Trends-in-Medicine

March 2007
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Quick Pulse

Trends-in-Medicine
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WORLD VACCINE CONGRESS

Washington, DC
March 20-21, 2007

The World Vaccine Congress brought together about 300 experts in the vaccine field, including manufacturers, contract research organizations (CROs), contract manufacturing organizations (CMOs), and device and service companies that work with those companies. It was an opportunity for them to share the status of various vaccine projects and ideas for future development.

The vaccine industry was described as "doing pretty well" and "becoming more profitable, not less profitable." That was the conclusion of Michel Greco, former president of Aventis Pasteur, who said this is due to:

- **Increased recognition of the value of vaccines.**
- **Higher prices for new vaccines.**
- **Potentially very high prices for future vaccines.** He said, "If you look at future vaccines and think of therapeutic vaccines or autologous vaccines, the price could reach six figures. It is not low hanging fruit, but it is coming."
- **Comparatively lower commercial costs** (up to now vaccines have been cheaper to market than pharmaceuticals).

Lance Gordon Ph.D., former president/CEO of VaxGen, cited four areas where he sees opportunities for vaccine development:

- **Developed country markets –** for HIV, MRSA, improved flu, meningitis B, RSV, *H. pylori*, enteric disease, and cancer. He said, "I think we are missing a lot of the opportunities in flu vaccines. The real issues are developing a product with broader protection, longer duration of protection (>1 year), and better efficacy in the high risk elderly population."
- **Developing markets –** for malaria, tuberculosis, enteric, and parasitic diseases.
- **Biodefense –** for anthrax, attenuated smallpox, plague, tularemia, ebola, etc.
- **Emerging diseases –** the next SARS, West Nile, or bird flu.

Drivers that experts predicted will guarantee continued expansion of the vaccine market over the middle- to long-term.

- **Demographics:** aging populaton, migrations.
- **Pathology:** resurgence of old diseases, "new diseases," antibiotic resistance.
- **Policies:** stronger national prevention policies, international initiatives, bio-defense, pandemics.
- **Innovation.**

Future of Vaccine Development

Positives	Negatives
Improved vaccine pricing in recent years.	Escalating costs and time required for vaccine development.
Recent vaccine launches and acquisitions of vaccine biotech companies have generated investor interest.	Approach zero risk tolerance regarding safety and predictability.
Improvement in adult markets and opening of an adolescent vaccine market.	Changing corporate governance, F&A requirements, and environment.
Growing awareness in government and the public health community of the need to strengthen our industrial base.	

The global vaccine pipeline is "very dense," an expert said, citing several innovations the industry is making, including new uses of existing vaccines, new delivery systems, new combinations, new routes of administration (e.g., mucosal), new formulations, new antigens, vaccines for "non-infectious" diseases, and therapeutic vaccines.

Experts pointed to several trends in the vaccine field, including:

- **The Big 5** in vaccines have been GlaxoSmithKline, Merck, Novartis, Sanofi-Aventis, and Wyeth, but other big pharmas – Baxter, Pfizer, and Schering-Plough – may be entering the field. Greco said, "Pfizer is testing the water, but it is not yet clear what they are up to. Schering-Plough is acquiring Akzo Nobel's Organon BioSciences, which has biotech/vaccine activity." He added that big pharma needs a supportive environment, clear pricing policies, hates discontinuity, and likes predictability, "What is of most interest to them is market development, making sure normal markets can evolve, and long-term contracts, not a one-year contract…Big pharma is entering the field for blockbuster vaccines and high margin products…We may see a fractionization of the vaccine market in the future with cherry pickers going for the big targets, and treating vaccines just as a traditional pharmaceutical. It will be even more the case if we go to therapeutic vaccines."
- **New money** has been generated to support vaccine R&D and immunization programs, though biodefense "hasn't developed as much as expected."
- **Biotech companies** are becoming more important in the vaccine arena and innovation is increasingly being fueled by biotech with: a better understanding of etiology, design of new vaccines (antigens, constructs, adjuvant), and production and control of vaccines. Greco said, "Biotech also needs a supportive environment, but it is different. They need access to capital, and partnerships are a life or death issue for them…Biotechs are more open to (non-blockbuster vaccines), whether through good feelings, partly naiveté, or because they are more flexible…I think we still need big machinery (pharma) to pick up what biotechs may start initially."
- The **supply of traditional vaccines** is expanding through the involvement of developing country manufacturers. An expert said, "The vaccine area was a well-knit field with a few participants, easy to capture and understand. It will become less so in the future…But you will still have classical prevention vaccines which may not always be blockbuster vaccines which still need to be marketed."
- **Developing country vaccine manufacturers** are increasing, and they need support in meeting quality standards, appropriate pricing – not too low – and technology transfers and partnerships with big pharma. In particular, India is poised to become a very active, and lower price, vaccine manufacturer. Greco said, "My view is big pharma has been maybe a little slow on this."
- **More partnerships and less out-licensing.** Allan Jarvis Ph.D., vice president of corporate development at Sanofi-Aventis's vaccine division, Sanofi Pasteur, said, "Out-licensing is falling out of favor because the developer wants a more active role in what happens with the product ...Partnerships show an increasing degree of flexibility, and I think that is a good thing...Most partnerships will self-optimize over time, but that takes a long time. It is definitely a slow route. It is better to structure the business in terms of the capabilities of the partners. And it is best to first structure the development program, then add the appropriate business structure to it."

Asked if the vaccine environment is better or worse for a new startup than a big pharma, Greco said, "I think it is better. There is room for creativity." Dr. Gordon added, "I think it is getting better. Several new product indications are giving people confidence that products can get through the regulatory process. BioShield, despite the risks, is an opportunity…(And) there is a lot of money available in the venture capital and institutional funding worlds...But the business environment is a lot harder."

The challenges

Significant issues that the global vaccine industry is facing, include:

- **Supply.**
- **Regulatory.** An expert said the typical length of developing vaccines is increasing, not decreasing, "We need a single standard for quality and safety. New requirements may have a dramatic impact on supply."
- **Innovation.**
  - Biotech "has opened a wide array of opportunities for innovation, maybe too many because there are more risks and an increased failure rate for vaccines, which is approaching the failure rate for the pharma industry."
  - Delayed proof-of-concept.
  - Regulatory constraints.

- **Access,** which was described as a "huge and very complex issue."
  - A long-term strategy is needed.
  - There are already a lot of individual country initiatives.
  - Pricing policies need to be improved. Greco said, "Up to now, vaccines have been cheaper to market than pharmaceuticals."
  - New funding mechanisms need to be found.
  - Efforts need to be coordinated.
- **Cost.** An expert said the cost of vaccine development is increasing 15% a year.
- **Relationship with public authorities,** which Greco described as "at best, 'arduous.'"
  - Lack of transparency of negotiating mechanisms, which may be disrupted by political concerns, making it "not a very supportive environment."
  - Lack of consistency in goals.
  - Lack of real partnerships. An expert said, "I would argue that we might need to take a new perspective if we…don't want to end up in a lose/lose situation. Once (there is a) signed contract, I would say both parties should be willing to do their best to help the agreement to succeed."
- **Public perception and societal issues,** which may heavily impact immunization policies. Several sources described the vaccine market as "fragile," and there were numerous complaints that vaccine opponents get too much publicity. There was even speculation that Hollywood is making a movie that will glorify vaccine opponents, and experts are afraid that would have a very chilling effect on vaccination programs. Concerns center on:
  - Fear of the disease vs. fear of the vaccine. The fear of the vaccine may be greater than the fear of the disease when the disease has almost disappeared.
  - Individual rights vs. collective benefits.
  - Right and access to information (Internet).
  - Principle of precaution (risk free society) vs. protection of public health.

Dr. Gordon warned that building a sustainable vaccines business may not always be attainable. He cited several issues that need to be addressed, including:

- Can new players (vaccine manufacturers) compete with established multinationals?
- Are new markets – third world, biodefense, emerging disease targets – reliable? He said, "The experience with SARS, West Nile, and very likely bird flu is they are very important public health threats, but they are unvalidated and unconfirmed threats. In all three cases, companies have been asked to meet with governments and divert resources to address these threats. I know companies that spent tens of millions of dollars, and…found commercial losses."
- Is the pull incentive of advance market commitments sufficient to allow prediction of development costs and timelines?
- There is a tradeoff between established technologies and innovation.
- Untested pathways bring the potential for great benefits ***and*** new pitfalls.

What is needed to give the vaccine industry "a shot in the arm"?

- Support of upstream (academic) research, more epidemiology data, and more clinical trial sites, including increased interface between the academic world and industry. Greco said, "In this country, this is not so much of an issue any more, but in some parts of the world it is still a major issue."
- Even more creative alliances.
- Upholding of intellectual property (IP) protection.
- Appropriate pricing of vaccines.
- More transparent and more practical government procurement rules.
- Diversified financial support.
- Balanced regulatory requirements.
- Clear immunization policies.
- Responsible communication practices.

MANUFACTURING ISSUES

Dr. Helene Pora, director of marketing at Pall Life Sciences, which supplies filtration and separation technology to drug and vaccine manufacturers, predicted that novel technologies could have significant benefits for vaccine manufacturers by:

1. Providing more flexibility and higher throughput, which could help address potential shortage issues.
2. Helping to enhance the safety or robustness of the processes, which would also help supply.

U.S. manufacturing supply

Are there vaccine manufacturing supply constraints in the U.S.? Dr. Pora said, "At the moment, no, not strictly speaking. The truth is every now and then you get issues reported about a batch that is rejected, etc., so the potential shortage issue is always possible."

Is there sufficient manufacturing capacity in the U.S. for scale-up in case of a pandemic or other sudden increase in demand? Dr. Pora said, "At the moment, I would say it depends on the vaccine. Obviously, there are a lot of efforts to

build extra capacity for the flu vaccine in the U.S. because a lot of the existing capacity (for that) was in Europe, more than the U.S. For avian flu, existing capacity is probably a little stronger in Europe, but this should be overcome by the strong program in the U.S. in building added capacity."

Contract manufacturing organizations (CMOs)

Are U.S. companies building new vaccine manufacturing capacity or looking to outsource to CMOs? Dr. Pora said, "For flu, they are building out, not contracting. They really want to control it."

What is the role of CMOs? Dr. Pora said, "A lot of vaccine manufacturers are short of manufacturing capacity for clinical trial batches. While you are producing clinical trial batches you can't produce commercial product, so it ties up capacity. That's why CMOs have a very strong role in clinical batch production."

Several non-U.S. CMOs exhibited at the meeting, and even more attended the meeting. An official with a U.K. CMO said, "There is plenty of manufacturing capacity for monoclonal antibodies and proteins but not specialized vaccines using whole cells. There are only a handful of CMOs that can do Biosafety Level 3, which includes flu."

A U.S. CMO, which does mammalian cell vaccine manufacturing for Phase I-II-III trials, is considering offering commercial production capabilities as well. An official said there is a viral vaccine manufacturing shortage in the U.S., "The Big 5 have capacity but scale-up is a challenge even for them…And they have other products that compete for the capacity they have…Companies are looking at their pipelines to see where they can outsource more early stage manufacturing."

The business development director for a contract manufacturing firm said some companies are coming to his firm with "some very aggressive programs." He added, "Some companies have very, very aggressive programs and time scales. One proposed starting a program in 2004/2005...doing process development from scratch, assay and formulation development, process and assay validation, and three clinical trials – with a launch in 2009. That is a lot quicker than we've seen before, and it probably won't happen – though they are on schedule so far, so maybe it will…It is a highly competitive sector...It is clear that clients are under commercial pressure... It is not enough to have a good vaccine, good clinical results, or great technology. Success depends on effective and ***timely*** product development."

Developing country manufacturers

Asked if developing country manufacturers are likely to become major vaccine suppliers for the U.S. and/or Europe, an expert said, "I don't see why what has been true for pharmas might not become true over time for vaccines…(At the same time) I am a strong proponent of bio-equivalence of vaccines…If we relax those rules, we are opening Pandora's box."

An official with a vaccine manufacturer in India warned that he respects intellectual property (IP), but he called some formulation patents "immoral," including those on aluminum phosphate or aluminum hydroxide buffers, saying they are an impediment for developing countries. He called for legal issues like IP and TRIPS (trade-related aspects of intellectual property rights) to be made "more flexible" for life-saving vaccines. He also predicted that there would be consolidation among Indian manufacturers over the next several years as well as some Indian firms becoming multinationals.

TECHNOLOGY

Ann O'Hara, general manager of bioprocess for GE Healthcare, told manufacturers that vendors can be an important partner. Vendors can help reduce development costs and timing, improve production, and aid when quick distribution is required in a short time.

She outlined some ways vendor technology simplifies vaccine development and production:

1. Leading edge analytical technology to speed up analytics during development and batch release.
2. Supporting technologies that drive efficiency and save capital expense for cell-based production.
3. Disposable manufacturing solutions that speed up operations and lower costs. In vaccine production, she said disposables offer higher throughput, safer operations, lower buffer consumption, and reduce cleaning procedures.
4. Services that address workflow to improve quality, time, cost, and security of supply.

Vaccine manufacturers appeared very interested in alternative delivery systems. Terumo, for instance, was talking about a new 33 gauge needle that is supposed to reduce pain. The company has initiated a limited launch of that product in Japan, but was talking with other pharmas, and at least one large vaccine manufacturer appeared very interested in this.

REGULATORY ISSUES

Dr. Karen Midthun, deputy director of the FDA's Center for Biologics Evaluation and Research (CBER) declared, "It is not business as usual at CBER. We have adapted to challenges through extraordinary effort and proactive measures. Such approaches were used to respond to the West Nile virus threat to the blood supply, to the 2004 flu vaccine shortage, and with our current activities (e.g., pandemic preparedness)."

Major FDA vaccine initiatives include:

- Pandemic flu and emerging threat preparedness.
- Enhancing product safety.
- Manufacturing and product quality activities to ensure safe and effective products – review management, policy, critical path, and research management.
- Global collaborations.

Asked to comment on the proliferation of new vaccine regulations, Dr. Midthun said she doesn't see any excess of regulations, "We have a lot of regulations, and we follow those, but I don't see increased regulation. From my perspective, we have really tried to emphasize pathway development, so that we can really facilitate the development of products."

Asked if there are areas where CBER has had to pull back because of lack of funding, Dr. Midthun admitted the FDA has "a full plate," but she said the supplemental funding for pandemic and flu efforts was extremely helpful.

Asked about regulatory challenges for development done outside the U.S., Dr. Midthun insisted the FDA's regulations are the same wherever the manufacturer is located.

BIODEFENSE

Vaccine manufacturers seemed leery of getting involved in biodefense projects. As one expert put it, "We are perilously close to saying the government is crying wolf. In the past, it was three strikes and you are out. And we've had three strikes – three cases where industry stepped up in response to a declared threat and lost money because the threat did not turn out to be significant – SARS, anthrax, and West Nile. Avian flu is starting to look like it may not happen either. It is getting much more difficult to get companies involved in pandemic protection."

An official of the U.S. Department of Health and Human Services (HHS) said, "All of this is evolving in real time over the past three years on how both government and industry will move forward." He said Emergency Use Authorizations (EUAs) can speed approval, but they have never been used yet, and they still require:

- An unmet need (no other approved vaccine available).
- Validated manufacturing process at commercial scale.
- An appropriate animal model, which he suggested may be best done in an academic setting.
- Demonstration of safety and efficacy in people.

Is there an opportunity for companies to focus only on biodefense? Experts recommended against that strategy. One said PharmAthene may be the only pure biodefense company right now. Another expert said, "We don't have pure biodefense companies, but companies that are biotech with biodefense projects. To my mind, it is an open question whether we will ever get there (to pure biodefense) or if it is appropriate…I think it is more about developing platform technology." A third said, "I don't think there is an opportunity for a purely biodefense company." A fourth source said, "We started as a biodefense company and diversified. That speaks to how we got where we are." The HHS official said, "This (biodefense) is a $10 billion area. There is a lot of money in the area. But on developing a cohesive infrastructure to respond to the needs on a long-term basis, I don't think we are at that point yet."

VACCINE CULTURES

Egg-based vaccines are more difficult to produce and are weakly immunogenic with or without an adjuvant, experts agreed. Mammalian cells are replacing egg-based vaccines. Vero cell lines also are gaining popularity, particularly the Vero cell line initiated from the African green monkey.

ENTERIC VACCINES

Cholera

This is mostly a disease of developing countries. In developed countries, there is a 0.5% incidence in long-term travelers to endemic areas or people who consume raw shellfish. There is a need for a vaccine for endemic areas, travelers, and the military.

- **Berna Biotech's Orochol** was found not to be efficacious and is no longer being manufactured.
- **SBL Vaccine's Dukoral** was described as 60%-70% effective.
- **Avant Immunotherapeutics' CholeraGarde**, a single-dose oral vaccine, has completed Phase II studies in the U.S. and Bangladesh, and more Phase II trials are planned in Southeast Asia. An Avant official said, "We were going to do a Phase III trial of (this) cholera vaccine for use in the U.S. and Europe, but because of the safety studies, the Phase III would have to be about 5,000 patients, and it became uneconomical for us to do it. So, we announced we can't develop the vaccine for the U.S. and Europe. We are doing it for endemic areas with Gates Foundation money – but not for travelers or the military."

Enterotoxigenic *E. coli*

About a billion cases occur annually in developing countries, with 300,000-500,000 deaths a year, mostly children. This disease also affects 10%-25% of military troops, and 10 million cases occur in travelers from developed countries. SBL Vaccine's Dukoral cholera vaccine has "some efficacy," but a speaker said there is a need for an oral vaccine, and one is expected to start Phase I later this year.

Malaria

GlaxoSmithKline's RTS,S is the first malaria vaccine candidate to graduate from a pediatric Phase IIb trial to a full-fledge multicenter Phase III trial – which is ongoing at seven trial sites in five countries.

Typhoid

In developing countries, there are 20 million cases a year, with 200,000 deaths per year, but in the U.S. there are only 1,000 cases a year. However, patients who have contracted typhoid are susceptible to recurrence. Again, there is a need for a vaccine for endemic areas, travelers, and the military.

- **Berna Products' Vivotif** (Ty21a), a live attenuated vaccine in oral capsules that requires a booster every five years.
- **Sanofi Pasteur's Typhim Vi** or **Typherix**, both of which are one-dose intramuscular injections that require a booster every three years.
- **Avant Immunotherapeutics'** ***Salmonella typhi*** **Ty800**, which is now completing a 50-patient Phase I-II study and will start a Phase II trial later this year. So far, a speaker said, a single dose appears superior to four doses of Vivotif.

HIV Vaccines

A speaker pointed out some special ethical consideration with development of an HIV vaccine, including:

- False positive HIV tests with the potential for "social harm."
- Theoretical enhancement of HIV infection, both ***biological*** and ***behavioral***.
- Inherent conflict of interest in conducting the trials. He said, "A successful trial means that the best efforts at prevention counseling must fail."
- High care and treatment imperatives, especially for those who become HIV-infected. The speaker explained, "Some people may alter their behavior because they are participating in a trial which they perceive as affording protection. That is in the individual's head and not what we usually think of as a trial-related injury…but medical ethicists argue about this…It is controversial." Another expert added, "It is also a practical issue...We have no choice but to offer treatment for these populations."

Novartis has completed a Phase I trial of its HIV vaccine, but the data from that are not expected to be available until 2008. Novartis is looking at both intranasal and intramuscular administration.

Human Papilloma Virus (HPV) Vaccines

In the U.S., about 7,000 cervical cancer cases a year are related to HPV, and 530,000 HPV-related CIN (cervical intraepithelial neoplasia) lesions are treated.

Merck's Gardasil

Gardasil, which is currently approved in more than 60 countries, uses a proprietary amorphous aluminum buffer. Some U.S. localities are mandating use, but outside the U.S. the only country that is mandating it is Australia, which a Merck official said has already purchased the vaccine for its national program.

Asked about cases of Guillain-Barre syndrome (GBS) in people getting Gardasil, Merck officials insisted that this is not a problem. There were no cases of GBS in the Gardasil clinical trials and only four in post-marketing – and three of those had other explanations for the GBS (2 got Gardasil with Sanofi Pasteur's Menactra meningitis vaccine, and 1 patient had severe flu before getting Gardasil). Merck officials also said there has been no effect on use of Gardasil due to GBS, but Merck is starting another 43,000-patient safety study in the U.S.

One of the most interesting questions came from a Merck official who asked an FDA official to comment on the FDA's role in communication not only with the scientific community but also with the public on the benefits as well as the risks of vaccines. The FDA official didn't really answer the question except perhaps to bounce responsibility to the Centers for Disease Control (CDC), "CDC has an important role in communicating those types of things, for recommending vaccines."

A speaker said France is not yet reimbursing for Gardasil, but efforts are underway to get it reimbursed, and he doesn't believe Merck will – or should – allow the price "to go below

Gardasil Safety

Side effect	Gardasil	Amorphous aluminum-containing placebo	Saline placebo
Pain	83.9%	75.4%	48.6%
Swelling	25.4%	15.8%	7.3%
Erythema	24.6%	18.4%	12.1%
Pruritis	3.1%	2.8%	0.6%
	Gardasil	**Unspecified placebo**	
Fever	10.3%	8.4%	
Serious adverse events			
Headache	0.03%	0.02%	
Gastroenteritis	0.03%	0.01%	
Appendicitis	0.02%	0.01%	
Congenital abnormalities to babies of women who took Gardasil while pregnant despite warnings against that			
Total	15 cases	16 cases	
When end of pregnancy (EOP) within 30 days	5 cases	0 cases	
When EOP >30 days	10 cases	16 cases	

certain levels," so he concluded the price will be high – $400. Another speaker commented, "The U.S. price is $360 (for a course). I was surprised to see France has a substantially higher price."

Dr. Eliav Barr, head of biologic clinical research at Merck, said there is an "excellent opportunity for vaccinating men with this (Gardasil). We felt men really wouldn't want to be vaccinated. The rationale wouldn't be strong enough just to protect spouses unless they had an immediate benefit, hence the (HPV serotype) 6 and 11 components (which are protective of genital warts)…Genital warts are incredibly common, and (our) vaccine was (shown to be) effective 99% at licensure and is still 99% effective at update." In fact, he reported that Gardasil's efficacy in preventing CIN 2/3 is higher now (41%) than at licensure (34%).

Dr. Barr said the company had an expert panel look at the congenital abnormalities, "Their conclusion was that these were diverse morphology or very late-stage abnormalities, and it was difficult to find causality, so the expectation was that these results were probably not vaccine-related but vaccination during pregnancy should be avoided."

Upcoming Gardasil data include:

- Phase III trial in 16-26-year-old women on cross-protection efficacy. The analysis of that study is nearly complete and will be presented "soon." A Merck source said the preliminary data are "encouraging," but the company is holding off reporting on the results until the analysis is finalized and any ascertainment bias is addressed.
- Study 019 in 24-45-year-old women, with data expected in 3Q07.
- Adolescents Study 024-025, with data likely in 3Q07, on concomitant use with two Sanofi Pasteur vaccines: Menactra and Adacel, a pertussis (whooping cough) booster vaccine.
- Two studies on prevention in men: one in 3Q08 and one in 3Q09.
- PATH studies in Vietnam, Peru, and India on alternate dosing regimens, with data in 2008-2010.

INFLUENZA VACCINES

A speaker said the two main factors that determine the seriousness of an epidemic are: (1) degree of pre-existing immunity, and (2) the pathogenicity of the virus. In the flu epidemic of 1918, half the people in the world got sick, and more than 20 million died. Another speaker estimated that only one in three of at-risk people (35%) in Europe are vaccinated with seasonal flu vaccines, "The message is there are 144 million at-risk people who are not vaccinated. A preventable disease is not being prevented…and that makes pandemic management problematic."

Avian Flu (H5N1) vaccines

The avian flu doesn't just make people feel ill; pathological findings include lymphoid depletion, hepatic necrosis, renal tubular necrosis, and foci of necrosis in the brain and skeletal muscle. A speaker predicted that in a pandemic, without a vaccine, preventing the spread of infection of a highly transmissible virus will be difficult, surge capacity is limited, and the impact of antiviral drugs is uncertain. He said, "The Department of Health and Human Services (HHS) estimates that there may be enough vaccine in a year to immunize 15-20 million Americans, though the current estimate is six million doses in the U.S." He estimated that:

- 62% of patients who get avian flu will require advanced organ support.
- 76% will develop multi-organ failure.
- 58% will develop acute respiratory distress syndrome, and 90% of those will die.

Dr. Luc Hessel, executive director of medical and public affairs for Sanofi Pasteur and a member of the International Federation of Pharmaceutical Manufacturers & Associations' (IFPMA's) Influenza Vaccine Supply International Task Force, suggested that a pre-pandemic vaccine might be more effective than a vaccine given only when a pandemic occurs. With this approach, people would get one or even two pre-pandemic vaccine injections prior to the onset of any pandemic. The challenges with a pre-pandemic vaccine include: cross-protection, public health issues, acceptance by

Avian Flu Vaccine Status

Company	Vaccine	Type	Regulatory status
Pandemic vaccines			
GlaxoSmithKline	Daronrix	H5N1	Positive EMEA opinion 12/2006
	Pandemrix	H5N1	Accepted for EMEA review 01/2007
Novartis	Foccetria (panfluad)	H9N2 and H5N3	Positive EMEA opinion 02/2007
	---	H5N1	Submitted to EMEA 11/2006
Sanofi Pasteur	---	H5N1	FDA Advisory panel recommended approval 02/2007
Pre-pandemic vaccines			
GlaxoSmithKline	Pre-pandemrix	N/A	N/A
Novartis	Aflunov	H5N1	Additional data submitted in 11/2006

regulatory authorities and the public. Dr. Hessel called a pre-pandemic vaccine "a very interesting concept that needs to be further developed" and said it relies on three assumptions:

1. Developing appropriate immunological and virological methods to assess the protective effect of a pandemic vaccine.
2. Assess cross-protection of avian flu vaccine against the mutated human forms of the virus: **very promising results.**
3. Confirmation of the "prime-boost" effect observed in current studies when two doses of pre-pandemic vaccine is given several months apart: **encouraging results.**

European regulators have already issued guidance for registration of pandemic and pre-pandemic vaccines, and the FDA has put out draft guidelines. The World Health Organization (WHO) guidelines prepared for human pandemic vaccination are under review.

The U.S. government has admitted that there currently is not enough vaccine in the event of a bird flu pandemic, at least at the beginning of the pandemic. The WHO has ranked a global bird flu pandemic Level 3, which means "no or very limited human-to-human transmission," out of a possible 6 levels. Worldwide, there have been 275 confirmed cases of humans infected with H5N1 since 2003, and 167 of these have died. The most recent case was in Laos on February 27, 2007.

Sanofi-Aventis/Sanofi Pasteur's H5N1 vaccine

On February 27, 2007, an FDA advisory committee unanimously recommended approval of the first avian flu vaccine. Even though the data submitted to the FDA was from a small trial with only a small benefit, the panel concluded Sanofi's vaccine is safe and sufficiently effective to serve as a stop-gap until a better vaccine is available.

A speaker at the World Vaccine Congress said that data presented at that panel meeting on Sanofi's H5N1 vaccine indicate there are "no really remarkable adverse events after either the first or second dose," and he called this "pretty reassuring." He suggested the panel recommendation was predictive of FDA approval, but an FDA official emphasized, "We did discuss an H5N1 vaccine last month, but we haven't made a decision. We got a recommendation from the panel, but we have not acted on it yet."

Meningitis Vaccines

There was no information at the meeting on ACWY meningitis vaccines. However, an official of the U.K.'s Health Protection Agency said they had a meningitis-B vaccine in Phase I that has been licensed to the Serum Institute of India, which will incorporate it into their penta-valent vaccine (which is not intended for the Western world). He also indicated the Agency is in licensing discussions with Chiron.

Pneumococcal (PnC) Conjugate Vaccines

In the U.S. each year, pneumococcus causes:

- 700 cases of meningitis.
- 13,000 cases of bacteremia/sepsis.
- 71,000 cases of pneumonia.
- 5 million cases of otitis media (ear infections).

There are 90 serotypes of pneumococcus, but about seven cause the majority of disease throughout the world. Babies are the main transmitters of this infection. For every one case of pediatric vaccine-type invasive pneumococcal disease (VT IPD) prevented in the U.S., an expert estimated that more than two cases are prevented in adults, which he said makes vaccinating children even more cost effective.

GlaxoSmithKline

Glaxo is developing a PnC conjugate vaccine to compete with Wyeth's Prevnar but the FDA has asked for more information. Sources insisted that Glaxo will not give up on its vaccine, but they thought it likely that Glaxo will need a new trial, but likely only a bridging study, not a major trial.

Wyeth's Prevnar

Prevnar, which was approved in the U.S. in 2000, is now approved in 73 countries. It is currently the only FDA-approved pneumococcal conjugate vaccine. Peter Paradiso Ph.D., vice president of new business and scientific affairs at Wyeth, said Prevnar, a 7-valent vaccine, has had a significant impact on penicillin-resistant strains of pneumococcus.

An increase in pneumococcal infections due to the 19A serotype has been observed in the last several years. The concern is whether this is due to the vaccine or not, but Dr. Paradiso said that the same increase in 19A-associated disease has been seen in Korea, where the vaccine has not yet been introduced.

Wyeth is now working on a next-generation Prevnar with activity against 13 serotypes. In the completed Phase II trials comparing 7-valent Prevnar to 13-valent Prevnar, Dr. Paradiso said there was "quite a nice response" to both vaccines, with 90%+ response to each. He added, "We have shown that adding new serotypes with the same carrier protein will not adversely affect efficacy…Prevnar-13 will capitalize on the success of Prevnar and further increase the public health impact globally."

Dr. Paradiso also called for an improved PnC vaccine for adults. The current vaccine is 23-valent, but antibody titers and efficacy decline after five years, and re-vaccination with the same 23-valent PnC causes more severe adverse events, so it is generally only given once. And efficacy is very low in immunocompromised patients.

ROTAVIRUS (RV) VACCINES

Each year, rotavirus is responsible globally for an estimated:

- 111 million cases of gastroenteritis.
- 25 million visits to clinics/doctors.
- 2 million hospitalizations.
- 440,000 deaths in children under age 5. That's 50 deaths ***per hour*** every day worldwide, but only 50 deaths ***per year*** in the U.S.

There are many rotavirus serotypes, but most gastroenteritis is attributed to four serotypes: G1, G2P[4], G3, and G9P[8]. Dr. Leonard Friedland, senior director of vaccines at GlaxoSmithKline, said a meta-analysis of Phase II and Phase III studies of Glaxo's Rotarix RV vaccine found that, overall, 71.4% of RV was caused by the G2P[4] serotype. New data on this will be presented at a medical conference in May 2007.

Treatments are primarily limited to fluid and electrolyte replacement, and prevention is mainly good hygiene practices and frequent hand washing. The goal of rotavirus vaccines is to protect against moderate/severe disease, prevent hospitalizations and death, reduce morbidity and socioeconomic burden, and attenuate severity and duration of illness.

RV vaccine efficacy appears lower in developing countries (e.g., South America) than in Europe. Dr. Friedland said, "There is much speculation about why…Yes, the vaccine efficacy is slightly lower in Latin America than in Europe, but it is still high in Latin America and will have an important impact there."

One of the problems in convincing parents in developing countries to inoculate their children against rotavirus appears to be the fact that the vaccine is not 100% protective against gastroenteritis. An expert from a developing country said parents may think the vaccine is ineffective if a substantial number of children still get gastroenteritis even with the vaccine. Dr. Friedland responded that this makes it important to manage parent expectations, "A parent might feel if a child comes down with a gastroenteritis illness after vaccination that there was a vaccine failure…So, I think it is important for public health officials and practitioners to educate the patient population about the benefits of vaccination and the limits of vaccination as well. This is not an all-cause gastroenteritis vaccine. It is a rotavirus vaccine, and rotavirus is the most common cause of gastroenteritis…We need to educate people on limitations of the vaccine."

Wyeth's RotaShield

RotaShield was withdrawn from the market in 1999, less than a year after it was launched due to concerns over intussusception (bowel obstruction). Dr. Oren Cohen, Chief Medical and Scientific Officer of Quintiles Transnational Corp., pointed out that initially there were only two reports per month of intussusception (IS) with RotaShield, but the signal of a problem was clear from the beginning, "Even the first six cases of intussusception in 1Q99 represented a signal."

Some experts are now suggesting that the withdrawal of RotaShield was an over-reaction. A speaker called the withdrawal of RotaShield "a setback for rotavirus vaccination" but a stimulant for the development of new vaccines. However, new RV vaccines must now carefully monitor cases of IS.

Merck's RotaTeq

This 3-dose oral vaccine was approved by the FDA in February 2006, and it is currently the only FDA-approved rotavirus vaccine. It can be given with other pediatric vaccines.

On February 27, 2007, the FDA notified healthcare providers and consumers about 28 post-marketing reports of intussusception following administration of RotaTeq (some after 1 dose, others after 2 or 3 doses), and 16 of these infants required hospitalization and surgery. However, the Agency noted that (1) IS can occur spontaneously in the absence of vaccination, (2) how many of the 28 cases are due to the vaccine is unknown, and (3) the number of cases doesn't exceed the expected background rate. The FDA said it issued the notice to encourage reporting of other IS cases in the past or future and to remind people that IS is a potential complication of RotaTeq.

Several sources said the FDA notification on RotaTeq may have caused more confusion than clarity – with some doctors assuming that the notification meant there is a growing concern with IS, not that the IS rate remains within the acceptable range. The Centers for Disease Control and Prevention (CDC) also issued a notice, and some experts described that as a "clarification" of the FDA announcement. The CDC said, "We are not surprised by the number of reported intussusception cases following RotaTeq vaccination …The number of intussusception cases reported to date after RotaTeq administration is consistent with the number of cases we expected to see based on background rates in unvaccinated children…This notice does not mean there is a problem with the RotaTeq vaccine."

RotaTeq Efficacy

Measurement	RotaTeq
First RV season	
Efficacy against severe gastroenteritis	98.2%
Efficacy against any gastroenteritis	73.8%
Second RV season	
Efficacy against severe gastroenteritis	88%
Efficacy against any gastroenteritis	63%
Europe	
Reduction in hospitalizations/emergency department visits vs. placebo	95%

Dr. Max Ciarlet, associate director of vaccines and biologics at Merck and clinical lead for the RotaTeq franchise, provided an IS update at the World Vaccine Congress, based on post-market surveillance. He said that, so far, there have only been 6 confirmed IS cases with RotaTeq vs. 5 with placebo (for a relative risk of 1.2), concluding, "Among more than 3.5 million doses of RotaTeq in the U.S., 28 post-marketing cases of IS have been observed since introduction. The observed IS rates (with RotaTeq) are not greater than expected."

Dr. Ciarlet said data on the efficacy of RotaTeq in the third and fourth RV season post-vaccination will be presented at the end of this year, but he didn't say where that data would be available. However, he insisted that the third dose of RotaTeq is very important and urged doctors not to skip it. He said, "The third dose really does make a difference."

Ongoing and planned studies:

- Clinical trials in Asia and Africa to begin enrolling patients this month.
- Open-label vaccine effectiveness project in Nicaragua started in 4Q06.
- HIV positive infant study to start in 2Q08.

GlaxoSmithKline's Rotarix

Rotarix is already approved in 90 countries, starting with Mexico in 2004, but it is not yet approved in the U.S. Most experts said they expect U.S. approval "within a few months," but an expert said he isn't sure that Glaxo has even submitted it to the FDA yet. Rotarix is an oral, two-dose, live, attenuated, human, lyophilized vaccine with a $CaCO_3$ buffer. It is well-tolerated and can be safely and effectively co-administered with other pediatric vaccines. It has been tested in more than 40,000 people, primarily in Europe and South America. Glaxo's Dr. Friedland insisted Rotarix is ***not*** associated with an increased risk of IS.

Dr. Friedland outlined future plans for Rotarix:

- Post-marketing safety monitoring to detect adverse events.
- Safety studies in specific populations – e.g., pre-term infants in Europe, immunocompromised infants in South Africa, twins in the Dominican Republic.
- Surveillance for IS.
- Additional safety and efficacy data from Asia and Africa.
- Monitoring of vaccine efficacy and the impact on sero-type distribution.

A source said that Glaxo's Rotarix is unlikely to be priced less than Merck's RotaTeq because Glaxo's buffer is expensive. "It's not a difference in the container cost but the buffer cost that will keep the price of the two vaccines comparable," he explained.

Intussusception with Rotarix

Time period	Latin America and Finland Phase III trial (ROTA-023)		
	Rotarix	Placebo	Relative risk
0-31 days (most likely time period)	6 cases	7 cases	0.85
0-100 days	9 cases	16 cases	0.56
0-1 year (efficacy subset)	4 cases	14 cases	0.28

Specific Companies

Generex/Antigen Express

Antigen Express is working on a synthetic avian flu vaccine – that is not dependent on eggs or cell-based technology – that can be mass produced utilizing existing technology. The vaccine doesn't prevent infection and/or limit the severity of H5N1 infection in humans, but it may boost the effect of a traditional avian flu vaccine.

Antigen Express has two platform technologies to augment T-cell responses:

1. Ii-Key hybrids. This is the technology being used for the avian flu vaccine.
2. II protein suppression.

Ongoing and planned studies include:

- Formation of active hybrids in DR4 mice.
- Mouse challenge studies.
- Hybrids/rHA studies to further optimize immune response.

Efficacy of Rotarix

Measurement	European Phase II trial	Latin American Phase II trial	Asian Phase II trial	Latin American Phase III trial (ROTA-023) at 1 year	Latin American Phase III trial (ROTA-023) at 2 years	European Phase III trial (first season) *
Number of patients	N/A	N/A	N/A	Rotarix = 31,673 Placebo = 31,552	N/A	Rotarix = 2,646 Placebo = 1,348
Prevention of severe RV gastroenteritis (GE)	90%	86%	N/A	85%	81%	96%
Prevention of RV GE hospitalization	---	79%	N/A	85%	83%	100%
Prevention of any GE hospitalization	---	---	N/A	42%	39%	75%

*** Second season data will be presented at a medical conference in May 2007.**

- Phase I-II clinical trials in Lebanon are a hybrids-only vaccine, with individual hybrids by escalating the dose protocol. A Phase I trial is underway in healthy volunteers in ***Lebanon*** to see if the vaccine will generate immune responses. Why Lebanon? Remember that Generex did a trial of its transmucosal insulin in Ecuador. Douglas Powell Ph.D., director of immunobiology for Antigen Express, said the FDA wanted a proof-of-principle (Phase I) trial in healthy individuals, and the company is looking to partner with a larger company for the next stage.

Dr. Powell cited these advantages to a synthetic vaccine:

- May decrease the amount of conventional H5N1 needed, making a conventional vaccine go further.
- Manufacturing of Ii-Key peptides can be performed quickly, is cost effective, and can use existing facilities.
- May provide ***some*** level of protection in the absence of any other vaccine.

INTERCELL. Dr. Karen Lingnau, head of pharmacology and toxicology, said her company has two adjuvants in preclinical development:

- ISIS30.
- ISIS31. This just finished a Phase I clinical trial with a TB antigen, which found it safe in humans and "very immunostimulatory, especially for T-cell response." This will now go to a Phase Ib trial in TB patients.

MEDIMMUNE. Dr. Kathleen Coelingh, senior director of scientific affairs at MedImmune, said her company is working on several next-generation innovations:

- Plasmid rescue for vaccine seed strains.
- Cell culture for bulk vaccine production. She said, "There is a huge gap in the amount of vaccine that can be made for a pandemic compared to what we annually can produce. Using eggs in our facilities in the U.K., we can produce 50 million bulk doses of monovalent vaccine per month, which can easily be scaled up, but we also need to scale up egg production, which would be an issue if the avian flu decreased the number of eggs available." She added:
  - Cell culture has dramatically better process yields.
  - MedImmune plans to use a dog kidney cell (MDCK) line, which is more scalable and the "industry standard." She said, "We currently have cell culture manufacturing here in Maryland, and we are planning to ramp that up shortly so we can produce 360-500 million doses within a few years."
- Alternative delivery devices, including blow/fill/seal and multi-dose delivery systems.

SANOFI PASTEUR. An official said his company is focused on:

- New antigens.
- Alternate routes of administration (non-intramuscular).
- Agents to enhance immune responses.
- Tools for improving R&D and manufacturing.

MISCELLANEOUS

Passive immunotherapy. Omrix Biopharmaceuticals currently markets an intravenous vaccinia immunoglobulin (VIG) for the treatment of smallpox vaccine-related complications and is working on a high-titer intramuscular formulation (HT-VIG) for smallpox vaccine-related complications and treatment of smallpox. The company also is developing a West Nile virus immunoglobulin (WNIG) for the treatment of severe West Nile virus infection. There was no information on these products at the World Vaccine Congress, and sources asked about them were dubious about their efficacy and utility.

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