April 22, 2019

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


To Whom It May Concern:

The Advanced Medical Technology Association (“AdvaMed”) appreciates the opportunity to provide comments on the Food and Drug Administration (“FDA” or “Agency”) draft guidance, “Nonbinding Feedback After Certain Food and Drug Administration Inspections of Device Establishments” (“Draft Feedback Guidance”).

AdvaMed is the world’s largest association representing manufacturers of medical devices, diagnostic products, and medical technology. AdvaMed’s member companies range from the largest to the smallest medical product innovators and manufacturers, with nearly 70 percent of our members generating less than $100 million in annual sales. AdvaMed's member companies produce innovations that transform health care through earlier disease detection, less invasive procedures, and more effective treatments.

AdvaMed appreciates FDA’s publication of the Draft Feedback Guidance. Agency feedback on remediation of inspecational observations helps to assure that the remediation effectively and efficiently resolves quality system deviations. But as written, the Draft Feedback Guidance does not deliver these results. In particular, the 15-day deadline for feedback requests is too short. The deadline risks rushed remediation plans and incomplete feedback requests, leading to avoidable problems that emerge while remediation is underway. Further, the draft guidance sets overly-narrow eligibility criteria that preclude feedback requests that are appropriate and contemplated by FDA Reauthorization Act (“FDARA”) section 702. Taken together, these limitations counter FDA’s assertion that the nonbinding feedback process “can reflect least burdensome principles.” “The Least Burdensome Provisions: Concept and Principles, Guidance for Industry and Food and Drug Administration Staff,” p. 24. We detail these points in the general comments that follow and we enclose with this letter specific comments on the draft guidance.

General Comments

FDA should extend the deadline for feedback requests to 45 days after a manufacturer determines the need to address an inspecational observation.

By requiring nonbinding feedback requests within 15 days after issuance of the Form FDA 483 (“Form 483”), FDA apparently seeks to impose a deadline that matches the 15-day deadline for Form 483 responses. See, 74 Fed. Reg. 153 (August 11, 2009), p. 40212 (“FDA will generally allow firms
15 business days to provide a response to FDA 483 observations.”). But this 15-day deadline threatens exactly the same problems created by the Form 483 deadline: rushed answers without a root-cause understanding of underlying quality system deviations. Without this understanding, there is no assurance that remedial actions will effectively address quality deviations.

Too often, these rushed actions waste time and money on corrections that do not work. The resource commitments are considerable both for firms and FDA. One major medical device manufacturer reports that costs for remediation of FDA 483 observations can range from $100K-$500K, depending on the complexity and scope of the observation. See also, “A Bad 483 Could Cost a Company Millions, https://blog.fdazilla.com/2018/08/what-does-getting-an-483-or-warning-letter-really-cost-you/, (a biopharma executive reported, “Internal teams are put together to address the issues. (Expensive) external consultants are brought in for specific expertise. Hundreds, if not, thousands of hours of remediation, training, process redesign, process implementation, and meetings. It’s not hard to imagine the bill running up to $250,000.”). FDA also must invest time analyzing, evaluating, and monitoring remediation plans that are less likely to succeed than plans that reflect deep understanding of quality deficiencies and the actions needed to resolve them. The result – ineffective remediation that must be repeated – serves neither FDA nor firms nor patients.

Equally troubling, FDA’s proposed approach allows firms only one chance to seek feedback. But firms may need feedback more than once and more than 15 days after the Form 483. Remediation often proceeds for months or longer and there can be critical decision points that require FDA input. For example, a firm may realize that its corrections are not working. The right response is new actions that adequately remediate quality gaps. But the firm may first need Agency feedback about whether its new plan suitably addresses underlying observations. Without this input, the firm might stay the course for fear that FDA will regard new action as a failure to deliver remediation promised in response to the Form 483. Thus, the firm may complete suboptimal remediation to avoid Agency sanctions. Requiring firms to guess at what FDA wants failed remediations that require time and money spent on perpetual corrections that FDA must continuously oversee.

The answer is to provide more time for firms to develop thoughtful, well-supported remediation plans and not to make FDA feedback a one-shot proposition. We recommend that FDA allow firms to seek feedback within 45 days after determining the need for action that responds to a Form 483 and that involves a public health priority, major or systemic actions, or emerging safety issues. This recommendation provides two key benefits: first, it allows firms to understand the root causes of inspectional observations and develop solutions that address root causes and properly resolve the observations; and second, it allows firms to seek FDA input when they must revise ineffective action plans. These safeguards avoid companies dedicating time and money for remediation activities that meet FDA deadlines, but that may produce inadequate results.

While our recommendation broadens FDA’s feedback obligation, we believe that the benefits to product quality and patient health justify the expansion. Further, FDA can take process steps to gain efficiencies. For example, FDA might develop templates for manufacturers to submit when requesting nonbinding feedback. These templates would instruct manufacturers to provide relevant information about inspections, Form FDA 483 observations, potentially affected devices, the corrective actions that manufacturers propose to take, and other relevant data. The templates also could include checklists for feedback requests and FDA replies to ensure their consistency and completeness. The template and the checklists would allow manufacturers and FDA to clarify the requested feedback, such as confirmation of the manufacturer’s understanding of an observation or confirmation that a proposed action appropriately addresses the observation.
FDA should broaden its interpretation of the criteria for nonbinding feedback.

As amended by the FDARA, Section 704 of the Federal Food, Drug, and Cosmetic Act authorizes nonbinding feedback in cases “that involve a public health priority, that implicate systemic or major actions, or relate to emerging safety issues (as determined by the Secretary).” 21 U.S.C. § 374(h)(2)(B)(ii). The statute does not define the terms “public health priority,” “systemic or major actions,” or “emerging safety issues” and, in interpreting them, the Draft Feedback Guidance applies narrow criteria that foreclose meaningful access to Agency feedback. The result – rushed remediation without knowing whether the corrections meet FDA expectations – will cause FDA and firms to waste time and money on fixes that do not work and that could have been revised by appropriate FDA input.

As explained below, the draft guidance’s overly restrictive reading is evident in its explanation of public health priorities, systemic or major actions, and emerging safety issues.

**Public Health Priorities**

There are many examples of public health priorities that go beyond “conditions [that have or may] result in, the release of a violative product that may cause death or serious injury.” Draft Feedback Guidance, lines 186-187. The definition of priority – “a preferential rating” or “something given or meriting attention before competing alternatives” – shows this. Merriam-Webster online dictionary, [https://www.merriam-webster.com/dictionary/priority#synonyms](https://www.merriam-webster.com/dictionary/priority#synonyms). Actions to prevent non-serious injury, for example, merit a preferential rating or attention before competing alternatives, as do actions to prevent device shortages (which can indirectly cause serious and non-serious patient injury). Surely FDA agrees that the benefit to patients from avoiding all injury, including those that may result from device shortages, outweighs its investment to review and comment on firms’ remediation plans.

To avoid too narrowly bounding what is a public health priority, we propose the following reading:

A public health priority is:

- A matter in which use of the device, or absence of the device, may cause adverse health consequences;
- A matter related to efforts by FDA, industry, or other stakeholders to materially enhance the safety, performance, or quality of a device; or
- A matter involving a corrective action that might have public health implications, such as creating a shortage or slowing access to a breakthrough device.

This broader standard clarifies what is in and outside of FDA’s feedback commitment while assuring meaningful feedback on manufacturers’ remediation plans.

**Systemic or Major Actions**

Curiously, the Draft Feedback Guidance treats systemic or major actions as those designed to fix deficiencies that would result in “nonconforming, violative, and/or defective finished devices.” Draft Feedback Guidance, lines 191-192. Again, the draft guidance’s lines are too narrow. Historical interactions between FDA and manufacturers make plain that systemic remediation may be needed when there is little to no risk of nonconforming or defective finished devices. Indeed, a firm might
reengineer system-wide design, management, or document control practices to correct deficiencies that have no effect on finished device quality. The same might be true for a firm that makes enterprise-wide changes to its complaint-handling or reporting processes to resolve problems identified at individual sites. In either case these changes are systemic: “of, relating to, or common to a system.” Merriam-Webster online dictionary, https://www.merriam-webster.com/dictionary/systemic.

Undoubtedly, these changes are also major – their cost, scope, duration, and impact show this. To suggest, then, that these changes are disqualified from Agency feedback ignores the plain meaning of “systemic” and “major.” To correct the draft guidance’s misinterpretation, FDA should expand its reading of “systemic or major actions”:

Systemic or major actions are:
- Proposed actions that require a substantial commitment by the manufacturer of time and/or resources for implementation;
- Proposed actions that have material impact on the manufacturer’s quality system;
- Proposed actions that have material impact on facilities; or
- Proposed actions that require retrospective review or re-work of completed quality system activities.

This broader interpretation properly extends nonbinding feedback to actions that remediate inspection findings irrespective of product impact.

Emerging Safety Issues

In explaining “emerging safety issues,” the Draft Feedback Guidance again returns to the “release of devices that are likely to cause death or serious injury.” Draft Feedback Guidance, lines 195-96. But why would FDA hesitate to offer feedback on remediation that prevents any emerging safety issue that threatens patients? For example, as noted above, FDA should offer feedback if it will prevent either serious or non-serious injury. Surely, FDA agrees that the resources needed for this feedback are eclipsed by the benefit to patients of avoiding any injury, serious or otherwise. Consequently, we propose interpreting “emerging safety issues” as new or emergent device safety concerns for which consultation with FDA staff may provide relevant information to the manufacturer to inform its response to the concerns. By leaving behind the connection to “death or serious injury,” this reading better aligns the draft guidance with the principles of FDA’s Medical Device Safety Action Plan: “to protect and promote the public health by minimizing unnecessary risks . . . .” “Medical Device Safety Action Plan: Protecting Patients, Promoting Public Health,” p. 3.

* * *

In closing, we note that the Draft Feedback Guidance contradicts least burdensome principles. FDA’s least burdensome guidance characterizes nonbinding feedback as an example of compliance policies that promote least burdensome practices. “The Least Burdensome Provisions: Concept and Principles – Guidance for Industry and Food and Drug Administration Staff,” pp. 23-24. But as noted above, the Draft Feedback Guidance forecloses meaningful use of nonbinding feedback: the 15-day deadline constrains thoughtful, well-researched remediation proposals, and feedback, if available, is a one-time exchange that discourages course correction when initial remediation is ineffective. Further, the draft guidance’s too-narrow definition of eligibility criteria permits only a minority of firms conducting remediation to seek FDA input. Our proposed revisions correct these
shortcomings and align the feedback process with FDA’s least burdensome obligation.

AdvaMed thanks FDA for its consideration of these general comments and the specific comments that follow in the attachment. Please do not hesitate to contact me at 202-434-7228 or jtrunzo@advamed.org if you have any questions.

Respectfully Submitted,

/s/

Janet Trunzo
Senior Advisor to the President and
Senior Executive Vice President
Technology and Regulatory Affairs

Attachment
<table>
<thead>
<tr>
<th>#</th>
<th>Line</th>
<th>Proposed Change</th>
<th>Comment: Rationale/Justification for Change</th>
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<tbody>
<tr>
<td>1</td>
<td>130</td>
<td>Add, “Timely feedback likewise benefits patients by promoting prompt and effective resolution of medical device quality concerns.”</td>
<td>This revision clarifies that timely feedback benefits patients as well as device firms by allowing firms to quickly and effectively fix quality issues.</td>
</tr>
<tr>
<td>2</td>
<td>148</td>
<td>Provide an avenue for the facility being inspected to report if guidance related to consecutive days, time frames and communications are not met.</td>
<td>It is helpful to companies to understand how they can communicate concerns.</td>
</tr>
<tr>
<td>3</td>
<td>154</td>
<td>Change “15 days” to “45 days.” Also add that firms may request written feedback more than once.</td>
<td>See Cover Letter from AdvaMed, pages 1 and 2.</td>
</tr>
<tr>
<td>4</td>
<td>167</td>
<td>Extend the opportunity for verbal communications to for cause inspections.</td>
<td>It is more expedient for companies to understand the investigator’s observations to support more timely corrective action.</td>
</tr>
<tr>
<td>6</td>
<td>189-192</td>
<td>Modify to state: “The FDA-documented observation(s) in the Form 483 indicate that the quality system or subsystem deficiencies represent systemic or major actions.</td>
<td>Revised wording reflects statutory language, which addresses needed changes that may be time-consuming and/or expensive to implement, whether or not a public health hazard is involved, as the draft guidance indicates on line 179.</td>
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<td>7</td>
<td>194-196</td>
<td>Modify the explanation of “emerging safety issues” by removing the language “likely to cause death or serious injury” to indicate that any potential or emerging safety issue may be cause for seeking feedback.</td>
<td>See Cover Letter from AdvaMed, page 4.</td>
</tr>
<tr>
<td>8</td>
<td>198, with conforming changes elsewhere as applicable</td>
<td>Revise to “V. Certification of Request”</td>
<td>The Draft Feedback Guidance repeatedly calls for “justification” of the feedback request, including an explanation of how “each individual observation meets one or more of the eligibility criteria within the justification.” Draft Feedback Guidance, lines 203-204. This goes too far. Nothing in FDARA section 702 requires a justification that includes a detailed connection of observations to feedback criteria. Rather, the statute simply clarifies that feedback requests should relate to public health priorities, systemic or major actions, or emerging safety issues. Certification by the firm that one or more of these criteria apply is sufficient to support a feedback request.</td>
</tr>
<tr>
<td>9</td>
<td>226</td>
<td>Revise to “…15 calendar days.”</td>
<td>Requestors should not be required to wait the entire statutory period just to find out whether their request is accepted.</td>
</tr>
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Add, “A firm may request clarification of FDA’s feedback, in writing, within ten calendar days after receiving the feedback. The written request should specify the points for which the firm seeks clarification. FDA will provide a written response within ten calendar days. A firm may change its response to the Form FDA 483 based on FDA feedback.”

The addition allows firms to seek clarification if they do not understand FDA’s feedback, which assures that firms understand and can appropriately act on this feedback as they undertake remediation.

Further, in some cases, firms may wish to amend their 15-day response to the Form FDA 483 (“Form 483”) based on the agency’s feedback. For example, should a firm seek feedback about actions detailed in its Form 483 response – and learn that the actions are inadequate or only partially adequate – then the firm may wish to both revamp its remediation and revise its Form 483 response.

Revise to, “known at that point in time. FDA’s feedback represents the consensus view of all FDA components responsible for review of and action on the underlying inspection. While the feedback is nonbinding, it will not change absent a material change in the information submitted in the feedback request.”

This revision assures that FDA feedback incorporates the views of all Agency components, e.g., CDRH and ORA staff, responsible for overseeing actions that respond to inspection observations. This avoids the risk of whipsawing firms between varying expectations from different Agency components. The revision also gives firms confidence that FDA will not change its position absent a material change in the information that they provided when seeking feedback. This is consistent with other CDRH guidance documents related to providing non-binding feedback.

Clarify that FDA will consider requests for nonbinding feedback when determining whether to issue a warning letter or take other action in response to an inspection.

FDA’s Regulatory Procedures Manual permits consideration of ongoing or promised corrective actions when deciding whether to issue a warning letter. Regulatory Procedures Manual, Chapter 4, section 4-1-3. Feedback requests inform corrective actions, showing that “[a firm’s] proposed actions . . . are adequate, possibly avoiding unnecessary investment in potential solutions not likely to satisfactorily address an inspectional observation.” Draft Feedback Guidance, lines 128-130. Thus, in considering the adequacy of the firm’s corrective actions, FDA should account for whether the firm has requested nonbinding feedback. This request signals a firm’s commitment to timely and effective solutions that may obviate the need for a warning letter or other agency action.