



**THE JOINT STAFF**  
**WASHINGTON, DC**

Food & Drug Administration  
Division of Dockets Management  
5630 Fishers Lane  
Room 1061  
Rockville, MD 20852

Reference: Docket Number 1980N-0208, Proposed Rule and Proposed Order: Bacterial Vaccines and Toxoids

Ladies and Gentlemen:

This comment pertains to section IV of the Proposed Rule and Proposed Order: Anthrax Vaccine Adsorbed – Proposed Order. Prompt FDA action to complete the administrative review of anthrax vaccine is very important to improving military and civilian preparedness to counter the very real threat of anthrax used against the United States or its armed forces by terrorists or potential adversaries.

The focus of this comment is the proposed order's discussion concerning the dosing schedule for AVA. The proposed order discusses the dosing schedule but fails to clarify its effect. As pointed out in the proposed order, the dosing schedule regulatory requirement had been set forth at 21 CFR 620.24(a). This provision, adopted in 1973, was removed in 1996 as part of the "Reinventing Government" regulatory streamlining initiative as no longer necessary within the Code of Federal Regulations (FDA, 1996). The requirement in section 620.24(a) called for "total primary immunizing doses of three single doses, each given at appropriate intervals." The "appropriate intervals" requirement was also applicable to another multi-dose vaccine, typhoid vaccine (§ 620.14(a)). The best indicator of "appropriate intervals" is, of course, the dosing schedule recommended in the product labeling. However, a question has been raised whether, in cases in which circumstances compel longer-than-recommended intervals, the result is still, in the course of medical practice, an appropriate interval and still consistent with the labeled dosing schedule.

Recognizing the logistical challenges faced by civilian public health clinics in their static locations across the United States, the Advisory Committee on Immunization Practices (ACIP) developed a series of prudent and flexible recommendations for quality immunization practices. The ACIP consists of civilian physicians who advise the director of the Centers for Disease Control and Prevention (CDC). The ACIP's general recommendations state: "... longer-than-recommended intervals between doses do not reduce final antibody concentrations, although protection might not be attained until the recommended number of doses has been administered. An interruption in the vaccination schedule does not require restarting the entire series of a vaccine or toxoid or the addition of extra doses" (ACIP, 2002). These guidelines recognize the biological fact that the human immune system contains durable memory cells that remember

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previous vaccinations and permit deviations from the rigid dosing schedules observed during clinical studies and field trials.

When the ACIP reviewed the data available in mid-2000, it concluded that those data support flexibility in the route and timing of anthrax vaccination under special circumstances. As with other licensed vaccines, no data indicate that increasing the interval between doses adversely affects immunogenicity or safety. On this basis, the ACIP concluded that interruption of the anthrax vaccination schedule does not require restarting the entire series of anthrax vaccinations or the addition of extra doses (ACIP 2000).

Multiple studies show that human antibody responses increase when greater than normal intervals elapse between doses of vaccine (Salk, 1984; Jilg et al., 1985; McBean et al., 1988; Hadler et al., 1989; Marsano et al., 1998; Wistrom et al., 1999). Health-care workers do not generally adopt these longer intervals, because longer intervals also involve a delay in achieving immunity. But the delay does not reduce the protection the individual ultimately achieves. This phenomenon has been observed with many vaccines, and is considered to be a general characteristic of vaccines.

The classic textbook of vaccines (Plotkin & Orenstein's *Vaccines*, 4th ed., p. 98) states:

Because of immunological memory, longer than routinely recommended intervals between doses do not impair the immunological response to live and inactivated vaccines that require more than one dose to achieve primary immunity. Similarly, delayed administration of recommended booster doses does not adversely affect the antibody response to such doses. Thus, the interruption of a recommended primary series or an extended lapse between booster doses does not necessitate re-initiation of the entire vaccine series.

This understanding of immunology is supported by several anthrax vaccine studies:

- Antibody-response data were collected from military personnel who had a prolonged interval between the first and second doses of anthrax vaccine. Antibody to PA was measured by enzyme-linked immunosorbent assay (ELISA) at 7 weeks after the first dose. Geometric mean concentrations increased from 450  $\mu\text{g/mL}$  among those who received the second vaccine dose 2 weeks after the first ( $n = 22$ ), to 1,225 for those vaccinated at a 3-week interval ( $n = 19$ ), and 1,860 for those vaccinated at a 4-week interval ( $n = 12$ ). Differences in titer between the routine and prolonged intervals were statistically significant ( $p < 0.01$ ) (Pittman et al., 2000).
- In 1992-93, scientists from the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) drew blood on 281 Fort Bragg soldiers. These soldiers received 1, 2, or 3 doses of anthrax vaccine 18 to 24 months earlier during the Persian Gulf War of 1990-91. Next, these soldiers received one additional dose of anthrax vaccine. Soldiers who received 1 dose of anthrax vaccine responded with an average 100-fold increase in their level of anti-anthrax antibodies. From 92% to 100% of these soldiers responded to a single dose of anthrax vaccine with increases in

detectable antibody levels. Soldiers who received 2 or 3 doses of anthrax vaccine during the Gulf War responded with even greater increases in antibody concentrations. All 281 soldiers had greater than a 4-fold increase in antibody level, the standard definition of an immune response. A high antibody-response rate after a single booster dose of a vaccine shows that the immune system remembers the previous vaccinations, even if antibodies were not detected just before the booster dose (Pittman et al., 2002a).

- Subsequently, a small randomized study was conducted among military personnel to compare the licensed regimen (subcutaneous injections at 0, 2, and 4 weeks, n = 28) and alternate regimens (subcutaneous [n = 23] or intramuscular [n=22] injections at 0 and 4 weeks). Immunogenicity outcomes measured at 8 weeks after the first dose included geometric mean IgG concentrations and the proportion of subjects seroconverting (defined by an anti-PA IgG concentration of > 25 µg/mL). In addition, the occurrence of local and systemic adverse events was determined. IgG concentrations were similar between the routine and alternate schedule groups (routine: 478 µg/mL; subcutaneous at 0 and 4 weeks: 625 µg/mL; intramuscular at 0 and 4 weeks: 482 µg/mL). All study participants seroconverted except for one of 21 in the intramuscular (injections at 0 and 4 weeks) group (Pittman et al., 2002b). This study established the proof of concept for an ongoing study coordinated by the CDC.

Because of the complexity of a six-dose primary vaccination schedule and frequency of local injection-site reactions, studies are under way to assess the immunogenicity of schedules with a reduced number of doses and with intramuscular (IM) administration rather than subcutaneous administration. In late January 2005, the CDC provided the FDA with detailed safety experience data for the 1,564 volunteers enrolled in the dose-reduction/route-change study, as part of Investigational New Drug # 10031, sponsored by CDC. We understand that CDC's report constitutes several thousand pages of detail about 1,564 volunteers who received 7,618 injections in a six-arm, five-site randomized controlled clinical trial with active solicitation of adverse experiences. These data add to the fact base about the immune response to anthrax vaccination under a variety of dosing intervals.

The clearly established understanding of immunology has led the CDC and its Advisory Committee on Immunization Practices (ACIP) to establish guidelines for managing vaccine shortages, which have become quite frequent in recent years. As summarized in a September 2002 General Accounting Office report: "In response to recent vaccine shortages, ACIP and CDC issued temporary recommendations to defer immunizations for some groups of children, so that the available supply can be directed to those considered at higher risk for contracting vaccine-preventable diseases. Five vaccines are included: Td [tetanus and diphtheria toxoids], DTaP [tetanus and diphtheria toxoids and acellular pertussis vaccine], PCV [pneumococcal conjugate vaccine], MMR [measles, mumps and rubella], and varicella. The revisions give guidance to providers that are facing shortages and are intended to ensure vaccine availability for priority needs." Another recent example is the February 12, 2004, recommendation of the CDC "that health care providers temporarily suspend routine use of the fourth dose of the pneumococcal conjugate vaccine" because of a shortage due to production problems of the manufacturer. A similar action was taken regarding the influenza vaccine shortage for the 2004-

05 season, the CDC and ACIP recommending that, rather than following the normal practice of giving children younger than nine years old two doses of influence vaccine in the first year in which they are vaccinated, "doses should not be held in reserve to ensure that 2 doses will be available," and "available vaccine should be used to vaccinate persons in priority groups on a first-come, first-serve basis" (CDC, 2004).

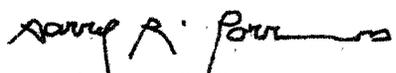
In addition to the special problems presented by vaccine shortages and the attending need to prioritize limited supply by deferring less clinically important vaccinations (i.e., people in lesser need of protection) to ensure the availability of product for more clinically important vaccinations (i.e., people with greater need for protection), the CDC has also established guidelines for dealing with the inevitable, day-by-day reality that patients and physicians and vaccine typically do not all come together on a precise calendar schedule that exactly matches a labeled dosing schedule. In fact, they do not so come together for millions of scheduled doses in the civilian sector every year. To deal with this reality of medical practice, the CDC National Immunization Program website includes guidelines "for children and adolescents who start late or are >1 month behind" a scheduled shot. The CDC provides tables that "give catch-up schedules and minimum intervals between doses for children who have delayed immunizations." The web site highlights the guideline that: "There is no need to restart a vaccine series regardless of the time that has elapsed between doses." (CDC 2005) The 2005 Childhood and Adolescent Immunization Schedule and Catch-Up Schedule, issued by CDC, was approved by the ACIP, the American Academy of Family Physicians, and the American Academy of Pediatrics.

It cannot be rationally disputed that these guidelines are not mislabeling of the vaccines, and health care providers who follow them are not conducting experiments or violating the Food, Drug, and Cosmetic Act. On the contrary, in cases in which circumstances compel longer-than-recommended dosing intervals, the result is still, in the course of medical practice, an appropriate interval and still consistent with the labeled dosing schedule.

The statement in the proposed order is correct that it is not significant whether certain doses in the labeled dosing schedule are considered "primary" doses or "booster" doses. However, what is significant is that the FDA provide a clear statement of the regulatory significance for public health programs of the labeled dosing schedule. Such a statement should confirm that the scientifically-supported, ubiquitous clinical practice of treating the inevitable longer-than-recommended dosing intervals as still, in the course of medical practice, appropriate intervals and still consistent with the labeled dosing schedule.

Thank you for your attention.

Sincerely,

 25 March 2005  
Darrel R. Porr, M.D.  
Major General, United States Army  
Joint Staff Surgeon

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