

The Smallpox Vaccination Plan: Challenges and Next Steps

Bill Number: Oversight Hearing

Hearing Date: January 30, 2003

Witness:

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Washington, DC

Testimony:

Improving and Creating Opportunities

To Develop Vaccines against

Bioterrorism Threats—

An Industry Perspective

Mr. Chairman, members of the Committee, thank you for the opportunity to speak today about smallpox vaccine and the threat of bioterrorism.

I am Kim Bush, President of Baxter Bioscience Vaccines. Baxter International Inc. is a global health care company that, through its subsidiaries, provides critical therapies for people with life-threatening conditions. Baxter's Bioscience, Medication Delivery and Renal products and services are used to treat patients with some of the most challenging medical conditions including cancer, hemophilia, immune deficiencies, infectious diseases, kidney disease and trauma. With 2002 sales of over \$8 billion, and approximately 48,000 team members in 110 countries, Baxter is a global leader in developing innovative medical therapies that improve the quality of life for people around the world.

Baxter has a total of five licensed vaccines worldwide, and a broad pipeline of vaccines with more than a dozen vaccines at all stages of development from pre-clinical to pre-launch, including influenza and various meningococcal combination conjugates. Baxter's NeisVac-C meningococcal vaccine was approved in the U.K. in 2000 and is now licensed in 29 countries. Our newest next generation influenza vaccine has been approved for Phase III clinical trials this year in the U.S.

Baxter Healthcare Corporation, in conjunction with Acambis Inc., is participating in the production of 155 million doses of smallpox vaccine for the U.S. Government.

Mr. Chairman, I would like to make the point that what has happened in the case of the smallpox vaccine partnership between Baxter/Acambis is extraordinary to the point of being unprecedented. As you may be aware, although smallpox vaccine has been around for many years, the process used by Baxter and Acambis – growing the vaccinia virus in cell culture – is entirely new insofar as large-scale production is concerned.

Under optimal circumstances, the development of a new vaccine from the beginning through product delivery to the ultimate end user is a process that may take 10 years and in some cases has taken much longer. In the case of our current smallpox effort, however, through an innovative public-private partnership, this time frame has been dramatically shortened and compressed so that the needs of national security can and have been met.

At the same time, neither product quality nor the need to demonstrate safety and effectiveness in clinical trials is being compromised. That is a remarkable feat made possible because the FDA and all of the other government agencies along with the manufacturers decided this was not “business as usual.” I am not sure many Americans

know or appreciate the long hours, weeks of intensive and exhaustive fact-finding, and all the other hard work and collaboration that went into this contracting process. If they did, I am sure they would be very proud – as I am – of what our civil service and political leadership can accomplish in partnership with the private sector when an urgent need arises. It took only 58 days to complete the decision making process to award a \$400 million contract. That is unprecedented!

At the same time, we believe there are some lessons from this experience and we appreciate this opportunity to share with you some thoughts and ideas based on our experience as to how the country can enhance its ability to prepare for and respond to other bioterrorism threats. It is unfortunate that a disease that scientists and health care workers throughout the world devoted decades to eradicating may now be a bioterrorist threat. We therefore must use whatever scientific and medical tools at our disposal to defend against the unthinkable.

We believe a number of issues need to be considered and resolved if we are to have a truly meaningful and productive public-private partnership in defending against bioterrorism. I can assure you that the barriers are not in the willingness or ability of the private sector to become engaged.

For example, Baxter currently has the capability to make vaccines for numerous bioterrorism threats. Now – today – we have the technical ability to produce and deliver vaccines for smallpox (2nd generation and next generation/MVA), as well as vaccines that utilize recombinant, cell culture and conjugate technology and can protect against a variety of both viral and bacterial diseases. We can respond to pandemic threats including influenza, with our proprietary cell culture based production technology that eliminates the need for egg-dependent growth platforms and decreases the risk of adverse reactions. Beyond that, another 5 to 10 vaccines are possible if we select the right partners. In short, Mr. Chairman, Baxter, like a number of other companies, is technically able to meet many of the country's vaccine needs. The questions are under what conditions and with what incentives can these capabilities be optimized and what are the factors working against them? Let me share with you some of the issues we and industry are dealing with.

Uncertainty of Market Conditions for Anti-Bioterrorism Products

Inside a company such as Baxter, proposals to fund vaccine projects must compete against each other as well as against non-vaccine projects for R&D dollars. To put it simply, when you do the math, vaccines often come out as a less appealing choice for investment than other medical or pharmaceutical products. If you add to this the current and growing attacks on intellectual property protection, particularly as it pertains to health needs of developing countries – along with liability issues facing the industry and the costs of meeting regulatory requirements – it's not hard to understand why vaccines are viewed by some in less and less favorable terms as an investment priority.

New vaccine development decisions are risky in and of themselves. Bioterrorism products present even more difficult challenges because such products, especially if they are vaccines, may represent one-time-only opportunities and the market is extremely unpredictable. Certainly a product that is to be stockpiled and used only in case of emergency is not one that can by itself create a sustainable business model or warrant a huge R&D expenditure. That is even more true when we factor in the reality that shifts in

government policy or perceived threats could change priorities and funding initiatives overnight. Today's urgent need may become tomorrow's minor concern, or vice versa. Beyond that, for a manufacturer of vaccines that often take months to move through the production process, scheduling and anticipating needs are critically important. Also, just as for up-front decisions regarding product research and development, expensive manufacturing and production funding priorities and resource allocation decisions also take place in an environment of competing and sometimes conflicting demands. Against this backdrop, it is critical that needs be clearly stated. This is not always the case for government needs. Numerous different agencies have responsibility to foster research related to bioterrorism. That is a good thing and, indeed, there is a lot going on. However, from the perspective of industry their activities are not always coordinated or visible. Sometimes the procurement process lacks transparency – RFPs are issued and announcement dates come and go, sometimes without good communication as to the reasons for delay or what the issues are. Highly regulated procurement systems that work well under normal circumstances and are set up to procure standard material goods or to support small business R&D, do not necessarily provide incentives for large, capable manufacturers of complex biopharmaceuticals – nor are these standard procurement practices necessarily the fastest way to get products, especially biopharmaceuticals, into the hands of the U.S. government.

Another factor adding to the risk is our awareness of the fact that, in some cases, what the government is willing or able to pay for a product may be determined according to the appropriations available, not the value of the product to be purchased or the cost structure of the manufacturer. Hence, when investment decisions for R&D programs or manufacturing are being made by vaccine producers, we must consider the possibility that the government agencies may be bound by artificial limits in terms of determining what constitutes a fair price for the final product.

To create improved incentives to invest in new bioterrorism vaccines, it would be very helpful to hear a clearer and more coordinate message from the federal government as to the definition of its needs.

Mr. Chairman, I would also like the Committee to be aware that the vaccine industry today is somewhat splintered in the sense that – on the one hand you have a small number of large integrated manufacturers – and, on the other, a host of small companies including some small start-ups, that have really focused on a particular niche or technical capability. From our standpoint, it would seem very beneficial to the government to gain a greater understanding of the strengths of all these different companies, and put together a comprehensive composite picture of how all of these companies might be used in varying partnerships or consortia to bring forth the best possible result in the shortest possible time.

Currently, the way the system works, the government will issue an RFP and ultimately award the work to one prime contractor. It may very well be that alternative processes might foster partnerships and collaborations between companies with strengths that complement each other. I can say from our own Baxter experience that our partnership with Acambis in producing smallpox vaccine has been optimal for the government and certainly has worked well for our two companies. Yet, that partnership came about only through a series of events and pre-existing relationships that would not normally occur and were almost serendipitous. We think the government could be much more proactive

in terms of acquiring a broader knowledge of the industry's capabilities and using that knowledge to foster public-private partnerships. This could more readily harness the diverse talents and capabilities of the private sector to achieve the best possible results in the shortest possible time.

Accordingly, Mr. Chairman, we recommend that all of the government agencies that are involved in biodefense preparation develop a process for working in a more collaborative fashion to establish and communicate clear national research and development targets, thoroughly educate themselves on the capabilities of the industry, foster partnerships among different companies, and establish an RFP process that has an overriding goal of getting the best product in the shortest possible time. That is what occurred in the case of the smallpox contract with truly remarkable results and we think that process can be replicated for other bioterrorism research initiatives.

Impact of Regulation

The current regulatory system for drugs and biologics was established around the concept of assuring that the American people have safe and effective medicines to treat or prevent the wide range of medical conditions that can afflict people in a normal lifetime. Biologic products such as vaccines, because they are made from living organisms and are generally injected into healthy people, are subject to particular scrutiny under our existing regulatory setup – and justifiably so.

The question I raise today, however, is whether a regulatory system that works well and is set up to deal principally with conventional and often predictable health needs is positioned to deal with the abnormal and the unpredictable. Can it be better adapted to expedite the availability of medicines to counter organisms that have been weaponized or are highly exotic and almost never encountered during normal times? Certainly, in the case of the smallpox contract, we have seen that the regulatory system can quickly adapt when faced with an issue of overriding national interest.

The FDA has also moved forward in giving the vaccine industry better guidance in the critical area of designing clinical trials for products to protect against bioterrorism threats. The FDA and the industry agree that, because of ethical and safety concerns, Phase III efficacy trials are not possible in the case of vaccines, therapeutics or drugs to treat bioterrorism agents if such trials would require challenging human subjects with a deadly organism or highly toxic substance. Accordingly, the FDA has been developing alternative testing methods to be used when human studies are not feasible – because the product being tested is intended to deal with chemical, biological, radiological, or nuclear substances. The FDA deserves enormous credit for undertaking this initiative, which was underway even before September 11, 2001. This new rule that was made final on May 30, 2002, should provide industry with clear guidance on how to construct clinical trials. There are still some issues remaining for which regulatory solutions remain elusive. Let me give you one example. Tick-borne encephalitis (TBE) is a viral infection of the central nervous system that can lead to a number of serious neurological problems and in a small number of cases, death. TBE is common in Europe, Eastern Europe and East Asia. It currently is not known to exist in the United States. Some bioterrorism experts have expressed concern that this virus could be weaponized, and there is also interest on the part of the U.S. Army in having a vaccine to protect troops that might be stationed in places where TBE is prevalent.

Baxter has a vaccine for TBE that has been approved and marketed in Europe for many years. It would be preferable if the U.S. Army uses that vaccine for our troops to have FDA approval. For that to happen, however, Baxter would have to invest millions of dollars to conduct large and lengthy clinical trials to gain U.S. regulatory approval of a vaccine already licensed in Europe. Baxter might make such an investment if there was a high probability of having a U.S. purchaser but, otherwise, it would not make sense to seek U.S. licensing of a vaccine to prevent a disease that does not exist in the U.S. and for which there is no medical need.

Mr. Chairman, we are very encouraged by the steps taken so far by the FDA to assist industry in moving forward with anti-bioterrorism research projects, and we are hopeful the agency will build upon this process to identify and address additional needs as they become apparent. We do hope to find ways to address issues such as with the TBE vaccine that, because of unusual circumstances, falls outside of the range of solutions that can be sought within the usual regulatory process. We recommend that there be better collaboration between international agencies that might help eliminate duplication of regulatory efforts and harmonize high standards for licensing quality products.

Issues Relating to Liability and Risk Management

Mr. Chairman, Baxter believes that liability exposure is one of the most serious impediments to new vaccine development, especially in the area of preparing for a bioterrorist threat. This is because, unlike the situation with childhood vaccines, there is no comprehensive regime in place today designed to provide rapid and predictable compensation to persons who may have suffered a vaccine-related injury from bioterrorism vaccines.

As you may be aware, when Baxter and Acambis first entered into the contract with HHS to produce smallpox vaccine, the indemnification protection that was made available to us was a hastily cobbled together extension of a 1950s Executive Order – originally developed for Department of Defense contractors. Under this system, should our smallpox vaccine be used and result in adverse patient reactions, Baxter and Acambis would have to go through the lengthy, costly and difficult process of defending all lawsuits brought against us, and pay all claims until our insurance was exhausted. Then, and only then, would the government step in and take responsibility for the claims. This system exposes a manufacturer to tremendous legal costs and creates enormous difficulties in negotiating an insurance portfolio with private insurers, not to mention the uncertainty of how the government might exercise its discretion in indemnifying claims. This system is less than optimal and provides a strong disincentive to get involved in future vaccine contracting even assuming that the Executive Order could protect companies contracting for vaccines other than smallpox.

The language included in the Homeland Security Bill relating specifically to smallpox is a significant improvement over the Executive Order. Under that legislation, if HHS makes the appropriate declaration concerning the need to immunize all or some of the public against smallpox, then the government will, in effect, stand in the shoes of the manufacturer for purposes of defending lawsuits and paying claims.

The system set up in the Homeland Security bill makes far more sense and we recommend that it be extended to all bioterrorism vaccine development programs undertaken by the government. We believe that, if a vaccine is developed and manufactured at the request of the government to specifications set forth by the

government, and is delivered to the government to be used only when, where and how the government specifies, and given only to those individuals that the government determines should get the vaccine, then the government should bear the responsibility in paying the claims of those who have experienced injury or adverse reactions.

We strongly urge Congress to look at the smallpox liability language in the Homeland Security bill as a template for handling liability issues for future bioterrorism vaccine development.

Intellectual Property Protection

Another point I would like to touch on is the need to continue to assure adequate intellectual property protection. In combination with adequate market opportunities, patents are the means by which manufacturers can recover the cost of development and fund future research projects. As I had previously mentioned, it usually takes 10 years to bring a vaccine to the marketplace. Thus, upon entry into the market following regulatory approval, most vaccines only have less than ten years of remaining patent protection. Manufacturers rely on this relatively short period of protected sales to recoup the considerable costs of research, development, and clinical trials. In recent years, especially with respect to diseases affecting developing countries, we have seen an effort to require compulsory licensing or otherwise undermine patent protection as a way of making medications affordable for those nations, many of which are poor. I should add that, in many instances, developing nations are also in tropical regions, and many of the targets of both conventional vaccine research and bioterrorism preparation are on diseases of tropical origin.

As a company strongly committed to improving access to healthcare, Baxter understands the laudable goals of those who want to make medications more available to developing nations. At the same time, we need to recognize that the vaccine industry cannot afford to develop products for the diseases affecting those areas, including diseases that can be weaponized, if it cannot rely upon strong protections for the inventions and know-how that create those products.

As the U.S. continues the process of developing a trade agenda for the WTO and related negotiations, we strongly urge Congress and the Administration to seek ways to assist the poorer nations in improving access to health care technologies without undermining the strong intellectual property protections that are, in the final analysis, the engine that drives discovery of those technologies in the first place.

Creating a Solid Base for the Vaccine Industry

Finally, Mr. Chairman, if the vaccine industry is to make a meaningful contribution to the defense against bioterrorism, the industry must be healthy and vibrant. That is not universally the case today. To the contrary, rising development costs, downward pricing pressure, high costs of regulatory approval and compliance, and the constant threat of predatory lawsuits have combined with the inherent difficulties of manufacturing vaccines to create a situation where the industry is having trouble meeting the country's basic needs for regular childhood and seasonal vaccines – let alone meeting the country's needs on an emergency basis for innovative vaccines to combat bioterrorism threats.

Unlike mass-produced pills and tablets, which are synthesized from chemicals according to a standard recipe and are manufactured in a highly mechanized and predictable fashion, vaccines are produced from living organisms – including viruses and bacteria and cell cultures and other living systems. Despite the best efforts of vaccine

manufacturers, there can often occur a great deal of variation and unpredictability in the way these organisms grow and behave. In some cases these organisms are cloned or are the result of recombinant DNA technology. The process of making a vaccine from beginning to end can take many months, with many opportunities for unexpected and unwanted variations to occur. Building facilities to mass-produce vaccines requires investments of hundreds of millions of dollars. In other words, making vaccines is a costly, lengthy, difficult and a complex process.

In recent years we have seen shortages of vaccines that guard against measles, mumps, rubella, pneumonia, meningitis, diphtheria, tetanus, pertussis, chicken pox and adult influenza. We have witnessed a constant decline in the number of vaccine manufacturers – for U.S. licensed vaccines, there were 26 different manufacturers in 1967. Today in the U.S. there are only four major manufacturers. To our knowledge there are no stand-alone manufacturers of licensed vaccines in the U.S. which demonstrates how difficult it is to build a sustainable business enterprise solely on a vaccine portfolio.

Mr. Chairman, shortages and contraction are not indicators of an industry in the best of health. If America wants to build a dynamic biomedical infrastructure to serve as a bulwark against bioterrorism, we cannot do so on a fragile foundation.

The market for vaccines today, both in the U.S. and around the world, is one that is focused on, if not obsessed with, getting the lowest possible prices. Given the financial issues facing many governments and the problems facing many developing countries, that's not hard to understand. But what we must also understand is that the natural and inevitable result of downward pricing pressure is that many vaccines have now become low margin products and, as such, have the ability to contribute only marginally to the funding of future research and development for vaccine initiatives.

We have developed an attitude as a country that vaccines should be cheap, readily accessible and treated as an entitlement. Vaccines have done such an effective job for so many years, there has been a tendency to take them for granted, and there is a general lack of appreciation in the public of how difficult it is to produce vaccines and of the complex and formidable regulatory environment that faces these products. We recognize clearly the need to ensure consumer safety with vaccine products, especially as in many cases these products are given to individuals who are not yet ill. However, the overall attitude towards emerging vaccines for bioterrorism threats cannot be "business as usual" or these products will never be available. As one manufacturer capable of and committed to assisting in this effort, we would be pleased to work with this committee, others in Congress, the FDA, and other relevant agencies to determine the best ways to re-tool this process to expedite the development and availability of essential vaccines.

Conclusion and Recommendations

In closing, we believe that government can take a number of steps to improve the investment climate and willingness of private companies to make a greater commitment to research on bioterrorism vaccines and drugs.

We are hopeful that industry can gain a clearer picture of the government's needs and develop a collaborative process to meet those needs. To assist in that process, we strongly encourage government agencies involved in biodefense to establish and communicate clear national research and development targets, and work to better understand and coordinate the capabilities of the private sector to achieve those targets. We also hope

that the contracting process will be structured in a way that reflects the urgency of the situation, and has the overriding objective of getting the best product in the shortest possible time, at a cost which is reasonable to both the government and the contractor. Obviously, the FDA must be a full partner in that process so that it can think about and address issues that would not normally be raised in the process of approving drugs and biologics for more conventional uses. International regulatory harmonization of high standards would be especially useful.

With respect to liability and risk management, we hope Congress will look closely at the smallpox liability language in the Homeland Security bill as a template for handling liability issues for future bioterrorism vaccine development. This is critical because we expect that many of the new vaccines that will be developed as part of this effort will – unlike the smallpox vaccine – have no previous history and therefore will raise much more speculative questions of liability than is the case with smallpox. Getting private insurance we expect will be next to impossible, so some different mechanism must be in place.

Finally, Mr. Chairman, we hope that future policy in the area of vaccines will reflect an understanding of the difficulties and complexity of the vaccine manufacturing process, the need for strong intellectual property protection, and the enormous financial investment and risks created for the industry due to liability issues and regulatory compliance. The overall facts and data concerning the vaccine industry in the U.S. do not paint a picture of a completely healthy industry. To the contrary, there are some fairly serious warning signs based on the overall contraction of the industry and the shortages of recent years.

We appreciate this opportunity to share our views with the Committee and would be happy to answer any questions you might have.