Medical Device Equivalence Analysis Examines 2 Factors

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A couple of weeks ago the U.S. Food and Drug Administration issued draft guidance, the "Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications [510(k)] with Different Technological Characteristics." This draft guidance seems based on the final guidance issued over a year ago, "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications."

Both guidance documents explain that safety and effectiveness are determined by “weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use,” according to the Federal Food, Drug, and Cosmetic Act. Thus, for both PMAs and 510(k)s, when the FDA makes benefit-risk determinations, it is actually evaluating the safety and effectiveness of the product.

The analytical structures described in the two guidance documents are very similar. Both include a discussion of the factors the FDA will consider when making benefit-risk determinations. The frameworks described are practically identical, both documents include the following criteria of benefits, risks and additional factors:

1. assessment of benefits (type; magnitude; probability; duration);
2. assessment of risks (severity, types, numbers, rates of harmful events; probability; duration; false positive/false negative for diagnostic); and
3. additional factors (uncertainty; characterization of the disease; patient tolerance for risk and perspective on benefit; risk mitigation; postmarket data).

Two structural differences between the two can be found in the additional factors section. The PMA guidance includes the “availability of alternative treatments or diagnostics” as an additional factor, but the additional factor in the same place in the 510(k) guidance is called the “benefit for the health care professional or caregiver.”

A careful analysis of the similarities and differences of these two categories is beyond the scope of this article, but at first glance, the substance of these two additional factors seem similar. The other
difference in the analytical frameworks is that that the PMA guidance includes an additional factor — “novel technology addressing an unmet medical need” — while the 510(k) guidance includes an additional factor, “innovative technology.” The descriptions of these additional factors are also very similar. In fact, much of the language of the 510(k) guidance was lifted wholesale from the PMA guidance.

But wait, you might be saying, “Aren’t 510(k) devices supposed to be substantially equivalent to a predicate device? And doesn’t substantial equivalence mean the new device has the same intended use and the same technological characteristics as the predicate device? What does safety and effectiveness, or benefit-risk, have to do with substantial equivalence? Is the FDA suggesting by this guidance that they are going to apply PMA standards to 510(k)s? Can they do that?”

Yes, the FDA can, though in a slightly different way for 510(k) products than for PMA products. The FDCA requires the FDA to consider the safety and effectiveness (i.e., the benefit-risk) of 510(k) products with different technological characteristics than the predicate device. The guidance document does a nice job of explaining.

In a nutshell, a new device is substantially equivalent to a predicate device when it has the same intended use and technological characteristics as the predicate device. If these two characteristics are the same, there’s no need for the FDA to conduct a benefit-risk analysis when determining whether the new device is substantially equivalent to the predicate. If the intended use and technological characteristics are the same, then it’s easy to conclude that the new device is substantially equivalent to the predicate. The benefit-risk determination for the predicate device has already been made and confirmed by real-world use of the product.

But what if the new device has different technological characteristics, such as material, design, or energy source changes? In that case, the new device can still be found substantially equivalent to the predicate device if:

- the new device does not raise different questions of safety and effectiveness than the predicate device; and
- the new device is as safe and effective as the predicate device.

If the FDA determines that the technological differences between the predicate and new devices raise different questions of safety and effectiveness, the agency will find the new device to be not substantially equivalent to the predicate.

On the other hand, if the FDA finds that the technological differences of the new device do not raise different questions of safety and effectiveness relative to the predicate device, then the agency “will evaluate the technological differences between the new device and the predicate devices to determine their effect on safety and effectiveness.” The new draft guidance should be helpful in understanding how the FDA will be making that safety and effectiveness determination.

What makes determining the safety and effectiveness of 510(k) devices different from the same determination for PMA products? First, as noted above, the FDA will evaluate the effect of the technological differences on the safety and effectiveness of the new device, rather than assessing the safety and effectiveness of the device as a whole. When reviewing PMA products, the FDA would consider the safety and effectiveness of the product as a whole.
A second difference is that the benefit-risk determinations for PMA devices do not require a comparison to any other device. In contrast, for 510(k) devices, the FDA considers the benefits and risks of the new device as compared to the predicate device.

Both differences between the 510(k) and PMA process should be kept in mind when determining the data and information to be included in a 510(k).

Additional Considerations

The question of whether the new device is as safe and effective as the predicate device doesn’t come up if the FDA determines that the technological differences of the new device raise different questions of safety and effectiveness. If the new device raises different questions of safety and effectiveness, the new device is found not substantially equivalent and the product review stops.

What constitutes a “different” question of safety and effectiveness? Another very recent final guidance, "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]," states that “a different question of safety or effectiveness is a question raised by the technological characteristics of the new device that was not applicable to the predicate device, and poses a significant safety or effectiveness concern for the new device.” The substantial equivalence guidance provides a few examples, but seems to describe obviously “different” questions of safety and effectiveness, so they may be of limited help in closer cases. Nevertheless, it’s important for 510(k) submitters to argue to the best of their ability that the technological differences between the new device and predicate device do not raise different questions of safety and effectiveness. It would be very helpful if the FDA were to articulate in its “not substantially equivalent” letters the different questions of safety and effectiveness raised by the technological difference of the new device, but unfortunately this does not always happen.

The FDCA also states that the FDA can require “appropriate clinical or scientific data if deemed necessary” to support an assertion that the new device is as safe and effective as the predicate device. Whether or not clinical data will be required to support a 510(k) with new technological characteristics is frequently unclear. The agency addressed this issue in the new Substantial Equivalence final guidance, stating that the FDA currently requests clinical data for less than 10 percent of 510(k) submissions.

According to this guidance, when analytical or nonclinical bench performance tests, nonclinical animal tests or biocompatibility tests are insufficient, or available scientific methods are not acceptable (e.g., because they have not been validated or are not supported by a valid scientific rationale), then the FDA may request clinical data to support a determination of substantial equivalence. As noted above, the need for clinical data should be limited to the impact of the technological differences of the new device and not the device as a whole.

On the whole, these new guidance documents are helpful in clarifying the FDA’s thinking about its review of 510(k)s. They are definitely worth a close read. Although you can comment on any guidance at any time, submit comments on the draft 510(k) Benefit-Risk guidance by Oct. 14 to ensure the FDA considers your comments before it begins work on its final version of the guidance.

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