September 12, 2013

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

Re: Docket No. FDA-2011-D-0790 – Comments of the National Venture Capital Association's Medical Innovation and Competitiveness Coalition

Dear Sir or Madam:

The National Venture Capital Association's (NVCA) Medical Innovation and Competitiveness (MedIC) Coalition, a partnership between NVCA member venture capital firms, entrepreneurs, and early-stage portfolio companies, appreciates the opportunity to submit these comments in response to the issuance of the *Draft Guidance, FDA Decisions for Investigational Device Exemption (IDE) Clinical Investigations* by the Food and Drug Administration (FDA) on June 14, 2013.

The NVCA is a trade association representing the approximately 400 venture capital firms in the United States, with a mission to foster greater understanding of the importance of venture capital to the U.S. economy and support entrepreneurial activity and innovation. Venture capital is particularly important in the medical device industry, where more than 80% of companies have fewer than 50 employees, and rely heavily on venture capital investment to bring their products to market.[1]

MedIC is comprised of NVCA member firms and their life sciences portfolio companies, and advocates for policies and regulations that advance and support U.S. medical innovation. MedIC seeks to 1) educate policymakers on the critical role America's medical innovation plays in the U.S. healthcare system; 2) establish incentives for investors and entrepreneurs to drive medical innovations in the U.S.; and 3) achieve broad-based FDA reform so that new technologies can be brought to market more efficiently.

MedIC would like to take this opportunity to thank FDA for its work in preparing this Draft Guidance, and applauds the thought and detail that went into its development. We strongly support FDA's efforts to improve the IDE process to reduce

[1] Josh Makower, MD, et al., *FDA Impact on U.S. Medical Technology Innovation: A Survey of Over 200 Medical Technology Companies* (November 2010).

the time to IDE approval for companies and to set the groundwork for a clear and efficient path to product clearance or approval. We commend FDA on creating a pathway that will allow sponsors of novel products or complicated studies the opportunity to interact early and often with FDA in an effort to ensure that a study is appropriately designed to support a marketing application. We believe that the suggestions we provide in these comments will help to improve what is already a document that will strengthen the IDE process.

1. The final guidance should make clear that benefit-risk considerations should be applied in assessing a clinical trial design.

On March 28, 2012, FDA issued a final guidance document, *Factors to Consider When Making Benefit-Risk Determinations in Medical Device Pre-Market Approval and De Novo Classifications*. That guidance describes the principal factors FDA considers when making benefit-risk determinations during the premarket review process for certain medical devices, and states: "The concepts discussed in this guidance are applicable to the medical device development process from design to market. As such, the benefit-risk factors set out herein should be considered during the design, non-clinical testing, pre-Investigational Device Exemption (IDE), and IDE phases as well as in assembling and assessing PMA applications or *de novo* petitions." *Id.* at 5. The IDE guidance should cross-reference the Benefit-Risk Guidance, and make clear that the factors described in the Benefit-Risk Guidance will be applicable in making decisions about the approvability of an IDE and when an IDE or pre-decisional IDE will support a marketing application.

2. The letter to the sponsor of an IDE or pre-decisional IDE should be very clear as to whether the study, as proposed, will support a marketing application.

The draft guidance document states: "FDA's decision letter will specify whether FDA believes the study design is adequate and may support a future marketing approval or clearance, if it is successfully executed and meets its stated endpoints without raising unforeseen safety concerns." Draft Guidance, at 9. We would suggest that FDA not state that a study design "may" support a marketing application, but rather be very clear as to whether it will or will not. Stating that a proposed study design "may" support an application does not provide sufficient assurance to the sponsor with respect to the status of the study and its role in a future application. FDA should be explicit as to whether it does or does not believe that the IDE **will** support a marketing application, or whether a pre-decisional IDE will lead to an IDE approval that will support a marketing application. The ambiguity created by the word "may" deprives sponsors of a clear understanding of the status of whether FDA believes the study will or will not support clearance or approval.

FDA generally develops template language used to respond to sponsors in a variety of circumstances (*e.g.*, upon receipt of a 510(k) submission, a not substantially

equivalent determination, etc.), and we would propose that FDA do the same here. It should develop a template that makes clear whether the study will or will not support a marketing application, leaving no room for doubt in the mind of the sponsor. Additionally, FDA should develop a means for clearly distinguishing between IDEs approved to support a marketing application versus those approved which will not. This could be achieved, for example, by creating two tiers of letters, Type A and Type B. A Type A letter would be a letter indicating that the IDE, as proposed, will support a marketing application. A Type B letter would indicate that, although FDA is approving the IDE, FDA does not believe that the IDE as currently proposed will support a marketing application. Similarly, a response to a pre-decisional IDE should make clear whether the IDE as proposed will or will not support a marketing application. Labeling a letter as "Type A" or "Type B" will allow the sponsor to easily understand FDA's view of its IDE proposal.

3. If the IDE is approved to support a marketing application, the approval letter should state that FDA's position will not change barring a substantive change in the study design by the sponsor or substantive new scientific developments that materially affect the risk/benefit profile.

The draft guidance states: "If FDA determines that a pivotal study design is adequate and may support a future marketing application, FDA intends to consider changes to its assessment of the study design only if the sponsor materially changes the device or the study design, or if important issues relevant to a determination of safety or effectiveness have emerged since the time of the IDE approval." Draft Guidance, at 9. We agree with FDA's position that a change in assessment of an IDE should occur only in limited circumstances, and would encourage FDA to revise the guidance document to make clear that FDA will include language stating this position in the letter to the sponsor. It is not enough for the guidance to state FDA's "intent" with respect to changing its position. The letter to the sponsor should state that FDA **will not** change its position unless certain specified circumstances arise.

We agree with FDA that one such circumstance should be a material change by the sponsor of the device or the study design, but suggest a modification to FDA's position about the emergence of issues related to the safety or effectiveness of the device. As currently written, the draft guidance implies that issues related to the safety or effectiveness of the device could "emerge" merely by FDA's failure to adequately consider those issues during an initial review of the IDE. We would propose that the final guidance state that FDA's position could change if substantive **new** scientific developments that could materially affect the risk/benefit profile have arisen since the approval of the IDE. This makes clear that both FDA and the sponsor are responsible for addressing all reasonably known issues pertaining to the safety and effectiveness of the device at the time of the IDE or pre-decisional IDE, and only the emergence of new information may cause FDA to later reconsider its original position.

4. If FDA approves the IDE with conditions, once those issues are resolved, FDA should clearly document resolution of those issues.

The draft guidance states that if FDA identifies issues with the IDE "that must be addressed in a timely manner but do not preclude initiation of the clinical investigation, the IDE will be approved *with* conditions." Draft Guidance, at 3 (emphasis in original). If a sponsor receives an approval with conditions, the study may begin, but the sponsor must address the issues identified by FDA within 45 days from the date of FDA's decision letter. If FDA determines the issues have been resolved, it will grant approval without conditions. *Id.* at 5.

In addition to granting approval without conditions, FDA should clearly document the issues that led to the approval with conditions, how and when those issues were resolved, and should state in the approval letter to the sponsor that the resolved issues are now considered closed and will not be revisited barring exceptional circumstances. FDA should be clear that once it states an issue is resolved, it will not raise the issue again. The sponsor must have certainty that closed issues will not resurface.

5. Repeat reviews during the pre-decisional IDE process should be subject to a shorter timeframe than the 30 days allotted for a new pre-decisional IDE submission.

If a sponsor opts to submit a focused response to full written feedback from FDA, the draft guidance states that FDA will review the response and provide feedback via email within 30 days. This timeframe is the same as that allotted for review of a new pre-decisional IDE submission, and seems unduly long for a review of a "focused" response addressing issues with which FDA is already aware. While there may be some responses that are very complex and address a number of concerns raised by FDA, those will not be the norm. For the pre-decisional IDE process to work as intended, *i.e.*, to "result in faster approval of IDE submissions that may support market approval or clearance," FDA's standard review time for a focused response should be no more than 15 days. The proposed timelines also will likely make the pre-decisional program less attractive to companies. If FDA believes that a longer response time is needed due to the complexity of the issues, it can discuss this with the sponsor. The presumption, however, should be a shorter response time, which will in turn allow the sponsor to proceed more quickly with obtaining approval of the IDE and beginning the clinical trial.

6. FDA should utilize the Center Science Council to resolve fundamental questions of science that arise during the course of the pre-decisional IDE program.

If the sponsor believes there are fundamental questions of science involved in the pre-decisional submission pertaining to whether the IDE will support a marketing application, the Center Science Council should be available at the request of the sponsor to advise in review of the submission. This approach will allow scientific issues

to be addressed up-front in a scientifically-oriented manner. Resolving these scientific issues efficiently at the outset will result in better study designs, minimize appeals, and allow innovative products to get to market more quickly.

7. A sponsor should have the option to appeal receipt of a letter stating that the IDE is approved but will not support a marketing application.

The draft guidance does not address whether FDA's determination that an IDE will not support a marketing application is appealable under either 21 C.F.R. § 10.75 or FDASIA Section 603, codified at FDC Act Section 517a. 21 C.F.R. § 10.75 allows a person to request supervisory review of "[a] decision of an FDA employee." This provision is very broad, and essentially permits an aggrieved party to appeal any decision of an FDA employee. There are no timeframes for review associated with appeals under this section, and appeals often take many months, if not longer, to be resolved.

FDC Act Section 517a contains provisions relating specifically to appeals of "significant decisions," and imposes deadlines within which appeals of those decisions must occur. The phrase "significant decisions" is not defined by statute. We believe that the failure to reach such agreement on a study design is a "significant decision." This view is supported by FDA. It issued a draft guidance document stating its position that "significant decisions" include decisions on 510(k)s, PMAs, HDEs, IDEs, and failure to reach agreement on a protocol under section 520(g)(7). This section is a rarely used provision that is essentially a codification of the proposed pre-decisional IDE program for Class III and implantable devices, *i.e.*, it describes a process by which sponsors can meet with and obtain agreement from FDA with respect to a clinical trial protocol prior to submission of an IDE. Because FDA considers the failure to reach agreement under that statutory provision to be a "significant decision," and that provision provides for a process similar to that proposed in the draft guidance as the pre-decisional IDE program, a failure to reach agreement as part of the pre-decisional program should also be considered a "significant decision" subject to appeal under the FDASIA timeframes.

Additionally, if FDA approves an IDE, but issues what we have referred to above as a "Type B" letter, the sponsor should be able to appeal that decision, subject to the FDASIA timeframes. A Type B letter means that the IDE will not support a marketing application, and that is a "significant decision" because as a practical matter it delays the initiation of clinical trials for new, innovative products. For a variety of reasons, in most circumstances, the issuance of a Type B letter is the equivalent of a denial. Therefore, if a sponsor believes that an IDE, as proposed, will support a marketing application, and FDA disagrees, but nevertheless approves the IDE as required by FDASIA, the sponsor should have the option to appeal that decision subject to the timeframes in FDC Act section 517a.

8. A staged IDE approval or staged approval with conditions should only be utilized when no other viable options exist.

According to the draft guidance, a "staged" approval means that "FDA will grant approval or approval with conditions for a subset of the planned subject cohort while the particular outstanding questions are addressed." This means that a small number of subjects can be enrolled while the sponsor resolves outstanding issues with FDA, and enrollment can be expanded once an IDE supplement is approved.

As described in the Draft Guidance, the presumption with respect to a staged approval appears to be that the study will not continue unless the IDE supplement is approved, which could lead to a stopping of the trial while FDA reviews and approves the supplement. The presumption should be changed in favor of assuming the study will continue unless there is evidence of risk of harm to the study subjects. The study should not have to stop while awaiting FDA approval of an IDE supplement. This creates an undue burden on administration of the trial with little added benefit.

Stopping and then re-starting a study creates practical difficulties for sites, investigators, sponsors, and institutional review boards. The guidance therefore should state that a staged approval will be used only in very limited circumstances in which there is no other reasonable means of beginning the study.

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NVCA would like to reiterate its commitment to working with FDA and other policy makers to ensure that FDA revisions to the IDE process will promote innovation and investment. It is our shared commitment and goal to ensure that FDA has an IDE process that both improves access to innovative technologies and affords patients timely access to safe and effective products.

Sincerely,

Jonathan S. Leff
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NVCA Board Member and MedIC Chairperson