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Public Notification of Emerging Postmarket Medical Device Signals ("Emerging Signals")

Guidance for Industry and Food and Drug Administration Staff

Document issued on December 14, 2016.

The draft of this document was issued on December 31, 2015.

For questions about this document, contact the Office of Communication and Education, 301-796-5660 or the Office of Surveillance and Biometrics, 301-796-6006.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Preface

Public Comment

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Public Notification of Emerging Postmarket Medical Device Signals ("Emerging Signals")

Guidance for Industry and Food and Drug Administration Staff

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction

The Food and Drug Administration (FDA or the Agency) is responsible for protecting and promoting the public health.[1] This includes helping the public get the accurate, science-based information they need about medical products to maintain and improve their health.[2] At the time a medical device is approved or cleared, it has a benefit-risk profile that health care providers, patients, and consumers use to make patient management decisions. Once a medical device is on the market, new information, including unanticipated problems, may change the benefit-risk profile of a device.

FDA is issuing this guidance to describe the Center for Devices and Radiological Health's (CDRH) policy for notifying the public about medical device "emerging signals." For the purposes of this guidance, an emerging signal is new information about a marketed medical device: 1) that supports a new causal association or a new aspect of a known association between a device and an adverse event or set of adverse events, and 2) for which the Agency has conducted an initial evaluation and determined that the information has the potential to impact patient management decisions and/or the known benefit-risk profile of the device. Information that is unconfirmed, unreliable, or lacks sufficient strength of evidence is not an emerging signal.

This guidance describes the factors CDRH intends to consider in deciding whether to notify the public about an emerging signal, and the processes and timelines it should follow in issuing and

[1] *See* section 1003 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 393.
[2] *See* http://www.fda.gov/AboutFDA/WhatWeDo/.

updating the notification. Timely notification about those emerging signals based on the factors described in this guidance document is intended to provide health care providers, patients, and consumers with access to the most current information concerning the performance and potential benefits and risks of marketed medical devices so that they can make informed patient management decisions about their treatment and diagnostic options. Public notification at an early stage may reduce or limit the number of patients exposed to the potential risk while the issue is being further evaluated, and may promote enhanced vigilance on the part of clinicians, risk managers, patients and consumers. This awareness may assist in the recognition of an adverse event before more serious complications or sequelae occur.

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

All medical devices have benefits and risks. FDA weighs probable benefit to health from the use of the device against any probable risk of injury or illness from such use in determining the safety and effectiveness of a device.[3] Once FDA has made its determination, health care providers, patients, and consumers must weigh these benefits and risks when making patient management decisions. However, not all information regarding benefits and risks for a given device may be known before the device reaches the market. New information about a device's safety and/or effectiveness, including unanticipated adverse events, may become available once the device is more widely distributed and used under real-world conditions and in broader patient populations than may have been studied in support of a marketing application. Also, subsequent changes made to the device, its manufacturing process, or supply chain may lead to new safety problems.[4]

This new information may include, but is not limited to, a newly recognized type of adverse event associated with a medical device, an increase in the severity or frequency of a known adverse event, new product-product interactions, device malfunctions or patient injuries potentially related to improper device use or design, or a reduction in benefit to the patient. An emerging signal may be associated with one product from one manufacturer, one type of product or similar products from multiple manufacturers, or multiple different product types from multiple different manufacturers (e.g., materials issues).

FDA strives to provide current information concerning the benefits and risks of marketed medical devices to health care providers, patients, and consumers so that they can make informed treatment and diagnostic decisions.[5] To ensure thorough assessment of new information and the timely communication of emerging signals, FDA's Center for Devices and Radiological Health

[3] *See* 21 U.S.C. 360c(a)(2) and 21 CFR 860.7.
[4] Such changes may trigger the need for a new premarket submission.
[5] FDA discloses such information pursuant to all applicable laws, regulations, and policies, including sections 301(j) and 520(c) of the FD&C Act, the Trade Secrets Act, the Privacy Act, and FDA disclosure regulations.

(CDRH) has established a process for the evaluation of signals that support a new causal association or a new aspect of a known association between a medical device and an adverse event or set of adverse events. This process, described further in Section IV below, typically includes: 1) collection of available information from multiple sources, 2) interaction with the impacted medical device company or companies, 3) review by a multidisciplinary team of subject matter experts, 4) other stakeholder engagement (e.g., external experts, other government agencies), as appropriate, and 5) management oversight.

III. Scope

This guidance document explains the factors CDRH intends to consider in deciding whether to notify the public about emerging signals related to devices and the processes and timelines it intends to follow in issuing and updating the notification. The guidance is only applicable to marketed products that meet the statutory definition of a device[6] regulated by CDRH, regardless of regulatory classification; however, it does not apply to investigational devices under FDA's Investigational Device Exemptions (IDE) regulations, 21 CFR part 812.

IV. Signals and Signal Management

Knowledge about a device's benefit-risk profile often increases as a device is more widely distributed and used under real-world conditions with more varied patient populations. Unanticipated adverse events may occur with increased device use and patient exposure. A signal represents a new potentially causal association or a new aspect of a known association between a medical device and an adverse event or set of adverse events.

The following provides a general outline of signal management within CDRH. The intent is to describe the typical CDRH signal management process; each specific situation will be device- and fact-specific.

Information about device-related signals may come to the attention of FDA through a variety of sources including, but not limited to, Medical Device Reports (MDRs), MedSun Network reports, data from mandated postmarket studies, clinical trials or data published in the scientific literature, epidemiological research including evaluation of administrative databases, health care claims data or registries, and inquiries or investigations from global, federal or state health agencies.

Following identification of a signal, a CDRH signal management team of multi-disciplinary subject matter and regulatory experts is convened. The signal first undergoes refinement, whereby additional information from other data sources is identified, gathered, and evaluated. The signal refinement phase includes interactions with the device manufacturer(s), unless time does not permit because of the risk of patient harm or it is not feasible, e.g., CDRH cannot reach all manufacturers. During the signal refinement phase, CDRH attempts to better understand the fundamental nature of the observed adverse event(s) or newly identified risk, including likelihood of a causal relationship between the use of the device and the adverse event or risk,

[6] Section 201(h) of the FD&C Act, 21 U.S.C. 321(h).

and to conduct a preliminary assessment as to whether the issue is limited (e.g., to one device model or one manufacturer) or may have a broader impact (e.g., products from multiple manufacturers across a device type). CDRH may also choose to seek information from, or consult with, other stakeholders, such as external clinical or scientific experts, patients, industry, and other government and regulatory agencies.

The gathering and interpretation of the additional data needed to adequately characterize a signal can be complex, and it may take time to conduct the analyses necessary to fully assess the issue, its impact on device performance, its clinical significance, and to identify appropriate mitigation strategies.

As a more complete understanding of the signal develops, the signal management team, with managerial input and oversight, identifies public health and/or regulatory actions to mitigate the identified risks, if any. FDA has numerous different tools that the Agency may employ depending on the situation, including, but not limited to: public communication and/or other outreach, request to manufacturer(s) for modifications to product labeling (including indications, contraindications, warnings/precautions, and directions for use), development of Agency guidance documents (including those related to premarket testing or requirements), and ordering the conduct of postmarket surveillance studies.

V. Considerations for Determining When FDA Should Issue a Public Notification About an Emerging Signal

FDA considers many factors in the course of evaluating and notifying the public about emerging signals about medical devices. This assessment does not focus on hypothetical benefits and risks, but rather on benefits and risks whose existence and characteristics are supported by scientific evidence. Although FDA has informed and continues to inform the public about emerging signals in the past, CDRH believes that application of the factors included in this guidance document will improve the consistency, transparency, and predictability of the process for notifying the public about emerging signals. These factors may include, but are not limited to, the following:

- Likelihood (probability) of the harmful event(s);
- Magnitude (severity), duration, and reversibility of the harmful event(s); ;
- Magnitude of the benefit (e.g., the degree to which a given condition, symptom or function is improved and whether the device provides life-sustaining or life-saving benefits);
- The quality of the data or information;
- The strength of the evidence of a causal relationship between the use of a device and the adverse event;
- Extent of patient exposure (e.g., how broadly is the device used, the duration of exposure, including whether the device is intended to be permanently implanted);
- Whether there is a disproportionate impact on vulnerable patient populations (e.g., children, pregnant women, elderly, cancer patients, chronically ill patients, at-home/unmonitored patients);
- Potential for preventing, identifying, monitoring or mitigating the risk;

- Availability, risks, and benefits of alternative therapies;
- Potential for patients to not receive treatments they should even in light of the new information;
- Implications for similar or related devices (e.g., multiple models from multiple manufacturers);
- Anticipated time for completion of FDA's assessment of the available information and development of recommendations; and
- Accuracy and availability of information already in the public domain.

The decision to provide public information about an emerging signal is intended to give health care providers, patients, and consumers access to the most current information about a device that may help inform their patient management decision making. It does not mean that FDA has definitively concluded that there is a causal relationship between the medical device and the emerging signal; nor does a public notification about the emerging signal mean that FDA is advising health care providers, patients, or consumers to limit their use of the device. Furthermore, such a notification does not necessarily imply that specific actions are expected on the part of the manufacturer(s) at that time. However, CDRH generally does not intend to issue a public notification unless 1) credible scientific evidence supports a new causal relationship, but the Agency needs additional time to reach a more definitive conclusion, for example by conducting additional analyses or 2) FDA has concluded a causal relationship exists, but the Agency needs additional time to develop recommendations, for example if the Agency believes advice should be sought from one of its advisory panels. FDA's communications should be clear about what the Agency knows and does not know, as well as whether or not the Agency recommends specific actions and why.

Whenever FDA discusses medical device safety, the Agency exercises its best judgment based on the available information in determining whether and when to communicate and what to say. CDRH staff intend to strongly consider public notification about an emerging signal when all of the following statements apply:

1. the information supports a new causal association, or a new aspect of a known association (e.g., increased rate or severity of event or reduced benefit), between a medical device and one or more adverse events or clinical outcomes; and
2. the available evidence is of sufficient strength; and
3. the information could have important clinical implications for patient management decisions and/or could significantly impact the known benefit-risk profile of the device.

CDRH staff intend to conduct an initial assessment of the need to issue a public notification about an emerging signal about a medical device within 30 days of receiving the information that has generated the emerging signal. If during the evaluation of an emerging signal, a decision is made to NOT issue a public notification, FDA staff intend to conduct an internal reassessment of the decision within 30 days of receiving new or substantive information, using the considerations described above.

VI. Content of Public Notification and Follow-up/Closure

FDA strives to keep all communications clear and understandable. The Agency considers the potential impact of our communication on different stakeholders, as well as elements of human behavior, in our decision to communicate and in the content of our communication. FDA realizes that risk information provided without context may alarm patients, causing them to discontinue therapy with a beneficial device or to avoid a potentially beneficial therapy, or may lead to questions among health care providers about which treatment option(s) may be best for their patient. In some circumstances, however, the benefits of providing early information to the public outweigh these risks if the information is communicated carefully and thoughtfully. This guidance document describes the factors and process FDA intends to use in deciding whether to notify the public about an emerging signal. FDA believes that application of this guidance will aid the Agency in meeting its public health mission by providing the public with the accurate, science-based information they need to maintain and improve patient health.

The contents of an emerging signal public notification may vary depending on the type of information available and the specific benefits and risks of the impacted device(s). In general, a public notification regarding an emerging signal for a medical device should include:

- a description of the device(s) to which the public notification applies;
- a summary of the emerging signal, including the objective evidence on which the decision to issue a public notification is based;
- information on the known benefits and risks of the device and its use.

In addition to interacting with the impacted company or companies during the signal management process, FDA will inform the impacted company or companies shortly before issuing a public notification, unless time does not permit because of the risk of patient harm or it is not feasible, e.g., CDRH is not able to reach all manufacturers.

Once a public notification for an emerging signal is issued, the Agency may provide updates that:

- provide new information related to the emerging signal collected since the prior public notification;
- notify the public that no additional substantive information is available and/or that no known change in the benefit-risk profile of the device has occurred since the last posting;
- notify the public of additional actions being taken or completed by FDA and/or the manufacturer(s); or
- notify the public when FDA has completed its evaluation and determined that additional regulatory or public health actions are not required.

Updates to the public notification should be posted to the FDA website at least twice per year, or more often as necessary and appropriate (e.g., following receipt of new substantive information), until the signal evaluation is completed and the public is notified of the Agency's conclusions.