

**TESTIMONY OF
STEPHEN PORTER
TO THE GOVERNMENT REFORM COMMITTEE
ON OCTOBER 11, 2000
10:00 A.M., 2154 RAYBURN**

VDDI was formed in order to capitalize on the opportunity to develop early stage pharmaceuticals. The Company licenses attractive product development opportunities from academic institutions, biotech firms and pharmaceutical companies. VDDI focuses on pharmaceutical product opportunities where general proof-of-principle has already been established in pre-clinical or early human testing, and where the products are novel and offer significant potential advantages over those currently in the market or in development. VDDI pursues early-stage products qualifying for fast track approval, primarily in cancer, cardiovascular disease and infectious disease. As its name suggests, VDDI utilizes a virtual business model. Virtual drug development entails: (i) a small core group of employees responsible for strategic management, regulatory strategy, and financial control, (ii) outsourcing all non-core business functions, including manufacturing preclinical and clinical drug development, (iii) global strategic resources and internet based enabling technology, and (iv) electronic data capture and data submission to regulatory authorities. By adopting this model, VDDI believes it can reduce total drug development program costs by at least 25% and development times by up to 50%.

In principal, a vaccine for anthrax is a good and necessary part of a complete protection "package" against anthrax, but the present vaccine program has suffered from a number of problems. Providing effective interdiction for persons threatened with exposed to anthrax endospores must remain a national priority. Despite numerous animal studies, the efficacy in humans of the AVA vaccine in the face of inhalational anthrax remains in serious doubt. Practical issues surrounding providing the vaccine to those in need of it also constitute real problems. The rapid progress and fatal nature of this disease, the vague early symptoms and the distinct possibility of human-engineered multiple antibiotic resistance suggests traditional antibiotic intervention may be of limited utility. More importantly, recent knowledge of the cloning of additional virulence factors (e.g., toxins from other bacteria) into the *B. anthracis* host raises the possibility that the nature and pathogenesis of the disease can be manipulated to the point of rendering our current interdiction strategies impotent. Clearly, new ways to block the disease state, at its earliest stages --before dissemination and production of its lethal toxin-- represent an exploitable and potentially valuable addition to our abilities to combat this disease.

Questions:

Would the utility of a novel prophylactic antibiotic regimen that provides active protection against all forms of anthrax natural and engineered, be a useful addition to our treatment armamentarium against this bioweapon?

Vaccines function by initiating the development of host antibodies that will quickly recognize *B. anthracis* or a component of its protein toxin. Unfortunately, it may be relatively easy for the enemy to genetically alter the surface of proteins (this

also occurs naturally, without intervention by man) that these antibodies recognize, thereby making vaccine treatment ineffective; or to use molecular biological techniques to insert the virulence genes into a different bacterium. More importantly, recent knowledge of the cloning of additional virulence factors (e.g., toxins from other bacteria, cereolysin ab) into the *B. anthracis* host raises the possibility that the nature and pathogenesis of the disease can be manipulated to the point of rendering our current interdiction strategies impotent.

Wouldn't the ability to use a technology that would allow for the near immediate deployment of our troops and personnel be of strategic and practical advantage over an immunization schedule that requires months to be deemed as possibly effective?

Wouldn't the ability to deploy and store a treatment regimen that is stable in field conditions, offer advantages over a regimen that requires refrigeration.

Wouldn't the ability to offer very rapid scale up and production of an alternative prophylactic and/or treatment regime confer significant advantages over an immunization regimen?

The UAB NADs technology is mature and ready for optimization. The key to success will be a discovery program that creates a pharmaceutical product, which has appropriate stability, absorption, metabolism, and safety profiles to allow its use in animal experimentation. Following completion of this work, a formal preclinical development program will optimize the doses; institute allometric scaling; characterize the safety in at least two animal models; and complete the anthrax efficacy, dose response, and pharmacokinetic (PK) profile in animal. Then, a formal Investigational New Drug (IND) application will be submitted to the FDA, and two normal volunteer studies will be conducted: a single-dose, dose-escalating safety, tolerance, and PK Phase I clinical trial, to be followed by a multi-dose safety, tolerance, and PK Phase I clinical trial. These studies will be correlated with information from preclinical (animal) safety, PK and efficacy with the human trial experience. Since it is unethical to conduct anthrax interdiction trials in humans, surrogates of plasma and tissue concentrations obtained from animal interdiction studies will be used as correlates and inferences of the human experience.

The Food and Drug Administration has recently proposed regulations for the development of new drugs to be used against lethal or permanently disabling toxic substances, including agents that may be used in biological warfare (published in the Federal Register Vol. 64, No.192, (Oct. 1999: "Evidence Needed to Demonstrate Efficacy of New Drugs for Use Against Lethal or Permanently Disabling Toxic Substances When Efficacy Studies in Humans Ethically Cannot Be Conducted). The recent approval of Ciprofloxacin for *B. Anthracis* treatment partially validates this approach.

In collaboration with PPD Discovery, and The University of Alabama, VDDI has developed a preclinical and clinical strategy in accordance with these new regulations, and will discuss this strategy with the FDA at a pre-IND meeting to be scheduled.

In summary, the specific design of our lead compounds, in conjunction with our preliminary *in vitro* and *in vivo* data suggest that:

- The lead compounds have minimum inhibitory concentrations (MIC) values against *B. Anthracis* that are quite acceptable.
- The lead compounds have minimum inhibitory concentrations (MIC) values against *MRSA* and vancomycin resistant *Enterococcus faecium* and *E. faecalis*, that is as good or better than clinically approved antibiotics
- Some of the lead compounds show specificity against gram positive, but not gram negative strains, thus reducing some adverse effects of clinically approved antibiotics
- Some of the lead compounds show excellent activity against virulent and attenuated strains of *B. anthracis*.
- The mechanism of action of the compounds is specific to prokaryotic cells, thus leading to a great safety profile for clinical use.

Product development issues that remain to be resolved include:

- Development of parenteral agents;
- Development of orally active agents; and
- Development of a relatively long half-life product.

DARPA has supported the initial funding for this program (\$6 Million). USAMRIID supported the early synthetic chemistry and *in vitro* studies with several strains of *B. anthracis* and has just agreed to refund \$300,000 for this work performed. VVDI has received an NIH R43 SBIR Phase I grant for \$135,000. Additional support is requested from the Department of Defense and will be used to complete the synthetic chemistry and initiate the preclinical development program. Specifically \$2 Million is needed immediately, and will be spent as allocated by the time and resources as outlined in the enclosed Proposal. Additional funds necessary to complete this development program and their respective utilization are shown in summary format in Table 1. A greatly detailed timescale and deliverable assessment for this program is also included in the proposal.

Table 1

Stage of Project	Estimated Duration	Estimated Cost
Synthetic Chemistry	12-24 wks	\$860,000.00
Drug Lead Profiling	30 days	\$300,000.00
Pre-IND Meetings (2)	90 days	\$67,250.00
Preclinical Drug Development	16 months	\$2,738,400.00
IND Filing	4 weeks	\$150,000.00
Clinical Drug Development	20 months	\$2,475,000.00
Nonclinical Drug Development	2.5 yrs	\$2,700,000.00
NDA Filing	6 weeks	\$650,000.00
Manufacturing	4 yrs	\$5,000,000.00
Administrative and Project Management	4yrs	\$2,250,000
Total		\$16,990,341.00

I submit the enclosed program outline for the development and commercialization of a novel oral pharmaceutical as testimony before your committee "The Anthrax Vaccine Immunization Program: What Have we Learned?" Oct 11th. I have removed proprietary and sensitive information, however, the essential elements of this proposal remain for consideration and review by this committee.