The 510(k) Coalition

March 28, 2016

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Public Notification of Emerging Postmarket Medical Device Signals ("Emerging Signals"), Draft Guidance for Industry and Food and Drug Administration Staff
Docket No. FDA-2015-D-4803

Dear Sir/Madam:

On behalf of the 510(k) Coalition (the Coalition), I am pleased to submit these comments regarding the Public Notification of Emerging Postmarket Medical Device Signals ("Emerging Signals"), Draft Guidance for Industry and Food and Drug Administration Staff (the "Draft Guidance"). The Coalition is a group of medical device companies dedicated to patient health and to the promotion of efficient, rational regulation of medical devices. The Coalition appreciates the opportunity to provide comments on the Draft Guidance.

The Coalition recognizes that FDA is attempting to embark on a major, multi-year effort to set up systems to collect massive amounts of real-world, observational data that are more difficult to analyze than data from controlled clinical studies. We applaud the fact that FDA is also working to develop and publish its methods on "Emerging Signals." However, there are numerous potentially serious issues in the Draft Guidance as it is currently written, described in greater detail below.

1. **Lack of statutory authority**

The Draft Guidance may be lacking in statutory authority. Unlike similar programs in the pharmaceutical sector (see 21 U.S.C. 355(k)(5)), FDA does not have clear statutory authority to enact this guidance. Notably, the Draft Guidance does not rely on any statutory or regulatory standards, but rather on a dozen bullet point "factors".

2. **There is no problem that cannot be addressed under currently available methods**

One of the primary problems with the Draft Guidance is that it is unclear if there is a specific problem that FDA is trying to resolve that it is unable to adequately address under current existing regulations and guidance documents. The Draft Guidance does not address how and whether this proposed Emerging Signals program will actually change anything that is already being done under current systems. If the Draft Guidance is intended to simply describe existing practice, then that

should be made clear, and the impact of the existing system analyzed and the authority for such a system described.

Additionally, the Draft Guidance does not address whether any experience or lessons learned from the existing system utilized in the pharmaceutical realm have proven to be effective and successful. Lessons learned from the pharmaceutical system should be explicitly set forth and utilized in developing this system.

3. Patient impact

The Draft Guidance fails to adequately consider the benefit-risk balance to the patient. The publication of Emerging Signals may actually present more risks to patients than benefits. Real world experience has repeatedly demonstrated that patients and physicians can make erroneous decisions based on FDA reports of potential product issues. Issuing a "notice" for an unconfirmed issue risks patients and physicians making wrong or misinformed medical decisions. Along these same lines, the Draft Guidance does not describe what happens if an Emerging Signal turns out to be false. It does not describe the method to "undo" the initial communication which may have gone out to numerous patients.

By publishing Emerging Signals as described in the Draft Guidance, FDA would be acting based upon preliminary information that is not scientifically verified and of unknown significance. The Draft Guidance notes that it "may" disrupt some patient benefit, but it is more than likely that these types of communications actually <u>will</u> disrupt and cause adverse impacts on some number of patients. The Draft Guidance fails to adequately consider the impact this will have on patients currently using the therapy or device. We appreciate that the Agency recognizes that there are "potential unintended consequences" of publicly announcing consequences prior to full evaluation, including the "possibility that a beneficial device's use may be avoided or inappropriately stopped because of uncertain or unproven risks or uncertainty around the benefits." (p. 5).

Early publication of Emerging Signals may unnecessarily alarm the public and confuse consumers. If the patient continues to use the product, it is unclear what action they should take upon receiving information about an Emerging Signal, especially if the communication is regarding an implanted device. The public may interpret these communications as an FDA recommendation to limit their use of the device, when, in actuality, that may not be the optimal result for patients or what their physician intends. Conversely, if FDA later finds no issue with a product following an Emerging Signal, it is unclear whether the public may then feel that this product somehow has an extra "stamp of approval" or endorsement from FDA, or whether there will still be the misperception that there is a problem with the device.

FDA states it wants to issue this Draft Guidance so that doctors, patients, and others can make "informed" choices. The Agency *intend*s for this action to impact patient care by reducing the number of patients exposed to the potential risk while it is being evaluated (p. 4). However, the Draft Guidance fails to consider the very real negative impact such notices will have on decision-making by physicians and patients in the future. It is unclear whether this program will have an impact on practice guidelines and the standard of care, as well. The guidance is lacking in that

there is no consideration of the risk of issuing the Emerging Signal as compared to the benefit of it. This risk must be considered and properly dealt with in order to determine the full impact on patient benefit-risk associated with publication of Emerging Signals.

4. Lack of evidentiary standards

The Draft Guidance currently lacks sufficient criteria and evidentiary standards for an Emerging Signal and is extremely vague. It is silent on the degree of confirmation needed before an Emerging Signal is published. The Draft Guidance appears to take the position of "guilty until proven innocent", which is bad practice. There should be more thorough criteria for assessing Emerging Signals, further clarification of the process through which the Agency determines whether or not something is an Emerging Signal, and a definitive process for handling unsubstantiated evidence. By contrast, there is currently a clear policy for medical device recalls, and a recall is a defined determinative decision. Unlike recalls, there is no clear process for "Emerging Signals" through which FDA explains whether or not there truly is a problem. Absent any clear standards, it is impossible for a company to disclaim or respond to notice of an Emerging Signal. Similarly, without clear standards, physicians, patients and consumers will not fully understand what it means when an Emerging Signal is published.

5. Lack of validated evidence or significance

As described in the Draft Guidance, communications regarding Emerging Signals may lack validity and certainty. The Emerging Signals plan outlined in the Draft Guidance allows FDA to publish information about devices using unreliable sources with uncorroborated data. Indeed, the Draft Guidance recognizes these problems and notes that the information that forms the basis for an Emerging Signal "has not been fully analyzed, validated or confirmed, and … the Agency does not yet have specific recommendations." (p. 4) The Draft Guidance appears to allow FDA to widely spread negative new information about a device after receiving unsubstantiated reports or anecdotal information. Although FDA is required to conduct an initial assessment about the need to communicate an Emerging Signal within 30 days of receiving a report, it does not contain any guidelines on how FDA should do the assessment.

Additionally, the Draft Guidance states that the communications, "may lack certainty about the significance of the information." (p. 4) This statement is problematic because both industry and consumers will be blindsided by the publication of an Emerging Signal which may or may not contain accurate information. Industry will not have adequate time to respond to FDA to determine whether or not an Emerging Signal is accurate prior to publication and before such potentially false or insignificant information will be published to patients and consumers. Given the dramatic impact the publication of Emerging Signals may likely have on patient care, it would be in the best interest of physicians, patients and companies if there were more certainty and validity associated with the information prior to publication.

6. Lack of discussion of process steps

Another significant concern with the Draft Guidance is that there is no discussion of procedural steps – both for the involvement of industry and internal processes for FDA to follow. We recommend that the final guidance include a discussion of both of these types of process steps.

It is critically important to include industry in the process prior to issuance of notification of an Emerging Signal. The company may well have additional or better information than what is available to the Agency. The Draft Guidance does not currently describe how the Agency will determine whether or not the standards have been met before it issues an official Emerging Signal. It is difficult for companies to know whether or not FDA will meet with them to discuss potential Emerging Signals because outreach to companies is not discussed in the Draft Guidance.

There are numerous reasons why it would be beneficial for FDA to include a process to meet with industry prior to the publication of an Emerging Signal. First, an Emerging Signal may be wrong, and industry is in a better position to explain why an Emerging Signal is or is not actually a problem. It would be appropriate for companies to weigh in to determine if something really is an Emerging Signal by sharing insight and information that they possess but the Agency does not. Involving industry in this process would also have the added benefit of allowing stakeholders to be better prepared when a notice comes out so that they are not blindsided with determining how to react and respond. Patients and physicians routinely reach out to companies for additional information or counsel when facing a product question. Furthermore, the companies need to be prepared with additional follow up responsibilities that may be required. For example, the companies may need to make SEC notifications or take other actions as a result of an Emerging Signal. Therefore, industry should be involved before the notice goes out.

Companies may also be unprepared to respond to additional inquiries from people (both medical and lay) about the potential risks of their products – inquiries that the companies may not be well-equipped to respond to, since the Draft Guidance does not mention or require prior consultation with the device manufacturer before publication of the Emerging Signal. Indeed, the Draft Guidance does not currently provide for any involvement of or notification of the affected companies prior to or during the publication of the Emerging Signal. If the companies are not notified in advance, they will not be well-positioned and prepared to adequately respond to inquiries following the Emerging Signal publication. The Emerging Signals program as described in the Draft Guidance will undoubtedly result in the potentially unnecessary and excessive consumption of resources by many parties to address something which may not even be true cause for concern.

7. The Draft Guidance does not explain the process when it is determined that something is not an adverse signal

There are significant communication concerns with the Draft Guidance, including the fact that it does not describe how final resolution will be reached once the Agency determines that something is not actually an adverse Emerging Signal. There will, no doubt, be a significant number of false notices related to products. The inevitable issue is, "How do you un-ring the bell?" Notably, the public can only absorb so much information. Another subsequent communication published

weeks, months or even years following an Emerging Signal may not be read by the intended audience. Once it is determined that the Emerging Signal poses no risk, it is unclear how quickly the FDA will post a notice or otherwise communicate to rectify the original communication. Additionally, the Draft Guidance is silent on the method of publication or announcement that an Emerging Signal was a false one and does not contain a timeline for retracting the Emerging Signal. If the Agency is committed to publicly issuing an update retracting or correcting an Emerging Signal, then there should be a more explicit requirement in the Draft Guidance regarding the timing and methodology for doing so, in order to enhance transparency and accountability.

It is unclear, how, or whether, FDA would be able to adequately publicly announce that an Emerging Signal was a false one and to also undo any damage in order to ensure that the product and/or company's reputation isn't forever tarnished. The Draft Guidance does not address this scenario, nor the likely long-term impacts that may result in a manufacturer's or a product's reputation being ruined for good. The impact of "early communication" will be very similar to that of a recall, but on a much larger scale. An early communication of signals or information not fully vetted will cast a shadow not only over a specific lot of devices or over a particular device from a particular manufacturer. Instead, it will throw doubt over all devices of the same type from all manufacturers. Further, it will cast a shadow over the physicians who are using the devices and the credibility of professional societies that recommend the use of such devices. Additionally, the public's confidence in manufacturers, physicians, and even FDA may be damaged if the issuance of, investigation of and conclusion to an Emerging Signal is not properly addressed.

8. Ancillary impacts

There is a significant risk that the publication of Emerging Signals by FDA could lead to increased frivolous plaintiffs' litigation targeting companies for potential device risks which may or may not be valid. In today's litigious environment, where institutions and physicians must endeavor to avoid even the appearance of negligence or malfeasance, it is hard to imagine an instance in which the use of a device which has been the subject of an Emerging Signal notice will not be diminished or stopped altogether. Indeed, there is no doubt that the plaintiff's bar will be advertising to find patients who have been treated with the product in question in order to provide a basis for lawsuits, many of which will be frivolous. There also remains the open question of whether Emerging Signals be admitted in a courtroom. Such information is an entirely unreliable notice, but it would nonetheless likely be exploited by the plaintiffs' bar. To avoid such an unintended consequence, the FDA should specify that the Agency's Emerging Signals risk statements are not admissible for any purpose in civil proceedings.

In addition to frivolous lawsuits, publication of Emerging Signals may lead to the unintended consequence of artificial spikes in adverse event reporting. This in turn will make it difficult to conduct an adequate assessment of true risk(s) associated with a product, because the spike would predominantly have been caused by the Emerging Signals report, rather than an actual adverse event or risk. Additionally, the publication of Emerging Signals may cause unintended ancillary impacts on imports and exports of medical devices, as foreign countries have different regulatory regimes and will inevitably have differing, and potentially confusing, interpretations of the significance of Emerging Signals.

Finally, there is the risk that the Emerging Signals publication could have a significant negative impact on the reimbursement of medical devices or cause other financial liability to a company. If the affected product is the sole product of a company, it could potentially drive a company out of business, thereby stifling innovation and resulting in potential long-term impacts to patient health by reducing the number of medical device companies that would have otherwise developed innovative life-saving technologies. The added burden this Draft Guidance will place on manufacturers to address Emerging Signals that may be false and may not lead to any real patient benefit is unknown and troubling.

9. Labeling and off-label questions

The Draft Guidance does not address whether a company would need to modify its device label due to an Emerging Signal. Similarly, the Draft Guidance does not discuss what a company is able to do if it disagrees with the Agency. For example, if an Emerging Signal relates to an off-label use that the company disagrees with, it is unclear what action the company can take in response to this notification.

Furthermore, the benefits of devices are as important as the risks. Through publication of Emerging Signals, FDA is proposing to announce unverified and unsubstantiated risk information, but is not giving industry the same opportunity to publicly state potentially beneficial information under similar lax evidentiary standards. This is not a balanced approach and it weighs heavily against industry's ability to provide information on the potentially beneficial aspects of devices on equal footing with FDA, which is able to speak publicly about unsubstantiated, unverified and potentially false negative information about devices.

10. Categorization of Emerging Signals

Although it is not discussed in the Draft Guidance, is our understanding that the Agency views emerging signals in three separate categories or "buckets". The first category involves instances where there is a confirmed signal, such as a causal relationship and a safety concern, but the Agency has no recommendation for a particular course of action. In this situation, the Agency believes that providing information to the public can be helpful for making clinical decisions and making use of the technology. Although a current issue relating to safety of duodenoscopes may be one example of this situation, the Draft Guidance does not specifically refer to this example. Perhaps providing this example and other similar instances will provide enhanced clarity and explanation of the need to release an emerging signal in this type of situation. The processes and issues relevant to this type of situation are different from the following two other situations. The Agency should consider whether one process fits all three situations.

The second "bucket" involves times when the Agency is responding to public concerns and publication of an Emerging Signal is necessary in order to put out additional information because it may be informative for the public and clinicians in making decisions. Again, it is unclear whether the process described in the current Draft Guidance fits this situation.

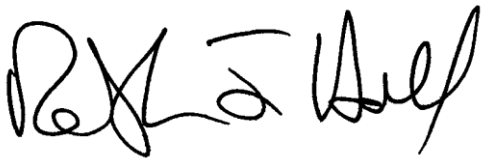
The third type of Emerging Signal involves instances in which there is some evidence of a connection but no confirmation. In this instance, it is particularly important to balance whatever

benefit there may be in issuing the communication against the impact on patients including potential anxiety, fear, discontinuation of therapies, etc., while also recognizing that there is no clear recommended course of action. Each of these "buckets" presents different issues. We recommend that FDA should specifically identify and address each of these situations separately in a final version of the guidance.

In conclusion, we restate that we understand FDA is embarking on a multi-year effort to set up systems to collect massive amounts of real-world data. We appreciate FDA's transparency in publishing this guidance. Our questions are large in the number, scope, and significance; we recognize that other stakeholders may have differing perspectives. This, we propose that the next step forward is a public conference where these topics can be discussed in depth by major stakeholders. We believe that public health would be greatly served by such a conference. We strongly suspect that all stakeholders will learn a great deal from such interaction and would likely conclude that more is involved than simply issuing a guidance document

Thank you very much for your consideration of our comments and recommendations. If you have any questions, please feel free to contact me at: 651-261-3467 or Ralph.Hall@leavittpartners.com.

Very truly yours,



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