS-1.

- **Box E:** The new data field included in Box E, “How soon after vaccination did these event(s) start?” is consistent with the ICH E2B data element, B.4.k.13.1, “Time interval between (vaccination) and start of reaction/event,” and is useful information.

However, “Date of the visit (where “event caused the patient to visit the doctor” is checked yes),” “List event (for a life threatening event),” “Date Admitted (to hospital),” and “List disability,” are new data fields that are not consistent with ICH E2B data elements.

**Recommendation:** All data fields should be consistent with ICH E2B data elements.

- **Box E:** The item, “Did this event cause the patient to visit the doctor?” no longer includes Emergency Room visit.

**Recommendation:** This item should be revised to include Emergency Room visits.

- **Box E:** The item, “Has patient recovered to his/her original state of health,” has added more clarity to the question; however, the reason for adding, “not yet,” is not obvious. Does this imply that recovery is anticipated?

**Recommendation:** Merck recommends that the Agency consider making the outcomes on the Form VAERS-2 consistent with the ICH E2B outcomes at the reaction/event (B.2.i.8) level which include: recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, and unknown.

- **Box E:** The item, “Check below if the patient,” lists several choices. The choice of “Required medical intervention to prevent any of the above outcomes,” and Item 5 of Box G, “Does this report qualify as an OMIC (Other Medically Important Condition),” are redundant. Title 21 CFR 314.80(a) and 600.80(a), define “serious” as, “Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgement, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (of serious adverse drug experiences)”. ICH E2A uses the following definition, “Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as 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 the other outcomes listed in the definition above. These should also usually be considered serious.” ICH E2B uses the phrase, “other medically important condition,” as defined by the ICH E2A Guideline.

**Recommendation:** Since each of the above definitions describes the same type of serious criteria for an adverse experience, the redundancy on the form should be eliminated and captured once in Box E as “other medically important condition,” thereby achieving consistency with ICH E2B data elements.

**3. Implementation of Database and Report Changes**

Implementation of the proposed changes to the database in support of the additional data fields on the Form VAERS-2 will require approximately 4 person months (85 person days) for design specifications, development, testing and validation. An additional 3 person months would be required for development, validation, testing and deployment of the actual form. Implementing these changes seems counterproductive given that many of the new data fields are not consistent with ICH E2B data elements and will not facilitate electronic reporting.

**4. Conclusions**

Merck commends FDA for its efforts to facilitate electronic reporting by making the Form VAERS-2 more user-friendly. Merck has participated with health authorities worldwide, in the harmonization of regulatory standards under the auspices of the International Conference on Harmonization (ICH). The objectives of ICH have been to identify and correct unnecessary redundancies and time-consuming inefficiencies in the regulatory arena worldwide. The addition of new fields unique to FDA, that are not consistent with ICH E2B data elements, may prove to be counterproductive by imposing additional burdens on manufacturers and may not facilitate electronic reporting.

We appreciate your consideration of the above comments and are available to meet with you to discuss these issues.

Sincerely,



Henrietta Ukwu, M.D.  
Vice President  
Worldwide Regulatory Affairs  
Vaccines/Biologics



Linda S. Hostalley  
Executive Director  
Adverse Experience Reporting Worldwide  
Worldwide Product Safety & Epidemiology

119

252

**FedEx** USA Airbill  
Express

FedEx  
Tracking  
Number

8312 8300 1570

Form  
I.E. No.

0215

Recipient's Copy

**1 From** This portion can be removed for Recipient's records.

Date 11/21/02 FedEx Tracking Number 831283001570

Sender's Name Linda Hostalley Phone 484344-2416

Company MERCK RESEARCH LABS

Address 518 TOWNSHIP LINE RD BLX-30

Dept./Floor/Suite/Room

City BLUE BELL State PA ZIP 19422-2313

**2 Your Internal Billing Reference** 577267746040

**3 To**  
Recipient's Name \_\_\_\_\_ Phone \_\_\_\_\_

Company Dockets Management Branch (HFA-305)

Address Food and Drug Administration  
To "HOLD" at FedEx location, print FedEx address. We cannot deliver to P.O. boxes or P.O. ZIP codes.

5630 Fishers Lane, Room 1061

Dept./Floor/Suite/Room

City Rockville State MD ZIP 20852



0195793280

**4a Express Package Service**

**Packages up to 150 lbs.**  
Delivery commitment may be later in some areas.

- FedEx Priority Overnight  
Next business morning
- FedEx Standard Overnight  
Next business afternoon
- FedEx First Overnight  
Earliest next business morning delivery to select locations
- FedEx 2Day  
Second business day  
FedEx Envelope rate not available. Minimum charge: One-pound rate
- FedEx Express Saver  
Third business day
- NEW FedEx Extra Hours  
Later drop-off with next business afternoon delivery for select locations

**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

**5 Packaging**

\* Declared value limit \$500

- FedEx Envelope\*
- FedEx Pak\*  
Includes FedEx Small Pak, FedEx Large Pak, and FedEx Sturdy Pak
- Other Pkg.  
Includes FedEx Box, FedEx Tube, and customer pkg.

**6 Special Handling**

Include FedEx address in Section 3.

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

**Does this shipment contain dangerous goods?**

One box must be checked.

- No
- Yes  
As per attached Shipper's Declaration
- Yes  
Shipper's Declaration not required
- Dry Ice  
Dry Ice, 9 JAN 1845 \_\_\_\_\_ kg
- Cargo Aircraft Only

**7 Payment Bill to:**

Enter FedEx Acct. No. or Credit Card No. below.

- Sender  
Acct. No. in Section 1 will be billed
- Recipient
- Third Party
- Credit Card
- Cash/Check
- Obtain Recip. Acct. No.

Total Packages

Total Weight

Total Charges

\*Our liability is limited to \$100 unless you declare a higher value. See the FedEx Service Guide for details.

**8 Release Signature** Sign to authorize delivery without obtaining signature.

By signing you authorize us to deliver this shipment without obtaining a signature and agree to indemnify and hold us harmless from any resulting claims.  
**Questions? Visit our Web site at fedex.com**  
or call 1.800.Go.FedEx® 800.463.3339.  
SRS • Rev. Date 7/01 • Part #1572325 • ©1994-2001 FedEx® PRINTED IN U.S.A.

447