Guidance for Industry

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

DRAFT GUIDANCE

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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, while reporting of *adverse events*[2] related to widespread use of influenza-related products 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 the Federal Government Response Stages[3] of an influenza pandemic. FDA believes this approach will make it possible for firms with reporting responsibilities to focus their limited resources on reports related to influenza-related

[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.

[3] The U.S. Government has identified the stages of an outbreak in terms of the immediate and specific threat a pandemic virus poses to the U.S. population (see table 1 of this guidance).

products and other specific types of reports indicated in this guidance, as well as on reports related to any other products presenting special concerns as specified by FDA.[4]

This guidance does not address monitoring and reporting of adverse events that might be imposed as a condition for products authorized for emergency use under section 564 of the Federal Food, Drug, and Cosmetics Act (FD&C Act) (21 U.S.C. 360bbb-3).[5] 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 IV.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.

Table 1 summarizes Federal Government Response Stages mapped to the World Health Organization (WHO) Global Pandemic Phases. This guidance provides recommendations for reporting adverse events based on the Federal Government Response Stages.

[4] FDA will specifically communicate with applicants regarding which products present special concerns; for example, these may involve important product-related safety issues where ongoing monitoring will need to continue during the influenza pandemic.

[5] 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 www.fda.gov/oc/guidance/emergencyuse.html.

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66 **Table 1. WHO Global Pandemic Phases and the Federal Government Response Stages[6]**
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WHO Phases		Federal Government Response Stages	
Inter-Pandemic Period			
1	No new influenza virus subtypes have been detected in humans. An influenza virus subtype that has caused human infection may be present in animals. If present in animals, the risk of human disease is considered to be low.	0	New domestic animal outbreak in at-risk country
2	No new influenza virus subtypes have been detected in humans. However, a circulating animal influenza virus subtype poses a substantial risk of human disease.		
Pandemic Alert Period			
3	Human infection(s) with a new subtype but no human-to-human spread, or at most rare instances of spread to a close contact.	0	New domestic animal outbreak in at-risk country
		1	Suspected human outbreak overseas
4	Small cluster(s) with limited human-to-human transmission but spread is highly localized suggesting that the virus is not well adapted to humans.	2	Confirmed human outbreak overseas
5	Larger cluster(s) but human-to-human spread still localized suggesting that the virus is becoming increasingly better adapted to humans, but may not yet be fully transmissible (substantial pandemic risk).		
Pandemic Period			
6	Pandemic phase: increased and sustained transmission in general population.	3	Widespread human outbreaks in multiple locations overseas
		4	First human case in North America
		5	Spread throughout United States
		6	Recovery and preparation for subsequent waves

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[6] Homeland Security Council. 2006. National Strategy for Pandemic Influenza: Implementation Plan Briefing Book. This table (with more detailed information for each of the federal response stages) is also available at http://www.pandemicflu.gov/plan/federal/fedresponsestages.html.

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 avian and pandemic flu information Web site (www.pandemicflu.gov), which displays both the current "WHO Pandemic Alert Phase" and the "U.S. Pandemic Stage." Manufacturers should keep abreast of the current federal government response stage. In addition, to facilitate communication between FDA and industry, firms should ensure that all contact information provided to FDA on forms and reports is up-to-date. FDA also recommends that firms subscribe to the Agency's MedWatch E-list,[7] which is used to notify E-list subscribers about medical product and dietary supplement safety issues.

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

Each firm should develop a continuity of operations plan (COOP) to ensure that its operations continue during all stages of pandemic influenza. Guidance on developing COOP plans is available. 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*,[8] which addresses the development and implementation of a "Continuity of Operations – Essential (COP-E)" plan. The DHS Federal Emergency Management Agency (FEMA) Web site[9] also provides information on pandemic influenza COOP planning.

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.

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

1. Reporting Requirements During Federal Government Response Stages 0, 1, 2, 3, and 4

During Federal Government Response Stages 0 through 4 (see Table 1), normal adverse event reporting processes should be maintained. All adverse event data should be handled using each firm's usual standard operating procedures, and regulatory and statutory requirements for adverse event reporting must be met.

Firms should develop and prepare to implement their COOP in the event that an influenza pandemic reaches Federal Government Response Stages 5 and 6.

[7] Subscribe at http://www.fda.gov/medwatch/elist.htm.
[8] Available at http://www.pandemicflu.gov under "Resources."
[9] Available at http://www.fema.gov/government/coop/index.shtm.

2. Enforcement Approach During Federal Government Response Stages 5 and 6

FDA anticipates that during Stage 5 of an influenza pandemic, industry and FDA workforces may be reduced at the same time that reporting of adverse events related to influenza-related products may increase. However, the extent of these possible changes is unknown. FDA encourages all firms to plan for these circumstances to maintain the highest feasible level of adverse event monitoring and reporting throughout the pandemic period. Recognizing that a pandemic may reduce a firm's capacity to comply with adverse event reporting requirements, however, FDA offers this general guidance to help manufacturers strategize use of their resources.

As explained below, FDA does not intend to object if, during Federal Government Response Stage 5, certain required adverse event reports are not provided within the timeframes required by statute and regulation, provided that any delayed reports are then provided during Federal Government Response Stage 6.

Table 2 indicates which reports firms may generally *store if necessary* during Stage 5, without FDA objection. Where Table 2 says that during Stage 5, a type of report may be stored if necessary, this indicates that FDA does not intend to object if firms maintain newly received information regarding the underlying adverse events but do not submit reports in the timeframes mandated by statute or regulation. However, any delayed reports must be submitted after Stage 5 ends.

This guidance is not intended to discourage adverse event reporting during Stage 5 by firms that are able to continue reporting operations. Firms that are able to report more than the minimum described in Table 2 should prioritize the order of report submission. 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. During Stage 5, all firms are strongly encouraged to submit as many required reports as possible to minimize reporting burdens once Stage 5 has ended.

As indicated in Table 2, if FDA has specified a product as presenting special concerns, firms must submit required adverse event reports as FDA indicates, regardless of the more general recommendations in Table 2. Aside from this circumstance, in Table 2, 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 pandemic influenza. 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 2 also includes reporting recommendations for other products and additional details.

During Stage 6, it is expected that firms will resume fulfilling all reporting requirements on time as well as submit reports that were stored during Stage 5. Firms are generally expected to submit stored reports to FDA within 6 months of the date that Stage 6 begins. 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.

164 **Table 2. FDA Approach to Postmarketing Safety Reporting During Federal Government Response Stages 5 and 6**
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FDA Approach During an Influenza Pandemic			Type of Report(s)/ Statutory or Regulatory Timeframe(s) [1]
Type of Product [or Type of Application] • **Subtype of Product**	**Federal Government Response Stage**		
	Stage 5	**Stage 6**	
Products with special concerns as specified by FDA (any product or application type below)[2]	Submit	Submit	As per regulation(s) and/or statute(s) relating to the FDA-specified product
Prescription drug products marketed without an approved NDA	Store if necessary[3]	Submit	15-day Alert report, 15-day Alert report -follow up / 15 calendar days
Approved NDA, Approved ANDA		Submit	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
• labeled indication for influenza	• Submit		
• approved within prior three years	• Submit		
• all other products	• Store if necessary		
Approved BLA		Submit	
• Pandemic influenza vaccines	• Submit		
• Nonvaccine biologics – fatal outcome	• Submit		
• Biologics (vaccines or nonvaccines) approved within prior three years	• Submit		
• Other biologics (vaccines or nonvaccines) – serious but nonfatal outcome	• Store if necessary		

[1] Refer to Appendix 1: Current Requirements for Postmarketing Safety Reports

[2] FDA will specifically communicate with applicants regarding which products present special concerns; for example, these may involve important product-related safety issues where ongoing monitoring and submission of reports to FDA will need to continue during the influenza pandemic.

[3] Refer to section III.C.2 of this Guidance.

FDA Approach During an Influenza Pandemic			Type of Report(s)/ Statutory or Regulatory Timeframe(s) [1]
Type of Product [or Type of Application] • **Subtype of Product**	**Federal Government Response Stage**		
	Stage 5	**Stage 6**	
Approved NDA: all products	Store if necessary	Submit	Periodic adverse drug experience report[4]/ Quarterly for 3 years from the date of U.S. approval of the application (or license) and then annually thereafter
Approved ANDA: all products			
Approved BLA: all products			
Nonprescription Drugs Marketed without an Approved Application	Store if necessary	Submit	Serious adverse event report / 15 business days
Dietary Supplement Products	Store if necessary	Submit	Serious adverse event report / 15 business days
Blood and Blood Components	Submit	Submit	Blood collection/transfusion fatality report / As soon as possible (oral or written) and 7 days (written)
Source Plasma	Submit	Submit	Donor fatality report / As soon as possible (oral)
Human Cells. Tissue, and Cellular and Tissue-Based Products (HCT/P)	Submit	Submit	Adverse reaction report / 15 calendar days

[4] Includes Periodic Safety Update Reports (PSURs) if applicant has a waiver allowing submission of PSURs in lieu of periodic adverse (drug) experience reports.

FDA Approach During an Influenza Pandemic			**Type of Report(s)/ Statutory or Regulatory Timeframe(s)** [1]
Type of Product [or Type of Application] • **Subtype of Product**	**Federal Government Response Stage**		
	Stage 5	**Stage 6**	
Medical Device	Submit	Submit	Manufacturer Medical Device Report (MDR) to FDA / 5 work days
	• Submit if patient death • Store, if necessary, if nonfatal serious injury or device malfunction	Submit	Manufacturer MDR to FDA / 30 calendar days
	• Submit if patient death • Store, if necessary, if nonfatal serious injury	Submit	MDR from importer to manufacturer and FDA / 30 calendar days
	• Submit if patient death • Store, if necessary, if nonfatal serious injury	Submit	MDR from user facility to manufacturer (and/or FDA) / 10 work days

167 **APPENDIX 1: CURRENT REQUIREMENTS FOR POSTMARKETING SAFETY REPORTS**
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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[1]	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

[1] 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 503(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 (21 U.S.C. 379aa(a)(2)).

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
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 medical or surgical intervention	Establishments that manufacture HCT/P
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