Dockets Management Staff (HFA–305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852


Dear Sir or Madame:

The Advanced Medical Technology Association ("AdvaMed") appreciates the opportunity to provide comments on the Food and Drug Administration ("FDA") draft guidance, "Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions; Draft Guidance for Industry and Food and Drug Administration Staff" ("Draft Uncertainty Guidance").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 commends FDA for recognizing in the Draft Uncertainty Guidance the uncertainty in making benefit-risk determinations for some medical devices, including breakthrough products and products that target small or underserved patient populations. Making these devices available both serves patients and provides meaningful clinical experience to inform review of follow-on devices. Importantly, even as products with some uncertainty enter the market, there are postmarket surveillance protections to monitor their safety and effectiveness, and postmarket data collection to advance product iteration and innovation.

The factors that the Draft Uncertainty Guidance describes, and the processes that it details, advance public health by affording patients timely access to medical devices that meet statutory standard for safety and effectiveness. To that end, we offer general comments on the draft guidance below, followed by comments related to specific parts of the draft guidance.
General Comments

FDA should minimize use of the term “appropriate” in the Draft Uncertainty Guidance, replacing it instead with “reasonable.”

The term “appropriate” appears seventy times in the Draft Uncertainty Guidance in myriad contexts, e.g., “FDA must consider . . . the least burdensome appropriate means of evaluating device effectiveness,” “factors that FDA considers in assessing the appropriate uncertainty about a device’s benefits and risks,” and “the likelihood that the necessary postmarket data collection will be completed within appropriate timeframes . . .” Draft Uncertainty Guidance, lines 127-129, 232-233, and 284-285 (emphasis added). This term is problematic because what is “appropriate” is subjective and is neither well understood nor well established in FDA regulatory practice. For example, in considering “appropriate uncertainty about a device’s benefits and risks,” one might ask who determines whether the uncertainty is appropriate and what criteria they use in making this decision.

We recommend replacing “appropriate” with “reasonable.” The “reasonable” standard is well understood in law and it is an integral part of FDA practice. Indeed, in reviewing premarket approval applications, FDA must consider whether there has been a “reasonable assurance of device safety and effectiveness.” 21 U.S.C. § 360(e)(5)(A) (emphasis added); see also 21 CFR 806.7(c)(1) (“[T]he agency relies upon only valid scientific evidence to determine whether there is reasonable assurance that the device is safe and effective.”). In other cases, FDA might simply delete the term “appropriate.” Thus, the Draft Uncertainty Guidance’s statement that “[t]he Agency intends to work with sponsors to determine an appropriate and reasonable timeframe for the particular device . . .” could be rewritten as “[t]he Agency intends to work with sponsors to determine a reasonable timeframe for the particular device . . .” Draft Uncertainty Guidance, lines 396-397. Such revisions will provide clear standards for Agency action and enhance comprehension and use of the draft guidance.

FDA should not default to advisory committee meetings when it has questions about postmarket data.

The Draft Uncertainty Guidance explains that FDA intends to hold advisory committee meetings when it requires postmarket data as a condition of approval and then has questions about that data. Draft Uncertainty Guidance, lines 419-422. FDA expects that these meeting will occur frequently enough to justify planning them in advance, “for a time soon after the timeframe for submitting the postmarket evidence under the conditions of approval . . .” Draft Uncertainty Guidance, lines 424-425.

We understand that FDA must answer its questions about postmarket data, but we do not believe that advisory committee meetings should be the Agency’s default mechanism. Advisory committee meetings may be needed in some cases, but in all cases they are massively time and resource intensive. It is not unusual for sponsors to commit thousands of hours and hundreds of thousands of dollars (or more) to preparing for these meetings. FDA and committee members likewise dedicate significant time and energy to advisory committee meetings.
Of course, in some cases, an advisory committee meeting is exactly what FDA requires to answer its questions. But the Agency should first consider whether other, less time and resource-intensive solutions are available. For example, FDA might first work with sponsors to identify missing information and then give the sponsor an opportunity to generate the necessary data. Or FDA might assign “homework” to its network of experts as an alternative to a committee meeting. Through such strategies, FDA could efficiently answer questions about postmarket data while avoiding the massive time and resource commitment that advisory committees demand.

**FDA should define “small patient populations” and provide venues for discussions with sponsors about the traits and significance of these populations.**

We support FDA’s position that there may be cases in which it accepts greater uncertainty about probable benefits and risks for small patient populations that exceed the Humanitarian Device Exemption 8000 individuals cap. But to best engage FDA in these cases, sponsors must understand how FDA defines small patient populations. What are the factors that FDA considers, for example, in determining that a small patient population exists, and what steps does the Agency follow in making this decision? Who at FDA should sponsors engage in small-patient-population discussions (e.g., the Office of Orphan Products Development?) and what is the venue for these discussions?

We suggest that FDA advise that it will make small-patient-population determinations on a case-by-case basis, weighing factors such as the size of the patient population, whether the patient population is traditionally underserved (e.g., rare disease populations), the condition to be treated, and alternative available treatments. If FDA has in mind an upper limit on the number of patients that could constitute a small patient population, then it should share this number with stakeholders for input.

Further, FDA should identify mechanisms, such as the Q-submission process, to work with sponsors to determine if a small patient population exists and, if so, the implications for considering uncertainty. FDA should also add to the Draft Uncertainty Guidance examples of these determinations so that sponsors can see them in practice and understand when to engage FDA about them.

Through these steps, FDA will help sponsors understand when a small patient population might affect device review and how FDA’s assessment would differ from other review scenarios.

**The Draft Uncertainty Guidance requires more discussion and examples of uncertainty considerations for Humanitarian Device Exemptions, De Novo Classifications, and standard Premarket Approval Applications.**

Taken together, Humanitarian Device Exemptions (HDEs), De Novo Classifications (“De Novos”), and standard Premarket Approval Applications (“PMAs”) comprise most premarket approval submissions. But the Draft Uncertainty Guidance affords these
submissions little discussion and even less illustration of how FDA will consider them. Instead, FDA dedicates nearly one-half of the draft guidance to discussion of Breakthrough Devices and small patient populations. These are important topics and we appreciate FDA’s treatment of them. But HDEs, De Novos, and standard PMAs are likewise important and sponsors of these submissions need guidance about the uncertainty considerations that will affect Agency review. To offer just one example, for a non-breakthrough PMA submission, will FDA consider the device’s public health importance and accept more uncertainty for devices with a greater health benefit?

As important, sponsors require real-world examples of uncertainty consideration across the range of premarket submissions, including HDEs, De Novos, and standard PMAs. Along with a clear discussion of FDA’s expectations and practices, these examples will help sponsors understand how FDA manages uncertainty for their products. This, in turn, will allow sponsors to work with FDA before and during submission review to assure that uncertainty in their products’ benefit-risk assessment is properly addressed.

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AdvaMed thanks FDA for its consideration of these general comments and the specific comments that follow. Please do not hesitate to contact me at 202-434-7243 or ssilverman@advamed.org if you have any questions.

Respectfully Submitted,

/s/

Steve Silverman
Vice President
Technology & Regulatory Affairs
AdvaMed

Attachment
<table>
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<tr>
<th>#</th>
<th>Line Numbers</th>
<th>Comment</th>
<th>Rationale/Justification</th>
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<tbody>
<tr>
<td></td>
<td>Lines 111-116</td>
<td>Revise to, “There is generally more flexibility in the amount of clinical evidence needed for devices than for drugs and biological products because they are subject to different statutory criteria. In addition, the mechanism of action and modes of failure are generally more predictable and better understood for devices than for drugs and biological products. Further, the design process for a device is more often an iterative process based largely on rational design and non-clinical testing rather than clinical studies.”</td>
<td>This revision makes clearer what was a complicated single sentence.</td>
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<td></td>
<td>Line 152</td>
<td>Revise to, “For example, FDA’s final guidance . . .”</td>
<td>This revision clarifies that the device under discussion is a final guidance.</td>
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<td>Lines 219-225</td>
<td>Revise to, “Furthermore, the continuous generation of evidence as part of a learning health care system is important to continuously refine our understanding of how medical devices are used and perform, and corresponding patient outcomes. This understanding can inform FDA’s regulatory decision making for medical devices.”</td>
<td>This revision makes clearer what was a complicated single sentence.</td>
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<td>Lines 230-232, Lines 389, 397-398, 403, and elsewhere where applicable</td>
<td>Revise to, “This guidance enhances transparency and consistency in the premarket review process by describing several factors that FDA considers in assessing reasonable uncertainty about a device’s benefit-risk profile when reviewing these types of premarket submissions.”</td>
<td>This revision resolves ambiguity in use of the term “appropriate,” which appears excessively in the Draft Uncertainty Guidance. To illustrate, “appropriate” appears twice in the following sentence: “The Agency intends to work with sponsors to determine an appropriate and reasonable timeframe for the particular device in situations where postmarket data collection is considered to be appropriate and the least burdensome approach to allow for marketing authorization.” Draft Uncertainty Guidance, lines 397-399 (emphasis added). What is</td>
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<td>Lines 278-280</td>
<td>Revise to, &quot;The feasibility of generating extensive clinical evidence premarket based on appropriate considerations, e.g., taking into account the rarity or prevalence of the disease or condition or known limitations of existing devices;&quot;</td>
<td>The description of assessing the feasibility of generating extensive premarket clinical evidence is too narrow. Not only may the rarity or prevalence of the disease or condition make it difficult to study, but so may known limitations of existing devices.</td>
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<td>Lines 303-307</td>
<td>Revise to, &quot;When considering a De Novo request, FDA expects that the risks associated with the device would contribute to its analysis of uncertainty, recognizing that the FDA may be able to accept greater uncertainty due to factors such as probable benefits related to the device (e.g., the device presents minimal risks), the imposition of special controls (e.g., the device presents higher risks but special controls mitigate those risks), or patient preference showing a greater risk tolerance among the indicated population.&quot;</td>
<td>The revision clarifies that there may be more factors than risks and special controls that affect FDA’s acceptance of uncertainty. The revision highlights patient preference as an example of such additional factors.</td>
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<td>Lines 312-317</td>
<td>Revise to. &quot;Other cases may include, but are not limited to, cases where the extent of uncertainty is small, risks to patients are minimal, patient preference data indicates a greater risk tolerance among the indicated population, or where postmarket data collection is not feasible and other postmarket controls help to mitigate uncertainty in the benefit-risk profile of the device being reviewed.&quot;</td>
<td>The revision clarifies that patient preference information may obviate postmarket actions to resolve or reduce the extent of uncertainty.</td>
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<td>Line 344</td>
<td>Revise to, &quot;high likelihood that relevant, complete data will be collected postmarket in a timely fashion . . . .&quot;</td>
<td>The revision resolves ambiguity associated with use of the term &quot;appropriate.&quot;</td>
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<td>Lines 358-364</td>
<td>Revise to, &quot;The postmarket controls described below could apply to non-Breakthrough Devices subject to PMA, depending on the circumstances.&quot;</td>
<td>The text at lines 358-364 is redundant and the reader may be confused about why it is repeated at the close of Section A. The revision avoids this redundancy while preserving the transition into Sections A.1-3.</td>
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<td>Lines 403-407</td>
<td>Revise to, &quot;Where postmarket data collection is required as a condition of approval, FDA intends to consider whether it would be reasonable and useful (e.g., whether it would be</td>
<td>The revision avoids using the term &quot;appropriate,&quot; which is ambiguous. Instead, the revision predicates requiring disclosure of postmarket data collection on 2 clear requirements: (1) whether the requirement is</td>
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We commend FDA for creating the "small patient population" mechanism to accommodate uncertainty as sponsors provide a reasonable assurance of safety and effectiveness. But to effectively use this mechanism, sponsors need a better explanation of what is a "small patient population" and what are the circumstances in which such a population might exist. We suggest that FDA advise that it will make small-patient-population determinations on a case-by-case basis, weighing factors such as the size of the patient population, whether the patient population is traditionally underserved (e.g., rare disease populations), the condition to be treated, and alternative available treatments. If FDA has in mind an upper limit on the number of patients that could constitute a small patient population, then it should share this number with stakeholders for input.

Likewise, FDA should identify mechanisms, such as the Q-submission process, for determining whether a small patient population exists and, if so, the implications for considering and accommodating uncertainty. FDA should also add to the Draft Uncertainty Guidance examples of these determinations so that sponsors can see them in practice and understand when to engage FDA about them.

FDA could use this same approach to identify and consider a "clinically meaningful subset of a broader population." Draft Uncertainty Guidance, line 451. Thus, on a case-by-case basis, FDA could assess factors such as the size of the patient population, the condition to be treated, and alternative available treatments. Likewise, FDA should identify mechanisms for determining whether a clinically-meaningful subset exists and, if so, the implications for considering and accommodating uncertainty. And FDA should also add to the Draft Uncertainty Guidance examples of these determinations.
| Lined 591-593 | Revise to, “However, the indicated disease is serious, and there are no alternative treatments available, or existing devices have well-understood limitations. Considering the limitations or lack of existing treatment options, the device’s potential benefits. . . .” | This revision clarifies that, in considering uncertainty for small patient populations, FDA can account for the limitations of available devices as well as the availability of alternative treatment options. |
| General | Add to Section II a discussion of how the Draft Uncertainty Guidance differs from FDA’s final guidance. “Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications” (“Benefit-Risk Guidance”). | The Draft Uncertainty Guidance and the Benefit-Risk Guidance are complementary. An explanation of how the guidances work together, where they intersect, and where they are distinct would help sponsors use both documents to effectively engage FDA during PMA and De Novo reviews. |
| General | The Draft Uncertainty Guidance should provide more information about the use of patient preference and risk tolerance data to inform benefit-risk determinations. | The Draft Uncertainty Guidance biases towards use of postmarket controls to address uncertainty concerns. Patient preference and risk tolerance is an additional and critical mechanism for addressing these concerns. Patient preference studies can yield risk tolerance data that is valuable to FDA in making a benefit-risk decision – particularly in a marginal benefit-risk situation where patient tolerance informs FDA’s view of risk and tips the benefit-risk balance in a positive direction. Studies may determine that patients with a higher risk tolerance and an unmet medical need will accept more uncertainty than the standard significance level for clinical studies. Consequently, the draft guidance should detail how this data affects uncertainty assessments and demonstration that a device meets approval requirements. |
| General | FDA should publish draft guidance on consideration of uncertainty in making benefit-risk determinations for 510(k) submissions | Benefit-risk uncertainty does not apply exclusively to PMAs, HDEs, and De Novo submissions. Sponsors who file 510(k)s engage FDA about the benefit-risk profile of their devices and questions of |