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

Re: Draft Guidance: Consideration of Uncertainty in Making Risk-Benefit Determinations in Medical Device Approvals, De Novo Classifications, and Humanitarian Device Exemptions.
Docket No. FDA-2018-D-3130

To whom it may concern:

The Center for Science in the Public Interest (CSPI) appreciates the opportunity to comment on the Food and Drug Administration's draft guidance on uncertainty in medical device risk-benefit determinations. We have grave concerns about this draft guidance, which has the potential to further lower the already-too-low standards for approval of medical devices.

CSPI is a non-profit consumer education and advocacy organization that, since 1971, has worked to improve the public's health. CSPI's work is supported primarily by the 500,000 subscribers to its *Nutrition Action Healthletter*, one of the nation's largest-circulation health newsletters. CSPI is an independent organization that does not accept government or corporate donations.

The draft guidance starts with a reasonable presumption: that the amount of uncertainty (largely related to sample size) that the agency will accept when reviewing a medical device should be related to a number of factors, including 1) the extent of public health need, 2) the probable benefits of the device, and 3) the feasibility of collecting postmarket data. Based on these factors, the agency could allow an increase in postmarket data collection to compensate for premarket uncertainty.

The guidance then takes these concepts a step further by providing a series of tables describing highly specific scenarios as illustrations of this general point. (To our knowledge, the Center for Drug Evaluation and Research (CDER), while discussing uncertainty, has never before provided quantitative scenarios like these.) Companies will undoubtedly seize upon these scenarios to craft an argument about how a particular device should be the recipient of an even greater degree of uncertainty than the agency might have contemplated, and thus a shift in data requirements to the postmarket period, resulting in reduced premarket sample size. The benefits to industry of such a shift would be clear: a new emphasis on postmarket data would incur financial savings to manufacturers through smaller premarket studies and would result in an easier path to market.

For patients, however, such an outcome is potentially dangerous. While some important medical devices may come to market more rapidly, it is likely that more products will simply be able to take advantage of a *de facto* lowered approval standard, exposing patients to unsafe and/or

ineffective products. While this is commonly referred to as a regulatory slippery slope, this draft guidance actually lays out, in tabular form, clear stepping stones to reduced regulatory standards.

The Shift to the Postmarket Will Not Adequately Substitute for Reduced Premarket Testing

The fundamental assumption of this draft guidance is that the additional premarket uncertainty can be compensated for in the postmarket setting. There is ample reason to question this assumption.

First, the extent of the postmarket requirements is inadequately described. The draft guidance uses adjectives such as "modest" and "robust," terms that lack definitions in the guidance. Second, the limitations of the FDA's postmarket systems, though they may be improving, are well known and have at times had serious consequences for patients. Take, for example, the power morcellator that, until prompted by a well-publicized index case, produced not a single spontaneous adverse event report related to cancer dissemination despite dozens, if not hundreds, of affected women over almost 20 years. Would spontaneous adverse event monitoring constitute a "modest" postmarket program?

Most fundamentally, sponsors of medical devices understand well that a key to success is to get one's foot in the door. That's because, after a device is approved, the FDA is unlikely to remove it from the market. In the entire half century of medical device regulation, the agency has removed only two products (hair implants and powdered latex gloves) from the market, although companies do more frequently voluntarily withdraw products. If the FDA surrenders its strongest weapon—premarket approval—it must also increase its willingness to consider removal of products. If it doesn't, patients will suffer from this new, and entirely agency-created, glide path to approval.

The Draft Guidance Does Not Relate Only to Unmet Medical Need

Much of the introductory material in the draft guidance uses the problem of unmet medical need as the justification for the acceptance of greater uncertainty by the agency. The examples that the guidance provides are also related to breakthrough products, which, by definition, are designed for serious conditions with unmet medical needs.[1]

Yet the scope of the guidance, including its title, makes clear that its reach is much broader and does not end with breakthrough products. As the Scope (Section III) says: "However, these examples are not intended to imply that FDA's consideration of uncertainty in premarket benefit-risk determinations is limited to these scenarios." At a minimum, consistent with the logic and scenarios presented, the guidance should be restricted to breakthrough products.

The Scenarios Described in the Guidance Make Clear that It Would Lead to a Significant Weakening of Current Standards

While some degree of case-specific flexibility in the application of uncertainty may be justified, the scenarios contemplated in the draft guidance show that the guidance would precipitate a

[1] Food and Drug Administration. Draft Guidance: Breakthrough Devices Program, October 25, 2017. Available at: https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM581664.pdf.

major retreat from the agency's current default standards. For example, Case 3 in the scenarios for both Breakthrough Treatment Device (Scenario 1) and Devices for Small Patient Populations (Scenario 3) contemplates one-sided significance levels of 20%, which is eight times higher than the "conventional" significance level permitted (2.5%). This means that, in these scenarios, the probability of accepting a device as effective when in fact it is not is 20%, much higher than is typically accepted in science.

The Use of One-Sided Significance Testing Is Not Justified in the Draft Guidance

Focusing on the non-diagnostic devices (Scenarios 1 and 3), the draft guidance contemplates single-arm trials and establishes target effectiveness goals that the device must exceed if the agency is to declare the product effective. This justifies the one-sided significance testing described, which, in turn, lowers the sample size requirements. But providing only scenarios without control arms is itself a low standard. Would the agency accept the same one-sided significance testing if the study included a control group? Certainly, in most cases, CDER would not.[2]

In conclusion, the FDA's draft guidance provides industry with a roadmap to lower device approval standards. We urge you to withdraw the draft guidance or, at a minimum, to restrict it to breakthrough devices.

Yours sincerely,

Peter Lurie, MD, MPH
President

[2] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline. Statistical Principles for Clinical Trials E9. February 5, 1998. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf.