August 26, 2013

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

Re: Docket No. FDA-2013-D-0575

Dear Sir/Madam:

The National Venture Capital Association’s (NVCA) Medical Innovation and Competitiveness (MedIC) Coalition is pleased to provide comments to FDA’s *Draft Guidance for Industry on Expedited Programs for Serious Conditions—Drugs and Biologics* (“the Guidance”).

The NVCA is a trade association representing 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. NVCA’s MedIC coalition, comprised of NVCA member firms and small, emerging life sciences companies, advocates for policies and regulations that advance and support U.S. medical innovation.

Over the last three decades, the U.S. has been the global leader in medical innovation. Venture capital has been a primary force in translating scientific discoveries into medical advances for patients and remains one of few sources of capital to fund and nurture small, emerging companies focused on developing new drugs, diagnostics and medical technologies. The majority of new drugs and medical devices developed to serve significant unmet medical needs have had roots in venture capital-backed start-up companies.

However, venture capital investment in life sciences has been facing significant pressure in recent years. In fact, in 2012 and 2013 to date, the number of start-up companies receiving first-time venture capital funding—a leading indicator of investment in medical innovation—has fallen to the lowest levels seen since the mid 1990s. A primary reason for this decline is the increased time, cost and uncertainty involved in developing new drugs and medical devices.

We stand today at a critical crossroads for medical innovation. On the one hand, building on extraordinary insights in fields such as genetics, molecular biology, nanotechnology and others, the opportunities to harness science to save and improve human lives have never been better. On the other hand, the essential investments in translating scientific discovery into patient benefit have become increasingly difficult to make, as the time, cost and uncertainty of drug development have escalated relentlessly over the course of decades. While there are many reasons for this long-term increase, a major factor has been the expanding size, duration and complexity of clinical trials necessary to develop and obtain approval for novel medicines.
Against this backdrop, NVCA and the MedIC coalition believe that the passage of the Food and Drug Administration Safety and Innovation Act of 2012 ("FDASIA") represented a watershed moment. Last year, all stakeholders – including patients and consumers, industry, the medical community, and FDA – came together in the shared recognition that in order to advance medical innovation, we need to re-shape and modernize the way we think about drug development, particularly when it comes to serious and life-threatening conditions where existing therapies are not adequate. Underlying this consensus was, first and foremost, the needs of patients, and an appreciation that those suffering from serious and life-threatening diseases, including rare diseases, are willing to embrace greater uncertainty and greater risk in order to access the benefits of innovative new therapies.

The Congressional intent of Section IX of FDASIA is clear and reflected this stakeholder consensus:

"FDA should be encouraged to implement more broadly effective processes for the expedited development and review of innovative new medicines intended to address unmet medical needs for serious or life-threatening diseases or conditions, including those for rare diseases or conditions, using a broad range of surrogate or clinical endpoints and modern scientific tools earlier in the drug development cycle when appropriate. This may result in fewer, smaller, or shorter clinical trials for the intended patient population or targeted subpopulation without compromising or altering the high standards of the FDA for the approval of drugs.” FDASIA Section 901(a)(C).

We are deeply appreciative of FDA’s proactive leadership in helping to crystallize this stakeholder consensus, and in translating it into concrete steps and initiatives that have the potential to meaningfully accelerate the development and availability of important new medicines. Together with CDER’s “Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making” and its “Patient-Focused Drug Development” initiative, this draft Guidance on expedited programs demonstrates FDA’s clear commitment to this critical effort. Taken together, these initiatives are beginning to re-frame the dialogue about drug development and regulation, allowing FDA and drug developers to responsibly apply modern tools and innovative approaches to speed new therapies to patients with serious and life-threatening conditions. The underlying theme running through each of these initiatives is the fundamental recognition that the U.S. public health has an urgent interest in accelerating and streamlining development of new therapies for serious and life-threatening diseases. Patients and the public view the balance among benefit, risk and uncertainty in access to new drugs through the lens of that urgency.

This re-framing of the drug development and regulatory decision-making process is precisely what Congress intended with the passage of FDASIA, and was the driving force behind the creation of the Breakthrough Therapy designation and the enhancement and modernization of the Accelerated Approval pathway. The clear intent of Congress was to empower FDA with greater flexibility to responsibly expedite the development and availability of drugs to treat serious and life-threatening diseases, recognizing that new tools and approaches are necessary to strike the right balance on behalf of patients.

We congratulate FDA on the significant progress that is already being made toward this goal. FDA has already granted more than 25 Breakthrough Therapy designations. Sponsors report
that the enhanced dialogue involving senior FDA leadership and the willingness to embrace innovative approaches are having the intended effect of streamlining and speeding development. Moreover, there are clear signs that the promise of more rapid paths to market is already helping to attract investment capital to the development of new therapies that could benefit from Breakthrough designation and the broader use of the Accelerated Approval pathway.

However, drug development remains an extraordinarily long, costly and uncertain endeavor, and the U.S. medical innovation ecosystem continues to face tremendous pressure. NVCA and the MedIC coalition believe that the enhanced application of regulatory flexibility in approaching serious and life-threatening diseases will help attract venture capital investment to critical areas of medical need, highlighting the importance of continued focus on the rollout of these new initiatives, including Breakthrough Therapy designation, the expansion and modernization of the Accelerated Approval pathway, the Structured Benefit-Risk framework, and Patient-Focused Drug Development.

With this context in mind, we offer a number of specific comments on the draft Guidance.

1. **The Guidance appears to understate** the extent to which FDASIA endows FDA with increased flexibility to expedite the development and approval of drugs that address serious and life-threatening conditions.

   We appreciate and endorse FDA’s acknowledgment that the “FDASIA provisions facilitate somewhat broader use of accelerated approval to expedite patient access to important treatments for serious conditions” (line 445), and the recognition that the law is designed to “provide additional flexibility concerning the implications of available therapy on eligibility for accelerated approval” (line 447) as well as additional flexibility in assessing the advantage of a new drug over available therapy (line 498).

   However, the use of the word “somewhat” at line 445 could be erroneously interpreted as minimizing what we believe to be the fundamental Congressional intent behind Title IX of FDASIA. As noted above and as reflected in the Congressional findings, Congress very consciously intended to endow FDA with greater flexibility to use tools such as Accelerated Approval and Breakthrough designation as fully and frequently as possible, consistent with maintaining high scientific standards in the approval process. This critical intent should not be in any way understated or minimized, but rather, a central goal of this Guidance should be to communicate the ways in which FDA intends to use this enhanced flexibility to fully reflect the recognition, as rightly noted in the Guidance, that “patients and physicians are generally willing to accept greater risk (and uncertainty about benefit) for a treatment for a serious condition where there is an unmet medical need.” (line 47).

2. **The Guidance should be more explicit** in articulating the Accelerated Approval tradeoff: greater uncertainty about benefit and risk is acceptable and is in the interest of patients suffering from serious and life-threatening diseases, in the context of making drugs rapidly available while further studies are conducted to confirm benefit.
We believe that enhanced clarity about this fundamental tradeoff will help all constituencies to understand the rationale for Accelerated Approval when it is granted, as well as the need, as reflected in FDASIA, for FDA to have clear authority to withdraw Accelerated Approval in a straightforward fashion when confirmatory studies are not conducted or fail to support a favorable benefit-risk profile in the indicated population. FDA's streamlined withdrawal authority, now codified in the statute, should permit FDA to accept greater uncertainty when granting Accelerated Approval. This is the balance that was intended when the Accelerated Approval pathway was instituted in the 1990s, and FDASIA reaffirms the interest of the public in expediting availability of drugs to treat serious and life threatening conditions even when uncertainty remains about the benefit-risk profile, knowing that these approvals will only become permanent if confirmatory studies verify patient benefit.

In particular, this argues for greater willingness to grant Accelerated Approval, under appropriate circumstances, despite the uncertainty associated with the following types of situations:

i) Surrogate or intermediate clinical endpoints where the relationship to mortality or serious morbidity remains to be fully proven;

ii) Effect sizes on those endpoints where the ultimate clinical significance remains a matter of debate;

iii) Historically controlled studies;

iv) Underpowered studies or marginal statistical findings, particularly in rare diseases where large studies cannot be conducted or in settings where the best available endpoints have modest sensitivity to treatment effects;

v) New drugs with mechanistic diversity, even when superiority to available therapy has not been directly demonstrated (see item 9 below); and

vi) Drugs shown to work in combination, while full studies to elucidate the individual contribution to the effect of each component of the combination are conducted in the confirmatory setting.

We acknowledge and appreciate the recognition reflected in this draft Guidance that accepting greater uncertainty in various forms when granting Accelerated Approval, is appropriate and in the interest of patients with serious and life threatening conditions. FDASIA has now codified that the public interest is served by approaching Accelerated Approval with a maximum degree of flexibility and creativity, consistent with high scientific standards. Thus, we urge FDA to take this opportunity to provide as much clarity and guidance as possible about the circumstances in which flexibility of this sort is appropriate. We believe that this is one of the most important things that FDA can do to help enable sponsors to streamline clinical programs and reduce the
time and cost of drug development, which will help ensure the flow of critical investment capital into areas of highest unmet medical need.

3. Both FDA and sponsors would benefit from greater clarity and specificity about how enhanced flexibility will be applied to the Accelerated Approval pathway.

Examples of issues worthy of more detailed treatment include:

i) How the context of disease severity and rarity as well as unmet need influence the quantum of evidence necessary for a given surrogate endpoint to be considered "reasonably likely to predict clinical benefit";

ii) When and how historical controls may be utilized for Accelerated Approval;

iii) The use of intermediate clinical endpoints;

iv) The use of alternative clinical trial designs and adaptive techniques; and

v) The circumstances in which mechanistic diversity, even absent a showing of superiority to available therapy, can provide a basis to use the Accelerated Approval pathway.

4. The Guidance should address issues specific to the use of Accelerated Approval for rare diseases.

FDASIA clearly reflects a desire to address the unique and important circumstances of rare diseases. Thus, the law specifically requests that FDA provide guidance on "issues arising under the accelerated approval and fast track processes ... for drugs designated for a rare disease or condition ... and shall also consider any unique issues associated with very rare diseases" (Section 901(c)(1)).

While the goal of employing regulatory flexibility to speed the availability of new drugs to treat serious and life threatening conditions is intended to apply to both rare and more common diseases, the special issues of rare disease drug development highlight the central importance of such flexibility. Due to practical challenges of conducting clinical trials as well as commercial realities, it is often necessary and appropriate to accept even greater uncertainty regarding benefits and risks, when approving a new drug for a rare condition. FDA has consistently noted this reality in the past and has in fact shown greater flexibility in many orphan drug situations. This kind of flexibility should be highlighted in the Guidance, and consideration should be given to steps that can be taken to ensure that appropriate flexibility is consistently applied, and that the new tools created by FDASIA are fully utilized to serve the interests of patients with rare diseases.

It should also be noted that as drugs become more targeted based on specific genetic factors, patient populations become increasingly segmented. Thus the application of regulatory flexibility to rare and very rare diseases will increasingly become a central issue
in drug development across many disease areas. This is already becoming the case in many forms of cancer, as well as genetic diseases such as cystic fibrosis, among many others.

5. **The Guidance should make explicit that the application of regulatory flexibility and innovative development strategies are intended to be available to all Fast Track drugs when appropriate, whether or not designated as Breakthrough.**

As noted above, the Breakthrough Therapy designation is already having a very positive effect on drug development and investment in areas where potent benefits can be observed early in development. However, there are other areas which by their nature may not allow for seeing dramatic clinical effects early in development, but may still ultimately provide very substantial benefits to patients suffering from serious and life-threatening diseases. Thus, it is important for the Guidance to emphasize that Fast Track drugs which are not designated as Breakthrough will still be eligible for the same kinds of regulatory flexibility and the utilization of modern drug development tools, as appropriate to the specific situation.

This also highlights a potential second-order benefit of the Breakthrough Therapy designation. As the Medical Policy Council brings to bear creative, high-level thinking to expedite the development of Breakthrough Therapies, CDER and sponsors collectively will become more familiar and comfortable with the use of modern tools and flexible approaches to speed development. This should create a positive feedback loop, whereby the drug development and regulatory process for all drugs, and especially Fast Track drugs whether or not designated as Breakthrough, can be continually improved and modernized. We believe that this kind of institutionalization of the benefits of the Breakthrough program to the overall drug development paradigm should be called out explicitly as one of the program’s goals in the Guidance.

6. **A Breakthrough designation program should be implemented for companion diagnostics.**

Many drugs obtaining Breakthrough Designation are ones that will require companion diagnostics. It is critical that the development of these diagnostics be the subject of the same high-level attention and sense of urgency. This is especially important in light of the need for cross-center collaboration with CDRH.

7. **FDA should expand on the degree to which feedback and rationale will be provided to sponsors when denying Breakthrough designation.**

The Guidance provides that the Agency will send a “nondesignation letter” and will “explain the reasons for the Agency’s decision” (line 1055). We appreciate FDA making this proactive effort to provide transparency and clarity to sponsors. We believe that it would be valuable for this Guidance to further describe the level of detail that will be provided in these nondesignation letters. As a general principle, we believe that sponsors and the drug development process will benefit from as much detail as can be provided, giving sponsors
guidance, for example, on the kinds of new data that would cause FDA to re-visit the denial of a Breakthrough request.

8. Careful consideration should be given to the procedures for withdrawing Breakthrough designation.

While we fully agree that Breakthrough designation should be withdrawn if further data fail to support the early observations of substantial improvement over existing therapies, we believe that careful thought should be given to the procedures for doing so, in order to minimize the potential for misinterpretation by the public – including patients involved in clinical trials, investors and others – of the meaning of such withdrawal.

9. Further clarity should be provided regarding how superiority to “available therapy” can be demonstrated for purposes of Accelerated Approval would be valuable.

The draft Guidance makes clear that a new treatment would be considered to address an unmet need for purposes of Accelerated Approval if the new treatment provides some advantage over available therapy, such as improved efficacy or better safety. However, further clarity could be provided about the type of evidence required to demonstrate such an advantage.

In fact, we believe the language in lines 165-168 inadvertently and incorrectly suggests that such superiority should be “demonstrated in an active- or historically-controlled trial assessing an endpoint reflecting mortality or serious morbidity”. In the context of Accelerated Approval, it is understood that clinical studies would be designed to demonstrate a superior effect on an endpoint that is reasonably likely to predict an effect on mortality or serious morbidity, but not to demonstrate an effect on mortality or serious morbidity directly.

More broadly, we note the statement in the Guidance that “a drug that is not shown to provide a direct efficacy or safety advantage over available therapy may nonetheless provide an advantage that would be of sufficient public health benefit to qualify as meeting an unmet medical need” (line 185). The Guidance goes on to say that “FDA intends to consider a range of potential advantages over available therapy beyond those shown in head-to-head comparisons” (line 198) and provides examples, including a drug with a novel mechanism of action compared to available therapy. We strongly endorse this perspective, and view this as an example of precisely the kind of regulatory flexibility that FDASIA intended to provide to FDA, and we appreciate FDA’s proactive thought process on this issue. However, insofar as it may be difficult for sponsors to predict when this kind of regulatory discretion will be utilized, further guidance would be valuable regarding how an advantage over available therapy might be demonstrated in the absence of a head-to-head study.
Conclusion

NVCA and the MedIC coalition believe that modern drug development requires FDA and sponsors to have a range of tools at their disposal to expedite drug development and customize development programs to specific situations and patient populations. We thank and congratulate FDA for continuing to think creatively and expansively about how to evolve the regulatory process for new drugs as science advances.

We look forward to being part of the solution to help to ensure that patients get access to innovative new treatments and cures to those who need them most, and that critical medical innovations continue to attract investment capital.

Sincerely,

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