Facing the challenge of combination vaccines

WASHINGTON, D.C.—Several forces make development of combination vaccines an attractive calling. However, both technical and regulatory stumbling blocks need to be overcome before such vaccines will be ready for widespread use. Even though a specific combination-vaccine product is yet to test the system, products in the pipelines of several vaccine companies suggest that such a test is imminent. Combination conjugate products to prevent pneumococcal infections from companies such as Wyeth-Ayerst (Radnor, PA), Merck (West Point, PA) and Connaught Laboratories (Swiftwater, PA) or acellular multicomponent formulations of the pertussis (whooping cough) vaccine are likely first-round candidates. Later developments may include vaccines that confer protection across several diseases.

Anticipating a spate of such products, officials at the U.S. Food and Drug Administration (FDA, Rockville, MD) recently issued a draft guidance document, "Points to Consider for the Evaluation of Combination Vaccines: Production, Testing, and Clinical Study (1995)." In October, members of the FDA Vaccines and Related Biological Products Advisory Committee and industry representatives reviewed that document and tried—informally and in somewhat abstract terms to apply its precepts to pneumococcal vaccines under development. Their exercise illustrates some of the difficulties that lie ahead for developers of these vaccines.

Because pneumococci come in a substantial variety of virulent types, current vaccines to protect against this group of pathogens include a mixture of capsular polysaccharides from a number of distinct strains, known as serotypes. Although effective when administered to adults, the existing combination vaccines do not protect children well.

In the U. S., according to Jay Butler of the Centers for Disease Control and Prevention (CDCP, Atlanta, GA), the pneumococcus is the most common cause of community-acquired bacterial pneumonia, leading to some 250,000 cases, and about 40,000 deaths per year; and the second most common source of bacterial meningitis. It is also the leading cause of death of children in the Third World, responsible for about 4 million deaths per year.

"The pneumococcus is the most important cause of bacterial pneumonia, meningitis, and otitis media [middle ear infections]," points out Keith Klugman of the South African Institute for Medical Research (Johannesburg, South Africa), one of several experts on the pneumococcus who described recent vaccine studies earlier this fall during the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC, San Francisco, CA).

"With the increase in antibiotic resistance now accounting for about 25% of cases in the U.S., and similar high rates of resistance in other countries, the need for an effective vaccine to prevent pneumococcal infections takes on ever greater importance," Klugman says. "With meningitis, we're getting desperate, and that's where the new vaccine is exciting. Even with ear infections, there are many resistant bugs that are not responding to therapy."

To address the shortcomings of conventional polysaccharide-based vaccines, investigators say a conjugate vaccine is needed—that is, a product in which the bacterial polysaccharide components are linked to protein carrier molecules, thereby providing a more effective stimulus of immunity in young children. However, the need to use an array of capsular polysaccharide components from different pneumococcal pathogens complicates and raises the cost of current efforts to develop such a conjugate.

To complicate this effort still further, the mix of ingredients in such vaccines may need to be varied for recipients among the very young and older age groups and also those from one geographic region or another, reflecting the varied prevalence of different pathogen types in different target populations. For both technical and economic reasons, combining a very large number of components into a single universal mix would be impractical, most experts agree.

Industry representatives, drawn mainly from established vaccine and pharmaceutical producers, point to a number of problems that need to be faced for those developing complex combinations of pneumococcal conjugate vaccines. Perhaps the most perplexing regulatory questions revolve around the requirements they must meet when adding new components to established vaccines.

"The key issue will be the ability to add serotypes without having to do large clinical trials," says Jerry Sadoff of Merck (Rahway, NJ). Conducting such trials each time the pneumococcal mix needs to be amended would be prohibitively expensive, he and other industry representatives agree. Short of a full-scale clinical trial, some sort of surrogate marker to indicate that a new formulation will be safe and effective will be needed. "It is critical that we get guidance from FDA for what we can measure in order to add serotypes," he emphasizes. Although FDA officials seem open to the possibility, some members of the advisory committee voiced reluctance (and a few, outright opposition) to using surrogate markers for determining the efficacy of amended vaccines.

Achieving the right balance of components in a combination vaccine product will not be easy for additional reasons, says Dan Granoff of Chiron-Biocine (Emeryville, CA). If a particular multivalent vaccine lot fails to provide protective immunity because it is missing a critical component or because not enough of that component is present in the mix, the public may quickly lose confidence in the idea of a conjugate pneumococcal vaccine for children. Moreover, he notes, "The cost of adding more and more serotypes will be

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higher, and that may also be counterproductive."

Consumer advocates on the FDA panel agree, pointing out that U.S. users of such a vaccine will be reluctant to see components added if they offer little additional protection but perhaps more risk and certainly more cost. The question of escalating costs is even more troublesome when considering how to design combination vaccines for wide use in developing countries where budgets for public health programs to administer vaccines are extremely tight.

The World Health Organization (Geneva, Switzerland) sees the development and wide distribution of such vaccines "as a major priority," Klugman notes. Of even more immediate importance, the clinical testing of a multivalent conjugate vaccine containing nine distinct types of pneumococcal polysaccharides will soon begin in Soweto, South Africa, he says. "A major problem will be to get these vaccines to the third world, so it's quite exciting to begin these tests."

Provided that these and other clinical tests prove successful, making the conjugate vaccines available to countries in the third world is of global importance for another reason, points out Margaret Hostetter of the University of Minneapolis (Minneapolis, MN), who also spoke at ICAAC. It will help to address the problem of antibiotic resistance in these pathogens. To reduce or eliminate these pathogens, particularly the antibiotic-resistant strains that sometimes move rapidly about the globe, "we will want to do so everywhere," she says.

—Jeffrey L. Fox

Wyeth-Ayerst and Apollon sign vaccine deal

"It was very important for Apollon to have a partner that would contribute more than just money to the deal."

ALLENTOWN, PA—Vaccine development, so often in the shadow of its dashing therapeutic counterparts, is starting to shake off its tall-dark-dependable-but-unexciting image. If proof was needed that there is a lot of vaccine development to be done, the $100 million deal involving Wyeth-Ayerst Laboratories (Radnor, PA), a division of American Home Products (AHP, Philadelphia, PA) and Apollon (Malvern, PA) surely provides it. The deal concerns the development and commercialization of Apollon's facilitated DNA injection technology, Genevax, and specifically encompasses Genevax-HIV, an HIV vaccine currently in phase I/II clinical trials, and DNA-based vaccines that target herpes simplex virus (HSV) and human papilloma virus (HPV). In return for upfront and milestone payments, Apollon will manufacture the products and sell them to Wyeth-Ayerst for worldwide distribution.

"It was very important for Apollon to have a partner that would contribute more than just money to the deal," says Vincent Zurawski, Jr., president and CEO of Apollon. "We very much wanted to have a research collaboration, and someone interested in the development of this product in the long term."

Together with Merck (Rahway, NJ), SmithKline Beecham (London, U.K.), and Connaught Laboratories (Swiftwater, PA), American Home Products is a leader in the pediatric and adult vaccine market worldwide. In November 1994, Wyeth-Ayerst merged with Lederle-Praxis (Rochester, NY), a leader in pediatric vaccines, as part of AHP's acquisition of American Cyanamid.

Apollon's vaccine technology involves injecting the DNA for viral antigens, together with facilitating agents that enhance DNA uptake and gene expression. "In order to have a DNA-based vaccine for an infectious disease agent, it may require only local, transient, and low level expression of the DNA infected," says Allan Jarvis, vice president of business development and strategy for the Wyeth-Lederle Vaccines and Pediatrics division. He likens the transient antigen presence to subclinical infection with a natural pathogen: both result in a protective humoral and T-cell-mediated immune responses.

The Genevax-HIV product now in clinical trials in HIV-infected individuals contains genes for the gp160 viral envelope protein, other HIV accessory proteins, and the facilitating agent, bupivacaine. The company anticipates filing an IND for a prophylactic HIV vaccine construct by mid-1996. HSV may be a more straightforward target than HIV. Apollon expects that an effective prophylactic vaccine might target a single antigen, such as the gD2 envelope protein.

—Vicki Glaser

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European food rules creep forward

OXFORD, UK—After more than 12 months of wrangling, ministers from European Union (EU, Brussels, Belgium) member states have agreed to a form of wording for the European "novel foods" regulation that introduces a requirement to label some—but not all—genetically modified foods. Industry will accept the requirements, albeit reluctantly, on the basis that it can work with one somewhat unsatisfactory set of Europe-wide rules more easily than it can work with 15 sets of national rules. It would, undoubtedly, have preferred a less prescriptive approach.

Companies such as Zeneca (London, U.K.) and Unilever NV (London, U.K. and Rotterdam, the Netherlands) have long advocated that labeling should only be required if it is useful to the consumers. This view is shared by EU Industry Commissioner Martin Bangemann. Bangemann suggested that foods or ingredients that had not been substantially modified by genetic engineering or ingredients processed into another form (such as tomato juice from genetically engineered tomatoes) shouldn't be labeled. Labels like "substantially modified" or "sub-