

TESTIMONY OF JOHN MARAGANORE, PH.D.

CHIEF EXECUTIVE OFFICER, ALNYLAM PHARMACEUTICALS

HOUSE COMMITTEE ON ENERGY & COMMERCE, SUBCOMMITTEE ON HEALTH HEARING ON:

“FDA USER FEES 2012: HEARING ON ISSUES RELATED TO ACCELERATED APPROVAL, MEDICAL GAS, ANTIBIOTIC DEVELOPMENT AND DOWNSTREAM PHARMACEUTICAL SUPPLY CHAIN”

March 8, 2012

Chairmen Upton and Pitts, and Ranking Members Waxman and Pallone, it is my privilege to provide testimony before this Subcommittee today. My name is John Maraganore and I am the Chief Executive Officer of Alnylam Pharmaceuticals. As a scientist and businessman, I have over 25 years of experience in biopharmaceutical research and development. Prior to Alnylam, I served as Vice President of Strategic Product Development for Millennium Pharmaceuticals where I worked on products to treat cancer and cardiovascular, autoimmune, and metabolic diseases. Prior to Millennium, at Biogen (now Biogen Idec, Inc.) I invented and led the discovery and development of AngiomaxTM, a direct thrombin inhibitor that is used as an anticoagulant in over 750,000 patients every year. Currently, I serve on the Immunology Advisory Council of the Harvard Medical School and am a member of the Biotechnology Industry Organization Governing Board. I also serve as a board member of several innovative biotechnology companies that are focused on finding new medicines for cancer, autoimmune disease, and rare genetic diseases, and I am also an advisor to Third Rock Ventures.

Alnylam is a small biotechnology company located in Cambridge, Massachusetts. We are developing new medicines based on the science of RNA Interference, or RNAi, a major breakthrough in biology that was recognized by the award of the 2006 Nobel Prize for Medicine or Physiology to certain academic scientists. We were founded in 2002 and have invested over \$500 million to date in our R&D efforts. Today, we have 120 employees who are working on a pipeline of innovative medicines that could be transformative in the lives of patients afflicted with certain genetic diseases like systemic amyloidosis, hemophilia, sickle cell anemia, severe hypercholesterolemia, and Huntington's Disease. We also have therapeutic programs targeting the treatment of liver cancer and a lung infection caused by respiratory syncytial virus, the leading cause of pediatric hospitalization every year. All told, four of our programs are in

clinical testing stages, but RNAi technology affords the potential for an even greater number of programs to be advanced to patients. Indeed, if we're successful in our efforts, we can create a whole novel class of medicines that treat disease in a fundamentally new way.

I am here today to discuss the importance and benefits of Congressmen Stearns' and Towns' "*Faster Access to Specialized Therapies*" (FAST) bill, which would enhance the Accelerated Approval pathway at the Food and Drug Administration (FDA). The impact FDA's approval processes for new drugs and biologics has on innovation in the discovery and development of new treatments for diseases cannot be overstated. There is no question that protecting patients from harm is a critical component of FDA's mission. But so too is establishing regulatory processes that enable the timely development and availability of new safe and effective therapies for patients suffering from serious and life-threatening diseases. In a time when the U.S. medical innovation ecosystem is facing severe strains and increased global competition, it is imperative that FDA's policies and practices find the right balance between these two objectives to ensure we are able to deliver the next generation of breakthrough treatments and therapies.

Importance of Expanding and Modernizing the Accelerated Approval Pathway

The Accelerated Approval pathway was implemented by FDA in 1992 in response to patient groups who, after engaging the public in a dialogue about benefits of new HIV/AIDS treatments, were successful in advocating for earlier access to these life-saving medicines. Accelerated Approval allows for earlier approval of new drugs that provide a benefit for patients with serious and life-threatening diseases based on a new product's effect on surrogate or clinical endpoints that are deemed "reasonably likely to predict clinical benefit."¹ Under Accelerated Approval, FDA can approve the marketing of a drug to seriously ill patients based on earlier evidence of effect with a commitment from the sponsor to conduct further post-market studies to confirm and define the degree of clinical benefits to patients.

The Accelerated Approval pathway has been a great success story, in part. While its applicability has been largely limited to certain disease areas (mainly cancer and HIV/AIDS) and certain situations, the pathway has stimulated an explosion of investment in innovation in those

¹ 21 C.F.R. § 314.500; 21 C.F.R. § 601.40

diseases, and has brought immense benefit to patients suffering from these diseases. In HIV/AIDS, for example, there are now over 20 new medicines on the market. In oncology, FDA has granted Accelerated Approval to 49 new indications for 37 novel oncology drug products since 1995.²

However, there are several reasons why the Accelerated Approval pathway should be expanded and modernized. First, it is important that the ability to utilize an accelerated pathway is better understood by sponsors and more consistently applied by FDA. This is especially true when it comes to FDA accepting clinical endpoints, including those that can be measured earlier than irreversible morbidity or mortality, to demonstrate a reasonable likelihood of clinical benefit. While the pathway, which was codified in 1997, allows for approval based upon effects on clinical endpoints that are reasonably likely to predict clinical benefit, in practice the lack of clarity surrounding such approval options has led to very limited use by sponsors and FDA.

Additionally, the Accelerated Approval pathway has been largely limited in practice to drugs that treat cancer and HIV/AIDS, along with a handful of other situations, leaving many other rare and serious conditions effectively excluded from the pathway and creating confusion among sponsors on how to apply the pathway to these indications. While studies such as the National Organization for Rare Diseases (NORD) 2011 report show that FDA applied flexibility and allowed for more limited packages of data for a majority of the approved drugs for non-cancer orphan drugs, it is not always clear to sponsors when or how these approaches will be accepted by FDA.³ As NORD Chairman Sasinowski has stated, “It would be helpful for such flexibility and importance to be recognized in a formal FDA policy, and for FDA officials to incorporate and recognize that flexibility in a systematic way in their evaluations of each new therapy in development and under FDA review for Americans with any rare disease.”⁴ It is equally important that flexibility is applied in a systematic way for treatments for products for other serious and life-threatening diseases beyond cancer and HIV/AIDS.

² Dr. Paul Kluetz. ODAC. February 8, 2011, the U.S. Food and Drug Administration (FDA) Oncologic Drugs Advisory Committee (ODAC)

³ Sasinowski, Frank J. “Quantum of Effectiveness Evidence in FDA’s Approval of Orphan Drugs.” National Organization for Rare Diseases, October 2011.

⁴ “Landmark NORD Study Concludes FDA is Flexible in Reviewing Therapies for Rare Diseases.” NORD Press Release, 11 October 2011. <http://www.rarediseases.org/news-events/news/fda-flexibility-2011>

Second, while I have discussed the importance of expanding disease areas where an Accelerated Pathway could be applied, today there is significant uncertainty over how the FDA intends to apply the Accelerated Approval pathway in the future, and this uncertainty is directly impacting investment in innovative new therapies. In 2011, only 3 of the 35 New Molecular Entities approved by FDA and only 3 of 13 therapies that were granted “Fast-Track” designation utilized the Accelerated Approval pathway.⁵ Concerns over utilization of Accelerated Approval have become most acute for those developing cancer drugs. For the past two decades, cancer has attracted more investment capital than any other disease, and potential breakthrough anti-cancer medicines in the pipeline today vastly outnumber those for other therapeutic areas.⁶ One of the main reasons for this has been FDA’s historical approach of effectively balancing the benefits and risk to approve new cancer treatments. However, since late 2009, there appears to be a fundamental re-evaluation by FDA of the standards for approval of new cancer therapies. The resulting uncertainty is impacting investment in oncology drugs. In fact a 2011 National Venture Capital Association (NVCA)/Medical Innovation and Competitiveness Coalition (MedIC) survey showed that 39% of venture capitalists expect to decrease investments in cancer drugs over the next three years.⁷

Actions and public statements over the past year from FDA’s Office of Oncology Drug Products have introduced significant uncertainty over how the FDA intends to apply the Accelerated Approval pathway for cancer drugs. For example, at an Oncology Drugs Advisory Committee (ODAC) meeting in February 2011 and other settings, FDA has raised fundamental questions about the range of situations in which single-arm studies (*i.e.*, studies without a randomized control group, typically using tumor response rate as primary endpoint) and studies using measures of disease progression (such as Progression Free Survival) as primary endpoint should be sufficient to support Accelerated Approval for cancer drugs. Notably, of the 32 novel cancer drugs approved by the FDA from 2003 to 2010, 14 obtained Accelerated Approval, of which 11 were based on single-arm studies without a control group.⁸ Additionally, a recent analysis by

⁵ “FY 2011 Innovative Drug Approvals.” FDA. November 2011.

<http://www.fda.gov/downloads/aboutfda/reportsmanualsforms/reports/ucm278358.pdf>

⁶ Ernst & Young. Beyond Borders. Global Biotechnology Report. 2011

⁷ NVCA/MedIC Survey. Vital Signs. October 2011.

⁸ Johnson, John R., et. al. “Accelerated Approval of Oncology Products: The Food and Drug Administration Experience.” JNCI, Vol. 103, Issue 8. 20 April 2011.

BIO and BioMedTracker of cancer clinical trials conducted between 2004 and 2011 showed that more complex randomized, double blind, and multi-arm trials were not statistically more likely to translate into a successful Phase III clinical trial than single-arm open-label trials.⁹ Thus while it is appropriate to continually review and debate merits of endpoints and clinical trial designs, it must be recognized that a decision to, for example, narrow the situations where single-arm studies can be used to support Accelerated Approval in oncology would effectively represent a reversal of what has arguably been the most successful policy of the past two decades, in terms of speeding important therapies to patients and encouraging investment in innovative new treatments. In making such a profound change in direction, the FDA must consider the realities of oncology drug development and the needs of patients who have little time to wait for their breakthroughs. We must have policies that focus on how we can more efficiently and effectively deliver potentially life-saving medicines to patients – Accelerated Approval has done this historically and should strive to do so even more in the future. In oncology, the FDA appears right now to be moving in exactly the wrong direction. A critical element of the FAST bill is the clear message that it sends: that the sense of the Congress – reflecting the values of the American people – is that FDA should strive to use the Accelerated Approval pathway more for the benefit of patients, not less.

Third, it is time to have an expanded and modernized Accelerated Approval pathway that incorporates the remarkable advances in life sciences that have been, and will continue to be, made, including genomics, molecular biology, and bioinformatics, which have already provided an unprecedented understanding of the underlying biological mechanisms and pathogenesis of disease. These advances can enable novel drug development strategies that employ leading edge methodologies and tools such as biomarkers, pharmacogenomics, predictive toxicology, clinical trial enrichment techniques, and novel clinical trial designs like adaptive clinical trials. Improving clarity of when and how these tools can be utilized in an Accelerated Approval pathway will not only incentivize drug development for serious and life-threatening diseases but encourage the development and utilization of additional pharmacogenomic tools and methodologies that will create even more efficient, targeted, and personalized drug development strategies.

⁹ “Oncology Clinical Trials – Secrets of Success.” BIO and BioMedTracker, 24 February 2012. <http://www.biotech-now.org/business-and-investments/2012/02/oncology-clinical-trials-secrets-of-success>

FAST Bill Provides Critical Reforms to the Accelerated Approval Pathway

The FAST bill would achieve all of the objectives described above by expressing the Sense of the Congress that FDA should utilize the Accelerated Approval pathway as fully and as frequently as possible while maintaining FDA's safety and effectiveness standards, and by codifying, modernizing and expanding FDA's Accelerated Approval pathway with four targeted revisions. First it would empower FDA to consider a broad range of surrogate and clinical endpoints, including endpoints that can be measured early in the clinical trial process, and endpoints applicable to a wider array of diseases and conditions. Second, it would encourage FDA to consider a wider array of supporting evidence, in addition to clinical trial evidence, to help inform the Agency's assessment of whether there is a reasonable basis to predict clinical benefit. Third, the bill would ensure that FDA takes into consideration the severity or rarity of the condition and the adequacy of any alternative treatments. And lastly, the bill would increase the transparency, predictability, and consistency of the review process by ensuring that FDA develop new guidance and revise existing guidance and regulations to clarify the scope and process for utilizing the expanded Accelerated Approval pathway, including specifically for rare diseases. Nothing in this bill would alter FDA's efficacy or safety standards. These important reforms would create a robust Accelerated Approval pathway that would enable the safe and expeditious development of the next generation of modern medicines to treat particularly dire conditions.

There are many examples where the FAST bill and modernization of Accelerated Approval can have an impact in the development of new medicines. For example, Spinal Muscular Atrophy (SMA) is a genetic neuromuscular disease characterized by severe muscle atrophy and weakness. The disease generally manifests early in life and is the leading genetic cause of death in infants and toddlers. A number of biomarkers exist that allow for assessment of drug activity in SMA patients, but none would currently be considered sufficiently validated today to serve as a surrogate endpoint for Accelerated Approval. However, there are several clinical measures in SMA that can also provide an indication of drug effect in relatively short-term clinical trials. Under an enhanced Accelerated Approval pathway, a demonstration of a favorable effect on one of these so-called "intermediate clinical endpoints" could be judged by FDA to be reasonably likely to predict a clinically meaningful benefit. This would allow for a relatively rapid

Accelerated Approval of SMA therapies, with an obligation by the sponsor to conduct further studies to further confirm the clinical benefit.

Another example is Sickle Cell Anemia, a genetic blood disorder afflicting millions of people around the world with a concentrated U.S. incidence in African-Americans. This disease is caused by mutations in the hemoglobin gene that cause red blood cells to “sickle” and obstruct blood vessels, causing pain and organ damage. New medicines are emerging that are aimed at correcting or altering the hemoglobin gene defects and these could be made available to patients faster if their approval employs the use of biomarkers. Under the FAST bill, FDA will be encouraged to modernize the Accelerated Approval pathway to make full use of such biomarkers and other emerging scientific tools, and to clarify the pathway to Accelerated Approval for novel treatments for diseases like Sickle Cell Anemia.

PDUFA V and Additional Legislative Proposals

As a small biotechnology company CEO, I would like to take a moment to discuss how important timely reauthorization of PDUFA V is to the United States’ biotechnology industry. PDUFA V will enhance the drug development and review process through increased transparency and scientific dialogue, advance regulatory science, and strengthen post-market surveillance. The commitment made by FDA in the PDUFA V technical agreement to a philosophy that timely, interactive communication with biotechnology and life science companies during drug development is a core Agency activity will be of great value, especially to small biotechnology companies such as mine. Most importantly, from the standpoint of innovative companies, our hope is that PDUFA V will provide patients and doctors with earlier access to breakthrough therapies.

My testimony today focused on enhancing the Accelerated Approval pathway. There are other proposals being considered by this Committee that I also believe would serve to improve our ability to develop and deliver innovative medicines. FDA’s mission statement should be updated to reflect the Agency’s critical role in advancing innovation. This would encourage FDA to apply its rigorous standards in the most innovation-friendly manner possible, by striving to reduce the time and cost of drug development wherever possible, and by incorporating modern

scientific advances into review practices to ensure that innovative treatments and therapies are made available to the patients who need them. And lastly, reforming Advisory Committee conflict of interest rules to provide FDA with greater flexibility and discretion to select the most appropriate advisors, consistent with the rules that apply to other federal agencies, would help ensure that FDA decisions are informed by the best available scientific experts and in the best interest of patients.

Fostering Medical Innovation in the United States

It is imperative that we have policies that encourage research and development of the next generation of treatments and cures. Policies being considered by the committee, some of which I have highlighted today, as well as timely passage of the Prescription Drug User Fee agreement, would go long way in fostering medical innovation in the United States. While America has developed more cures and breakthrough medicines than any other country and is home to over 2,500 biotech companies, this is not a position that will be sustained without a concerted policy focus on supporting and incentivizing the next frontier of biomedical discoveries, treatments, and cures. There have recently been a few headlines touting increased investment in the biomedical field. However, these headlines oversimplify the actual state of affairs. The NVCA recently released their fourth quarter 2011 numbers for venture financing in biotechnology in the U.S. While the numbers showed an overall 18% increase in investment from 2010 to 2011, this is not reflective of the situation that most small, innovative biotechnology companies are facing.¹⁰ The 2011 investment in biotechnology is 12% lower than the peak we saw in 2007. Additionally, first round venture deals in 2011 fell below 100 for the third time in a decade and the total number of venture financing deals is down 8% since 2010. Most importantly, especially to small innovative companies, the number of venture-funded early-stage companies fell 19%.¹¹ The number and quantity of investments moving away from early-stage innovative projects is a very disturbing trend that has been growing over the past few years. In fact the number of first-time financing for life sciences companies is at its lowest level since 1996.¹²

¹⁰ NVCA/PWC MoneyTree Report: Q4 2011. Data provided by Thomson Reuters.

¹¹ "Venture Capital increases in 2011, but..." Inside BIO Industry Analysis. 24 January 2012. <http://www.biotech-now.org/business-and-investments/inside-bio-ia/2012/01/vc2011>

¹² NVCA/PWC MoneyTree Report: Q4 2011. Data provided by Thomson Reuters.

Over the past year we have seen several long-time investment funds announce they will no longer be investing in the medical science sectors. The October 2011 survey conducted by the NVCA and MedIC showed that 40% of venture capitalists expect to decrease investment in biopharma over the next three years, three times as many as the number who expect to increase. This same survey showed that 61% cited regulatory challenges at the FDA as the main reason for reducing investments.¹³ This is not entirely surprising given that the time and costs to develop a novel drug have continued to increase over the past decade. In fact, today, it requires an average of 10 to 15 years and \$800 million to over \$1 billion to develop a new drug, and not only is that cost increasing, it is increasing at an alarming rate.¹⁴¹⁵¹⁶¹⁷ In part this increase in cost can be attributed to the increased complexity of regulatory requirements. For example, between 1999 and 2005 the average length of clinical trials grew by 70%.¹⁸

In addition to fiscal constraints here in the U.S., we are facing unprecedented competition from around the globe to be the leader in biomedical research. In 2008, China pledged to invest \$12 billion in drug development,¹⁹ and in 2011, the Chinese government named biotechnology as one of seven industries that will receive \$1.7 trillion in government funding over the next five years.²⁰ The European Union's Innovative Medicines Initiative is pumping \$2.65 billion into Europe's biopharma industry²¹ and India's Bioconnect initiative has funded over 200 new biopharma projects.²²

¹³ NVCA/MedIC Survey. Vital Signs. October 2011.

¹⁴ "Returns to R&D on New Drug Introductions in the 1980s." *Journal of Health Economics* 13, no. 4 (1994): 383-406

¹⁵ H.G. Grabowski, J. Vernon, and J.A. DiMasi, "Returns on Research and Development for 1990s New Drug Introductions," *Pharmacoeconomics* 20, supp. 3 (2002): 11-29

¹⁶ J. Dimasi and H Grabowski J "The Cost of Biopharmaceutical R&D: is Biotech Different?" *Managerial and Decision Economics* no 28 (2007): 469-79

¹⁷ Munos, Bernard. "Lessons from 60 years of pharmaceutical innovation." *Nature Reviews Drug Discovery* 8, 959-968 (December 2009).

¹⁸ Tufts Center for the Study of Drug Development. 2008. "Growing Protocol Design Complexity Stresses Investigators, Volunteers." Impact Report. 10.1.

¹⁹ Daverman, Richard. "China Launches 'Mega Program' to Fund Drug Development." *ChinaBio Today*. 9 November 2008. <http://www.chinabiotoday.com/articles/20081109>

²⁰ Buckley, Chris. "China to invest US\$1.7 trillion over 5 years in 'strategic sectors': US official." *The China Post*. 23 November 2011. <http://www.chinapost.com.tw/business/asia-china/2011/11/23/323724/China-to.htm>

²¹ Hodgson, John. "€2 billion IMI launched with European pharma." *Nature Biotechnology* 26, 717-718 (2008).

²² Dandekar, Vikas. "India Draws Lessons From China To Help Foster Biotech Industry." *PharmAsia News*. 7 February 2012.

This is a time where everyone involved in researching and developing new medicines needs to step up their game. It is industry's responsibility to choose product candidates carefully with a focus on medicines that really matter, and to conduct scientifically valid clinical trials. It is equally important that FDA, as the regulator and ultimate arbiter as to whether promising medicines are made available to patients, has transparent and consistent processes in place that are understood by the patients, medical researchers, industry and its investors. Additionally, it is critical that the FDA engender an environment that is able, in a timely manner, to efficiently and predictably review innovative medicines and allow for the use of modern scientific tools and methodologies that are more efficient and better enable FDA to make determinations of benefit vs. risk. It is also imperative that drugs are reviewed in the context of the patients' needs and disease being treated. And finally, it is essential that FDA take into account the ever-increasing time and cost of drug development, and strive to ensure safety and efficacy in a manner that minimizes that time and cost, thereby speeding important new therapies to patients and encouraging continued investment in innovative treatments for disease.

The U.S. biotechnology industry is poised to be a major driver in an innovation-driven economy and we offer real solutions to our most pressing health care needs: curing disease, reducing costs, increasing quality, and ensuring that people enjoy not only longer lives, but better and more productive lives. Last year we witnessed several promising events: FDA approved 35 novel drugs marking the most approvals in over a decade; and biopharmaceutical companies successfully brought to market remarkable therapies to treat hepatitis C, melanoma, lung cancer, lupus, cystic fibrosis, and a broad range of rare genetic disorders. These advancements in patient care represent the leading edge of the next generation of biotechnology innovations. That said, as I have described, these successes can only continue and increase if we have a policy strategy – an innovation environment – focused on fostering these types of medical breakthroughs. I believe that encouraging scientific dialogue between sponsors working innovative products and the FDA earlier in the drug development process and aggressive strategies by the Agency to encourage the utilization of modern approaches to clinical research and development will serve to not only incentivize innovation but most importantly enable us to deliver game-changing solutions to address our nation's most critical public health needs.

Conclusion

Implementing an enhanced Accelerated Approval pathway, coupled with the new provisions in PDUFA V, will result in dramatic improvements for patients facing life-threatening diseases.

These reforms are critical to improving health care in this country. Thank you for the opportunity to share my thoughts with you today.