Guidance for Industry

Postmarketing Adverse Event Reporting for Medical Products and Dietary Supplements During an Influenza Pandemic

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Counterterrorism and Emerging Threats (OCET)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Center for Food Safety and Applied Nutrition (CFSAN)

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TABLE OF CONTENTS

Guidance for Industry[1]

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides recommendations to industry regarding postmarketing adverse event reporting for drugs, biologics, medical devices, and dietary supplements during an influenza pandemic. FDA anticipates that during an influenza pandemic, industry and FDA workforces may be reduced because of high employee absenteeism, while reporting of *adverse events*[2] related to widespread use of medical products indicated for the treatment or prevention of influenza may increase. The extent of these possible changes is unknown. This guidance discusses FDA's intended approach to enforcement of adverse event reporting requirements for medical products and dietary supplements during an influenza pandemic. FDA believes this approach will make it possible for firms with reporting responsibilities to focus their limited resources on the following types of reports:

- reports related to medical products indicated for the treatment or prevention of influenza
- other reports indicated in this guidance
- reports on products presenting special concerns as specified by FDA

[1] This guidance has been prepared by the Office of Surveillance and Epidemiology in the Center for Drug Evaluation and Research (CDER) in cooperation with the Office of Counterterrorism and Emerging Threats (OCET) in the Office of the Commissioner and the Centers for Biologics Evaluation and Research (CBER), Devices and Radiological Health (CDRH), and Food Safety and Applied Nutrition (CFSAN) at the Food and Drug Administration.

[2] For purposes of this guidance, the term *adverse event* includes adverse experience and adverse reaction. Appendix 1 lists in abbreviated form the current adverse event reporting requirements for drugs, biologics, medical devices, and dietary supplements. Refer to the relevant statutes, regulations, and guidance documents for complete information.

This guidance is not intended to discourage adverse event reporting during an influenza pandemic by firms that are able to continue reporting operations. In addition, this guidance does not address monitoring and reporting of adverse events that might be imposed as a condition for medical products authorized for emergency use under section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360bbb-3).[3] This guidance also does not address monitoring and reporting of adverse events as required by regulations establishing the conditions for investigational use of drugs, biologics, and devices. (See 21 CFR parts 312 and 812.)

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Pandemic preparedness is a global responsibility. It is expected that widespread human outbreaks of pandemic influenza, whether overseas or in the United States, will affect industry's normal functions. Although overseas outbreaks may not seem to directly affect domestic operations, international medical product and dietary supplement production, availability, and adverse event reporting may be disrupted if a firm's international sites are affected. Thus, industry should develop plans to ensure continuity of operations during an influenza pandemic (discussed in section III.B). It is important that firms consider the adverse event reporting functions of their U.S. locations and their international locations in the face of a potential pandemic.

III. PREPAREDNESS FOR ADVERSE EVENT REPORTING DURING AN INFLUENZA PANDEMIC

A. Information on Pandemic Influenza Preparedness

The Department of Health and Human Services (HHS) manages the U.S. Government flu information Web site (www.pandemicflu.gov), which provides a variety of information about influenza, including general information on pandemic influenza preparedness planning. Manufacturers should refer to the Web site frequently for updated information on influenza.

B. Development of a Continuity of Operations Plan in the Case of an Influenza Pandemic

To access general information on pandemic influenza preparedness planning, firms should refer to the pandemicflu.gov Web site.[4] This site recommends that each firm should develop a

[3] For information regarding Emergency Use Authorizations (EUAs), please refer to the guidance on *Emergency Use Authorization of Medical Products* (July 2007), available on the Internet at http://www.fda.gov/RegulatoryInformation/Guidances/ucm125127.htm.

[4] Available at http://www.pandemicflu.gov under "For Professionals, Business Planning."

continuity of operations plan (COOP) to ensure that its operations continue during all stages of pandemic influenza. Guidance on developing COOP plans is available from various sources. For example, the U.S. Department of Homeland Security (DHS) has issued a *Pandemic Influenza Preparedness, Response, and Recovery Guide for Critical Infrastructure and Key Resources,* which addresses the development and implementation of a "Continuity of Operations – Essential (COP-E)" plan.[5]

This guidance is limited to FDA recommendations for reporting adverse events during a period of pandemic influenza. Each firm's pandemic influenza COOP plan should include instructions for reporting adverse events and provide a plan for the submission of any stored reports not submitted in the regulatory timeframes.

C. FDA Expectations for Adverse Event Reporting During an Influenza Pandemic

1. Reporting Requirements During an Influenza Pandemic

During an influenza pandemic, normal adverse event reporting processes should be maintained to the maximum extent possible. All adverse event data should be handled using each firm's usual standard operating procedures, and regulatory and statutory requirements for adverse event reporting should be met to the maximum extent possible.

Firms should develop and prepare to implement their COOP in the event that they are not able to fulfill all adverse event reporting requirements because of pandemic-related high employee absenteeism. FDA recommends that in planning, firms consider the following types of factors (not all-inclusive):

- What activities are directly relevant to the processing and submission of mandatory adverse event reports to FDA?
- How would sites based in the United States and abroad be differentially affected by a pandemic?
- What are the relative amounts of resources dedicated to mandatory adverse event reporting at each site?

Firms that are unable to fulfill normal adverse event reporting requirements during an influenza pandemic should maintain documentation of both of the following conditions:

[5] Available at http://www.pandemicflu.gov under "For Professionals, Federal Government, Other Federal Agency Activities."

218
219 1. Declaration of an influenza pandemic (e.g., by federal government), including date of
220 declaration of the pandemic and ending date of the pandemic, and
221 2. High absenteeism and/or other factors (e.g., an increase in adverse event reporting) that
222 is/are preventing the firm from meeting normal adverse event reporting requirements

224
225The appropriate FDA organizational units responsible for adverse event reporting compliance
226should be notified when these conditions exist.
227
228 *2. Enforcement Approach During an Influenza Pandemic with High Employee*
229 *Absenteeism*
230
231FDA anticipates that during an influenza pandemic, industry and FDA workforces may be
232reduced because of high employee absenteeism at the same time that reporting of adverse events
233related to influenza-related medical products may increase.
234
235FDA encourages all firms to plan for these circumstances to maintain the highest feasible level
236of adverse event monitoring and reporting throughout the pandemic period when a firm is
237experiencing pandemic-related high employee absenteeism. Recognizing that a pandemic may
238reduce a firm's capacity to comply with adverse event reporting requirements, however, FDA
239offers this general guidance to help manufacturers strategize use of their resources.
240
241As explained below, FDA does not intend to object if, because of pandemic-related high
242employee absenteeism, certain required adverse event reports are not submitted to the FDA
243within the timeframes required by statute and regulation, provided that any delayed reports are
244submitted within 6 months of the restoration of adverse event reporting processes to their pre-
245pandemic state (see section III.D for discussion of prioritizing timeframes for submission of
246stored reports).
247
248Table 1 indicates which reports firms may generally *store if necessary* because of pandemic-
249related high employee absenteeism, without FDA objection. Where Table 1 indicates a type of
250report may be stored if necessary, this means that FDA does not intend to object if firms
251maintain newly received information regarding the underlying adverse events and do not submit
252reports in the timeframes mandated by statute or regulation. However, any delayed reports must
253be submitted after adverse event reporting processes have been restored to the pre-pandemic
254state. Firms should maintain records to identify what has been stored and when the processes
255were restored.
256
257This guidance does not apply to adverse event reporting during an influenza pandemic by firms
258that are able to continue reporting operations. Firms that are able to report more than the
259minimum described in Table 1 but less than that required by the statute and applicable
260regulations should prioritize the order of report submissions. For example, reports with
261regulatory timeframes of 30 days or less (e.g., 15-day reports, 30-day reports) should be
262submitted before periodic safety reports. During an influenza pandemic, all firms are strongly
263encouraged to submit as many required reports as possible. This will minimize reporting
264burdens once adverse event reporting processes have been restored to the pre-pandemic state.
265

FDA intends to communicate with firms if there are products and issues that present special concerns and for which the agency therefore expects compliance with normal reporting as required by statute and regulation during the influenza pandemic. Special concerns could include:

- product-related safety issues such as (but not limited to) newly emerging safety issues (e.g., an antihypertensive drug associated with liver failure or a non-influenza vaccine associated with anaphylaxis)
- product problems with associated adverse events (e.g., nonfatal serious infections associated with a pre-filled syringe that was recalled due to bacterial contamination)

As indicated in Table 1, if FDA has specified a product as presenting special concerns, firms must submit required adverse event reports regardless of the more general recommendations in Table 1. Aside from this circumstance, in Table 1, reporting recommendations for drugs and biologics are prioritized by type of product so that reporting can focus on products that are likely to have greater use and may necessitate greater monitoring during an influenza pandemic. Further, 15-day reports have priority over periodic reports. For medical devices, the reporting priority is specified by outcome (i.e., fatal outcome vs. nonfatal outcome). Table 1 also includes reporting recommendations for other products and additional details.

D. Reporting After the Influenza Pandemic

After the influenza pandemic, it is expected that firms will resume fulfilling all reporting requirements on time as well as submit reports that were stored because of pandemic-related high employee absenteeism**.** Firms should follow their plan for the submission of the stored reports not submitted in the regulatory timeframes. Firms are generally expected to submit stored reports to FDA within 6 months of restoration of the adverse event reporting process to the pre-pandemic state. Firms should prioritize the order of submission for stored reports. For example, reports with regulatory timeframes of 30 days or less (e.g., 15-day reports, 30-day reports) should be submitted before periodic safety reports.

Firms that cannot meet adverse event reporting requirements at the minimum levels identified in this guidance should consult the appropriate FDA organizational unit responsible for adverse event reporting compliance.

IV. PAPERWORK REDUCTION ACT OF 1995

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3043501-3520).

The time required to complete this information collection is estimated to average 50 hours per response to prepare an adverse reporting plan for a COOP and 8 hours per response to notify FDA when normal reporting is not feasible, to maintain documentation of influenza pandemic conditions and resultant high absenteeism, and to maintain records to indentify what reports have been stored and when the reporting process was restored, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. Send comments regarding this burden estimate or suggestions for reducing this burden to:

Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, rm. Xxxx, Silver Spring, MD 20993-0002.

This guidance also refers to previously approved collections of information found in FDA's adverse event reporting requirements in 21 CFR 310.305, 314.80, 314.98, 600.80, 606.170, 640.73, 1271.350, and part 803. These regulations contain collections of information that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520) and are approved under OMB control numbers 0910-0116, 0910-0291, 0910-0230, 0910-0308, 0910-0437, and 0910-0543. In addition, the guidance also refers to adverse event reports for nonprescription human drug products marketed without an approved application and dietary supplements required under sections 760 and 761 of the Act (21 U.S.C. 379aa and 379aa-1), which include collections of information approved under OMB control numbers 0910-0636 and 0910-0635.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this information collection is 0910-xxxx (expires xx/xx/xxxx).

332 **Table 1. FDA Approach to Postmarketing Safety Reporting During an Influenza Pandemic if Normal Processes of**
333 **Mandatory Adverse Event Reporting Are Not Feasible Because of High Employee Absenteeism**
334

Type of Product or Application	**Type of Report(s)/Statutory or Regulatory Timeframe(s)[6]**	**FDA Recommended Reporting During an Influenza Pandemic With High Employee Absenteeism**
Products with special concerns as specified by FDA (any product or application type below)[7]	As per regulation(s) and/or statute(s) relating to the FDA-specified product	Submit[8]
Prescription drug products marketed without an approved NDA	15-day Alert report, 15-day Alert report -follow up / 15 calendar days	Store if necessary[9]
Approved NDA, Approved ANDA 1. labeled indication for influenza 2. approved within prior three years 3. all other products	15-day Alert report, 15-day Alert report -follow up / 15 calendar days AND Reports to applicant (or licensed manufacturer) instead of FDA / 5 calendar days	Approved NDA, Approved ANDA 1. Submit 2. Submit 3. Store if necessary
Approved BLA 1. Pandemic influenza vaccines 2. Biologics (vaccines or nonvaccines) approved within prior three years 3. Other biologics (vaccines or nonvaccines)		Approved BLA 1. Submit 2. Submit 3. Submit death outcome reports. Store if necessary other serious outcome (non-death) reports.
Approved NDA: all products	Periodic adverse drug experience report[10]/ Quarterly for 3 years from the date of U.S. approval of the application (or license) and then annually thereafter	Store if necessary
Approved ANDA: all products		
Approved BLA: all products		

39[6]
40[71] Refer to Appendix 1 for Current Requirements for Postmarketing Safety Reports.
41[7] FDA will specifically communicate with firms regarding which products present special concerns. Refer to section III.C.2 of this guidance for further
42discussion of special concern products.
43[8] As used in this document, "submit" means that the Agency continues to expect compliance with the specific regulatory requirements for submission, including
44applicable timeframes.
45[9] Refer to section III.C.2 of this guidance.
46[10] Includes periodic safety update reports (PSURs) if applicant has a waiver allowing submission of PSURs in lieu of periodic adverse (drug) experience reports.
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Type of Product or Application	**Type of Report(s)/ Statutory or Regulatory Timeframe(s)**	**FDA Recommended Reporting During an Influenza Pandemic With High Employee Absenteeism**
Nonprescription Drugs Marketed without an Approved Application[11]	Serious adverse event report / 15 business days	Store if necessary
Dietary Supplement Products	Serious adverse event report / 15 business days	Store if necessary
Blood and Blood Components	Blood collection/transfusion fatality report / As soon as possible (oral or written) and 7 days (written)	Submit
Source Plasma	Donor fatality report / As soon as possible (oral)	Submit
Human Cells. Tissue, and Cellular and Tissue-Based Products (HCT/P)	Adverse reaction report / 15 calendar days	Submit
Medical Device	Manufacturer Medical Device Report (MDR) to FDA / 5 work days	Submit
	Manufacturer MDR to FDA / 30 calendar days	1. Submit if patient death 2. Store, if necessary, if nonfatal serious injury or device malfunction
	MDR from importer to manufacturer and FDA / 30 calendar days	1. Submit if patient death 2. Store, if necessary, if nonfatal serious injury
	MDR from user facility to manufacturer (and/or FDA) / 10 work days	1. Submit if patient death 2. Store, if necessary, if nonfatal serious injury

51[11] For purposes of section 760 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), *nonprescription drug* means a drug that is (1) not subject to section 52503(b) of the FD&C Act and (2) not subject to approval in an application submitted under section 505 of the FD&C Act. See section 760(a)(2) of the FD&CAct 53(21 U.S.C. 379aa(a)(2)).

APPENDIX 1: CURRENT REQUIREMENTS FOR POSTMARKETING SAFETY REPORTS

Type of Product or Type of Application	Section of 21 CFR or FD&C Act	Type of Report(s)/ Timeframe	Type of Information	Persons with Reporting Responsibility
DRUGS AND BIOLOGICS				
Prescription Drug Products Marketed without an Approved NDA	310.305	15-day Alert report; 15-day Alert report-followup / 15 calendar days	Serious and unexpected adverse drug experience; New information from follow up of 15-day Alert report	Manufacturers, packers, distributors
		Reports to manufacturer (or licensed manufacturer) instead of FDA / 5 calendar days	Serious adverse drug experiences	Packers and distributors
Approved NDA (prescription and nonprescription drugs), Approved ANDA (prescription and nonprescription drugs), and Approved BLA (biologics)	314.80, 314.98, and 600.80, respectively	15-day Alert report; 15-day Alert report-followup / 15 calendar days	Serious and unexpected adverse drug experience; New information from follow up of 15-day Alert report	Applicants (§§ 314.80, 314.98), licensed manufacturers (§ 600.80), manufacturers, packers, and distributors (§§ 314.80, 314.98, and 600.80) and joint manufacturers, shared manufacturers, or any other participant involved in divided manufacturing (§ 600.80)
		Reports to applicant (or licensed manufacturer) instead of FDA / 5 calendar days	Serious adverse drug experiences	Manufacturers, packers, and distributors (§§ 314.80, 314.98,and 600.80) and joint manufacturers, shared manufacturers, or any participant involved in divided manufacturing (§ 600.80)
		Periodic adverse drug experience report / Quarterly for 3 years from the date of U.S. approval of the application/issuance of license and annually thereafter unless otherwise required by FDA	• Individual case safety reports for each adverse drug experience not submitted to FDA as a 15-day Alert report, excluding reports from postmarketing studies, reports in the scientific literature, and foreign marketing experience • Summary portion: includes narrative summary and analysis of adverse drug experiences that occurred during the reporting interval including 15-day Alert reports previously submitted to FDA, an index of individual case safety reports included in the report, and history of actions taken since the last Periodic report.	Applicants (§§ 314.80, 314.98) or licensed manufacturers (§ 600.80)

Type of Product or Type of Application	Section of 21 CFR or FD&C Act	Type of Report(s)/ Timeframe	Type of Information	Persons with Reporting Responsibility
DRUGS AND BIOLOGICS (cont'd)				
Nonprescription Drugs Marketed without an Approved Application	FD&C Act Subchapter H Sec.760	Serious adverse event report, new medical information (followup) report / 15 business days	Serious adverse events	Manufacturers, packers, or distributors
DIETARY SUPPLEMENTS				
Dietary Supplements	FD&C Act Subchapter H Sec.761	Serious adverse event report, new medical information (followup) report / 15 business days	Serious adverse events	Manufacturers, packers, or distributors
BLOOD AND BLOOD COMPONENTS, INCLUDING SOURCE PLASMA				
Blood and Blood Components	606.170	Blood collection/transfusion fatality report / notification as soon as possible (by telephone, fax, e-mail or express mail) and written report of investigation within 7 days	Fatalities associated with complications of blood collection or transfusion	Blood collecting facility or transfusing facility
Source Plasma	640.73	Donor fatality report / as soon as possible (by telephone)	Fatalities associated with Source Plasma collection	Source Plasma establishments
HUMAN CELLS, TISSUE, AND CELLULAR AND TISSUE-BASED PRODUCTS				
Human Cells, Tissue, and Cellular and Tissue-Based Products (HCT/P)	1271.350	Adverse reaction report / 15 calendar days	Communicable disease associated with HCT/P if fatal, life-threatening, results in permanent impairment of body function or permanent damage to body structure or necessitates	Establishments that manufacture HCT/P

Type of Product or Type of Application	Section of 21 CFR or FD&C Act	Type of Report(s)/ Timeframe	Type of Information	Persons with Reporting Responsibility
			medical or surgical intervention	
MEDICAL DEVICES				
Medical Devices	803.50	Medical device report (MDR) to FDA / 30 calendar days	Device may have caused/contributed to death or serious injury, or device malfunctioned and would be likely to cause/contribute to death or serious injury if malfunction recurs	Manufacturers
	803.53	MDR to FDA / 5 work days	MDR reportable event necessitates remedial action to prevent unreasonable risk of substantial harm to public health, or report requested by FDA	Manufacturers
	803.56	Supplemental (followup) reports / within one month	Followup information received on a previously submitted 5-day or 30-day MDR	Manufacturers
	803.40	MDR to manufacturer and FDA / 30 calendar days	Device may have caused/contributed to death or serious injury	Importers
	803.40	MDR to manufacturer/ 30 calendar days	Device has malfunctioned and would be likely to cause/contribute to death or serious injury if malfunction recurs	Importers
	803.30	MDR to manufacturer and FDA / 10 work days	Device may have caused/contributed to death	User Facilities
	803.30	MDR to manufacturer (or FDA if manufacturer not known) / 10 work days	Device may have caused/contributed to serious injury	User Facilities
	803.33	Annual Report / yearly by January 1	Summary of previously submitted reports (not required if no reports)	User Facilities