



National Venture Capital Association

July 28, 2004

2004-0233

Division of Dockets Management
5630 Fishers Lane
Room 1061
Rockville, MD 20852

**National Venture Capital Association Comments for Docket Number 2004S-0233:
Solicitation of Comments on Stimulating Innovation in Medical Technologies**

On behalf of the more than 460 members of the National Venture Capital Association, we respectfully submit the following comments in response to the Food and Drug Administration March 2004 report, "Innovation Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products" and the related docket.

Venture Capital Investment in Life Sciences

In 2003, the U.S. venture capital community invested \$5.05 billion in the life science industries (biotechnology/pharmaceutical, and medical devices). This constituted 27% of the \$18.7 billion of venture capital invested last year— representing the highest proportion directed to the life sciences sector in the last 12 years. Simply put, the venture industry is committed to investing in these high-risk, potentially high-growth businesses despite the fact that it remains the most highly regulated industry sector that receives venture investment. [Attachment #1]

Our interest and commitment to life science industries has not been satiated. Life science investment has dominated other industry interest for the past six consecutive quarters. Investments for the first quarter of 2004 totaled \$1.3 billion, or 27% percent of all venture capital investments. Biotechnology alone accounted for \$943 million or 20% of all investing. Medical devices garnered another \$325 million, or 7%. All told, 71 biotechnology companies and 51 medical device companies were funded in the first quarter of this year alone. A full third of the biotechnology companies were financed for the first time.

Venture Capital Helps Build Stronger Companies with a Changing Responsibility

A recent study by Global Insight, commissioned by the NVCA, shows that venture-backed companies fared better in job creation and revenue growth than their private company peers. In other words, the venture community helps to build stronger companies that can actively participate in the approval process and in hiring skilled employees. In the biotechnology sector (which broadly includes all pharmaceutical investments), jobs from 2000 through 2003 increased on a national average 5% and revenues a healthy 22%. Venture-backed biotechnology companies fared better, however, realizing a 23% increase in jobs and a 28% increase in revenue. For medical

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devices, a similar divergence exists as well; -2% versus 16% for jobs, and 6% versus 9% for revenue, again favoring venture-backed companies.

The creation of stronger companies allows for stronger science to emerge. It is these companies that, according to data from the National Science Foundation, are performing an increasingly greater share of the total U.S. research and development. The dollar value of small company R&D has increased nine-fold from \$4.4 billion in 1984 to \$40.1 billion in 2003. The share of U.S. R&D performed by companies with 500 or fewer employees rose from 5.9% in 1984 to 20.7% in 2003. According to the study, not only do these small companies fuel innovation on their own, but increasingly through licensing agreements, mergers and acquisitions they also 'feed' larger R&D efforts with a steady stream of idea generation. Also interesting to note, of the top 50 R&D companies in the U.S. last year, 41 were either originally venture-backed or major acquirers of venture-backed companies.

NVCA and Its Members are committed to Enhancing Life Science Innovation In Conjunction with HHS and FDA Efforts

It is our long-standing intimate relationship with these companies and their efforts in innovation that we believe may provide the Food and Drug Administration with a unique perspective on several key areas we have identified as roadblocks to encouraging small companies, which represent a growing portion of U.S. innovation efforts in life sciences today.

The venture community applauds FDA efforts to identify limitations on the life science innovation process—realizing that both science and regulatory process play a role. In addition, seeking comment from non-traditional parties demonstrates the agencies new commitment to seek solutions that are 'outside the box.' We whole-heartedly embrace this new era in the development of technology and process-based efforts to streamline and speed life science innovation.

NVCA Recommendations to Address 'Critical Path' Initiative

The following recommendations focus around three central themes: a reduction of uncertainty in the approval process, use of all available scientific information to speed approval decisions, and a modest shift in the stringency of existing regulation.

1. Reduce Uncertainties in the Approval Process

Increase the Number and Specificity of Guidance Documents in Areas Ripe for Innovation and Investment

We strongly encourage the FDA to proactively produce Guidance for most therapeutic areas under development, and update them on a regular basis. Special attention should be applied in areas where device/drug combinations are within the realm of possible solutions. We also request that the Agency adhere as closely and as consistently to the

Guidance as compounds progress through development. Compliance from both the FDA and industry to these Guidance parameters will lead to more-timely, cost effective drug development. The venture community appreciates the thoughtfulness required for rational development of guidance documents, but would encourage a more rapid process that even precedes early innovator approval applications if possible.

Following our recommendations is a discussion of several key disease areas that are likely to benefit with increased efforts in development and investment if clear and reasonable guidance is developed and published by the FDA.

Create Consistency within FDA Drug Development Requirements

We strongly encourage the Agency adopt as routine policy the adherence of prior decisions regarding a specific drug's development hurdles. There are an excessive number of instances where prior decisions of the FDA, in the context of FDA - Sponsor development meetings, are reversed later in time. This obviously creates additional time and expense to that drug's ultimate approval. A recent example is one company where a new medical reviewer requested a new primary efficacy endpoint for a compound, at the time of a pre-NDA meeting, after two pivotal Phase 3 trials had been completed. One way to ensure adherence is to retain the same reviewer for the full length of the approval process and to maintain incentives for the FDA reviewers to stay with the agency. The NVCA is well aware of the reports completed in the area of reviewer empowerment and retention. The retention of and recruitment of thoughtful and motivated reviewers must remain a top priority for both the FDA and industry. When this is not possible, and turnover of key reviewers of a sponsor's application occurs, it is only reasonable to expect the new reviewers to adhere to their predecessors' expectations of the sponsor.

We heartily endorse the purpose of the Special Protocol Assessment. It needs to be broadly expanded to provide sponsors with the confidence necessary to routinely proceed on the lengthy and costly development path free from the concern that the Agency's requirements will not be arbitrarily changed in the future. Allowing this document to be used multiple times during a drug's development is necessary, given the time and expense incurred. Another process change, which would incorporate the spirit of the SPA, is to ensure that the Agency publishes the minutes of meetings with sponsors routinely well within 30 days of the meeting, and that these include a statement that the FDA will adhere, and not unilaterally change, these requests in the future.

2. Use All Science Available to Speed Approval

Expand the Use of Surrogate and/or Biomarkers as Efficacy Endpoints for Approval and the Basis of Regulatory Decisions

The validation of surrogate markers for disease measurement and chemical or protein biomarkers against relevant clinical end points affects all diseases, and is relevant to both small molecule and biologic drug development. We strongly encourage the FDA to develop and encourage the use of biomarkers and/or surrogate markers for compounds

where the implementation of clinical endpoints imposes a prolonged and costly, and therefore inhibitory, development course. The FDA should prioritize its efforts to adopt surrogate and biomarkers on areas of significant unmet medical need, where current products (both approved and in development) are inadequate. An example is osteoporosis where bone markers and bone mineral density studies could be used for approval. A second example is the not uncommon Agency requirement of expecting a randomized trial with clinical endpoints in orphan, genetic deficiency diseases. Subsequent to approval, longer-term studies with clinical endpoints should be done to further guide clinical use with the drug. In this context, we support the continued requirement for clinical safety data prior to a drug's approval.

For reference, we have included our priority indications and described them below in more detail. Much of the work on surrogate markers or measurements could, we believe, be done relatively quickly by data mining FDA resources and pairing that data with clinical expert advice.

Expand the Use of Animal Models as the Basis of Regulatory Decision

The 'Critical Path' document identifies new animal models as a high priority particularly enhancing the predictive ability for safety issues prior to the introduction of new therapeutic products in man. As these models are developed, we encourage the FDA to provide ongoing guidance as to what criteria it would need in order to endorse the model for use by the pharmaceutical and biotech industries. We recognize that this would have to be an iterative process, but believe that as results develop and the end goal becomes clear, such guidance will shorten the time and reduce the costs for development, and perhaps make it easier for biotechnology companies to raise the capital necessary to develop fully the animal model.

Animal model identification (finding the best models to use for prediction of efficacy in different diseases) could be accomplished quickly. However, it may require extensive primary research and tool development to come up with good models in certain settings (since none may currently exist). The FDA in cooperation with NIH may want to consider a priority SBIR or other program to support the experiment necessary to validate the model. This funding, for example, might apply only when initial milestones approved by the FDA have been met. FDA support of animal model research also will enhance the Agency's knowledge of mechanistic rationales and surrogate markers for inclusion in future guidances.

3. Shift Regulation Stringency to Reward Innovation

Expand the Post-Marketing Pharmacovigilance System

For particularly innovative technologies and where there is a large unmet need, today's significant regulatory barriers are likely to result in avoidable delays in bringing medical innovation to the patient. These barriers include the stringency of manufacturing requirements, as well as better-known requirements for clinical safety and efficacy. The

venture community recommends additional flexibility (as spelled out in guidance) to lower the efficacy—and if appropriate the safety—threshold to speed products to the commercial phase sooner. With increased emphasis on the commercial phase, we encourage the FDA to shift its emphasis to post-market surveillance (pharmacovigilance) systems. While the current approval process does a good job of ascertaining the efficacy and quality of a potential therapeutic product, it is well understood that the safety profile becomes evident only after the product is widely used (i.e. once it has received FDA approval and is marketed to the general public). The venture community cautions against the expansion of pre-market clinical trials to ensure safety. Rising demands for clinical trial sample size pre-approval will only delay patient access and proof of principle.

Therefore, we suggest that in general, the bar be lowered for pre-market approval (so that products can get to market sooner), and raised for post-market safety surveillance (so that products are monitored more closely once they are on the market, especially from a safety perspective). Such a system would attract more novel therapeutic start-up innovators into the approval process and could have a meaningful impact on the pace of medical innovation. We have seen precedent for such a trade-off in the Fast Track rules promulgated to allow approval on the basis of surrogate end-points for HIV and oncology, which were coupled with increased pharmacovigilance.

The FDA should review recent gaps in compliance with previous PMS requirements and develop new approaches for partnering with sponsors to ensure that scientifically meaningful studies are performed on time and according to the commitments made at the time of approval. This approval approach would require that the FDA seek more timely information on post-market safety issues from the providers (i.e. doctors, nurses, pharmacists), who are best positioned to provide feedback. Since the FDA does not regulate providers, collaborative work with the Centers for Medicare and Medicaid Services and the Joint Commission on Accreditation of Healthcare Organizations might facilitate collection of this information as well. New development in healthcare payment systems and electronic health records, as proposed in the recent initiative from the Department of Health and Human Services, also should be exploited to ensure interpretable data is available in a timely manner.

Therapeutic Areas in Need of Established Specific Guidances

The venture community believes that FDA leadership in these disease areas is warranted because development is either drastically under-funded (as in Alzheimer's disease and sepsis) or significant investments in both research and development time and money has been relatively inefficient because endpoints remain unclear (as in stroke and diabetes). While our list of suggested therapeutic areas of interest to the venture community is by no means all-inclusive, we highlight the following areas to better demonstrate the need for implementation of the preceding recommendations.

Alzheimer's Disease: It's estimated that 4.5 million families in the US have a family member afflicted with Alzheimer's, and this number is expected to increase sharply as the baby boomer population continues to age.

At present, the treatment options for these patients are limited to acetylcholinesterase inhibitors (Pfizer's Aricept is the leading drug in this class) and the recently approved NMDA receptor antagonist (Namenda from Forest Labs). These drugs have been shown to have marginal clinical benefit, and physicians and families who care for these patients are clamoring for better medical care.

While physicians and investors alike recognize the severe unmet medical need in this area, investors have been wary to support programs due to the length and expense of clinical trials. One of the challenges of developing Alzheimer's drugs is the number of patients that are required to generate a clinical signal with the current endpoints that are the accepted standard in this area, namely the ADAS-cog endpoints. There are several other endpoints that clinicians feel are more sensitive and that could provide an earlier signal as to whether or not a drug is providing clinical benefit to patients. An active look led by the FDA along with leading neurologists to re-examine the use of ADAS-cog in approving drugs for Alzheimer's patients is certainly needed. Use of other endpoints for conditional approval followed by confirmation with ADAS-cog, or perhaps entirely new regulatory strategies would certainly increase investor interest in this area.

Although a daunting task, underwriting a Framingham-type study where healthy patient populations are studied for a period of decades would substantially enhance the scientific knowledge on the disease and, with time, facilitate the generation of diagnostics, disease management tools, and eventually a cure.

In the past twenty years, the venture community has made only the most limited investment in any company devoted to Alzheimer's.

In addition to the panel experts FDA has consulted, NVCA recommends the following scholars as valuable sources of expertise during guidance development. Both have consented to participate at the FDA's discretion.

Dr. Lon Schneider, Professor of Psychiatry, Neurology, and Gerontology, USC, (323) 442-3715

Dr. Jan Wallace, independent consultant, developed first acetyl cholinesterase inhibitor: Tacrine; (415) 921-3380

Systemic lupus erythematosus (SLE): Lupus primarily affects women, and current estimates state that the disease is present in as many as 400,000 patients in the U.S. alone, many of whom remain undiagnosed and under-treated. While there are available therapies to treat the acute manifestation of disease and prevent longer-term progression, these are typically strong immunosuppressive agents or toxic chemotherapeutics, leaving this often young, female patient population in severe need of better treatment options.

While development of new drugs for SLE has been left to smaller biotechnology companies due to the perceived market potential being too small for large pharmaceutical companies, these smaller companies face the daunting problems of a disease whose

underlying biology is unclear, whose clinical measurement is problematic and whose regulatory pathway is especially murky. Thus venture capital investment into this area of drug development has been rare, and primarily restricted to companies that are developing an approved and marketed immunosuppressive agent in SLE. The difficult clinical and regulatory path faced by publicly held biotech companies in SLE has highlighted the difficulties and high hurdles for achieving a return on investment.

To date, only seven companies with lupus related therapeutics have received venture funding; only one in the past five years with a financing round of \$14 million.

Based on its understanding of the disease itself and clinical approaches to treating SLE, the FDA has recently held a panel discussion to consider the appropriate design of clinical trials in this area. As part of the Critical Path initiative, the FDA has the opportunity to build on this recent discussion, and with the help of its internal data and scientific knowledge, provide guidance to industry as to useful surrogate markers of disease, clinical measurements and diagnostic tools, and clinical trial design that would help expedite the development of future drugs to treat SLE. We strongly believe that such guidance would encourage the application of venture capital investment towards new SLE development programs to benefit under-served patients with SLE.

In addition to the panel experts FDA has consulted, NVCA recommends the following scholars as valuable sources of expertise during guidance development. All three have consented to participate at the FDA's discretion.

Dr. Vibeke Strand, Stanford University (650) 529-0150

Dr. Jill Buyon, New York University School of Medicine, Hospital of Joint Diseases
(212) 598-6522

Dr. Michelle Petri, Johns Hopkins University (410) 955-9114

Stroke: An estimated 700,000 Americans each year suffer a stroke. Current treatments for ischemic stroke are limited since there is only one FDA-approved product for this indication, Tissue Plasminogen Activator (TPA).

Despite a tremendous unmet medical need and a significant market potential, large pharmaceutical companies and investors have backed away from financing development of stroke treatments. The private sector is cautious when investing in stroke due to some high-profile failures in the field, especially in late-stage clinical trials. There is an ongoing debate among academic, government and industry leaders as to the underlying causes of such failures; with most agreeing that the field would greatly benefit from better-designed clinical trials that correlate more closely with pre-clinical animal data and have better patient selection criteria.

Fifty-three companies devoted to stroke have received venture financing; thirteen have had public offerings and six have been merged or acquired. Venture investment in stroke during the past five years has been \$848.06 million, but patients have gained little from this investment.

Recent advances in basic science, many of them government funded, are improving our understanding of the pathophysiology of stroke and enabling the discovery of novel therapeutic targets. The key elements in turning this cutting edge science into useful treatments are clearer regulatory guidelines that in turn encourage investment in the area and funding of start-ups.

We encourage the FDA to work closely with the industry on developing guidelines and trial designs that will lay the groundwork for drug and device development and approval. According to some industry and academic experts, current trials diverge too far from pre-clinical study designs; may have inappropriate entry criteria (some are too broad and some too restrictive); and lastly the size of the trials impacts their ability to achieve reliable results.

Due to the importance of the field and the opportunities emerging based on advances in basic research, we encourage the FDA to reopen the dialogue with the industry regarding clinical trial design. In addition, we recommend a frequent and open communication between the FDA and individual industry sponsors conducting clinical trials to ensure that both sides adhere to pre-negotiated study designs.

Metabolic Diseases: There are many approved drugs for the treatment of diabetes, however the cost of approval is high, and the net clinical effect of these medications generally yields patients who do not achieve the recommended hemoglobin A1C range. Therefore, diabetes remains a therapeutic area of high unmet need.

We need no reminder that drug treatment for obesity remains sorely lacking. Behavioral, exercise, and nutritional therapies are simply insufficient for the vast majority of patients inflicted with this disease.

Drug development in metabolic diseases is a broad and important therapeutic area, which could benefit from some of the recommendations put forward by the NVCA. As a recently held panel organized by the FDA and NIH explored, the development and consistent implementation, throughout the development of a compound, of surrogate biomarkers for diabetes, would be a significant advance to further the much-needed new therapeutics in this area. For obesity, similar application of consistent guidance will do much to aid the sponsor in their drug development.

Of all the disease areas the venture community believes require additional FDA leadership, metabolic disease has received the most financing during the past five years. Two hundred and ten companies have received \$2.082 billion in venture support. As previously mentioned, however, much of this funding may eventually produce limited advancement in the therapeutic field because no clear direction on surrogate endpoints exists.

A well-known expert to FDA, and willing to continue to work in this area is David Nathan, MD, of the Massachusetts General Hospital.

Sepsis: Sepsis, severe sepsis, septic shock, systemic inflammatory response syndrome (SIRS), and multiple organ dysfunction syndrome (MODS) cases have increased from 160,000 to over 650,000 per year in the United States. Overall mortality is 20%, but rises to over 60% in the more affected patients.

This syndrome is mostly treated supportively, depending on the organ system or systems affected. Treatment of infection, hemodynamic support, and respiratory support if and when needed are the common therapies employed. This therapeutic area is very much in need of further drug development and new therapies to deal with this large, and growing, area of unmet need. Development and maintenance of up-to-date guidance in this area, including surrogate markers, is very much needed.

Only two companies in the last five years addressing Sepsis have received \$12.1 million in venture financing.

Conclusion

We would like to thank the FDA for the thoughtful approach to resolving many challenging issues associated with providing effective medicines for the multitude of diseases affecting patients. The venture community agrees with the FDA conclusion that there is a widening gap between basic science and innovation approval and patient access. We appreciate the opportunity to provide comments associated with the concepts embodied in the Critical Path report and look forward to a continued dialogue with the FDA as to how best implement policies that will promote medical innovation and speed patient access to these needed therapies. Nancy Saucier of the NVCA is the industry point of contact and can be reached at nsaucier@nvca.org or 703-524-2549.

Attachment #1: Venture Investment Totals 1995-Q1 2004 Compared to Life Science Totals and Overall Percentages

1995	1,616	7,884	127	711	176	872	9.0%	11.1%	20.1%
1996	2,188	11,906	158	1,036	206	808	8.7%	6.8%	15.5%
1997	2,647	15,366	166	1,249	252	1,239	8.1%	8.1%	16.2%
1998	3,087	21,854	185	1,261	279	1,486	5.8%	6.8%	12.6%
1999	4,580	56,158	176	1,671	296	1,952	3.0%	3.5%	6.5%
2000	6,587	107,782	202	3,173	331	3,738	2.9%	3.5%	6.4%
2001	4,007	42,920	195	2,323	282	3,004	5.4%	7.0%	12.4%
2002	2,612	21,619	171	1,762	258	3,074	8.2%	14.2%	22.4%
2003	2,376	18,776	192	2,026	268	3,029	10.8%	16.1%	26.9%
1Q04	685	5,049	48	506	84	807	10.0%	16.0%	26.0%
Totals	30,385	309,314	1,620	15,716	2,432	20,010			

Source: PricewaterhouseCoopers/ Thomson Financial Venture Economics / National Venture Capital Association MoneyTree™ Survey

Run date: 7/23/2004