

## Clinical Trials for Bioterrorism Agents

By Ketan Desai

The threat of bioterrorism has had one positive outcome: It has helped stir renewed interest in the prevention and treatment of infectious diseases. This specialty had become so unattractive that major pharmaceutical companies had stopped research on most anti-bacterials and anti-virals. That trend reversed with the anthrax attacks of 2001 and 2002 and the growing problem of treatment-resistant bacterial infections. Now, many companies are working on medicines to treat infectious agents, including bio-warfare agents.

There is, however, a difficult problem: How should clinical trials for bioterrorism agents be conducted? Trials for common infectious diseases such as sinusitis follow a hallowed tradition, since *Streptococcus pneumoniae* infections are prevalent in the community. But *Bacillus anthracis* infections are very rare, while variola, the smallpox virus, is now confined to a few high-security labs. IRBs are unlikely to approve studies that deliberately infect study subjects with lethal diseases to evaluate the efficacy of antidotes.

### Alternative Approaches

For diseases, such as anthrax, that exist in nature, one can, in theory, test treatments in populations that have a relatively high rate of infections. For example, for anthrax, the appropriate population in the U.S. would be farmers exposed to sheep and cattle. However, even the highest rates of infection in the U.S. are still too low to be practical. Prior to the bioterrorism attacks, there were no reported human cases from 1993 to 2000.<sup>1</sup> Anthrax is more prevalent in other parts of the world, such as the Middle East and Central Asia. Unfortunately, these areas are geographically large and generally do not have suitable medical infrastructures.

Nevertheless, there are practical approaches, albeit usually with some limitations that can be applied to the three main classes of medication: vaccines, small molecules, and antibodies.

If infection is rare or unknown, immune response can be measured as a surrogate for the clinical response. Thus, one can evaluate a vaccine against anthrax by measuring the IgG antibody titer formed against the major anthrax antigens. If a large and sustained effect is found in healthy volunteers, the vaccine is probably effective. Conventional Phase I and Phase II dose-finding and safety studies can be conducted, but Phase III efficacy studies cannot.

As of March 9, 2006, [www.clinicaltrials.gov](http://www.clinicaltrials.gov) listed nine trials for smallpox. Of these, the largest sponsor is the National Institute of Allergy and Infectious Diseases (NIAID) – four studies are listed for anthrax, with recombinant protective antigen (rPA) being the most common active component. Other sponsors include the National Child Health and Human Development (NICHD) and Dynaport. One 200-subject NIAID study is assessing the effect of a vaccine for people exposed to anthrax.

In the absence of a therapeutic setting, testing a new chemical entity (NCE) against a bioterrorism agent is more complex. The FDA allows safety studies in healthy human volunteers. These studies are generally one month in duration, reflecting the maximum

likely long-term exposure to the medication. Needless to say, single-dose, dose-rising studies should precede the repeat-dose one-month studies with two or three dose groups.

Human efficacy studies, on the other hand, are impossible. Instead, they may be conducted in animals such as primates that are exposed to the infectious agent in a controlled environment. Because there are very few laboratories, such as at Fort Detrick in Maryland, that can carry out research in primates with bioterrorism agents (as opposed to general toxicology studies), the waiting line can be quite long. Positive data from the human safety and animal efficacy studies can lead to FDA approval. However, it should be cautioned that the label is generally very narrow and the option of off-label use for general infectious diseases is consequently limited. However, for agents such as smallpox that have no natural infections anymore, this is the only path forward.

Testing human monoclonal antibodies to bioterrorism agents is perhaps the most difficult challenge. Safety tests in humans can be conducted as usual, but efficacy tests in other species are prone to antigenicity problems, depending on the species. For example, an antibody that may work in humans cannot be tested in primates since anti-idiotypic antibodies (antibodies against the therapeutic antibody) develop, reducing the efficacy of the therapeutic antibody. In addition, antibody complexes could give false indications of safety problems that would not occur in humans. A way around this problem is to evaluate the treatment for a shorter-than-normal time period, for example, two weeks, before the anti-idiotypic antibodies start rising in titer. Theoretically, a primate antibody could be tested in primates, but the results would be far from conclusive for a human antibody in humans.

Medarex ([www.medarex.com](http://www.medarex.com)) and PharmAthene ([www.pharmathene.com](http://www.pharmathene.com)) are jointly developing an antibody (MDX-1303) to bacillus anthracis. The treatment is presently in Phase I testing. NIAID is also evaluating an inhaled antibody to anthrax for Phase I trials in June 2006.

More than with any other therapeutic area, it is critical to communicate frequently and openly with the FDA. Further information about conducting trials for bioterrorism agents is at [www.fda.gov/oc/bioterrorism/role.html](http://www.fda.gov/oc/bioterrorism/role.html).

## Reference

1. [http://www.worldwidehealth.org/Anthrax/epidemiology\\_of\\_anthrax.htm](http://www.worldwidehealth.org/Anthrax/epidemiology_of_anthrax.htm)

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