Trends-in-Medicine

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by D. Woods

SUMMARY

Vaccine growth will be ~8% annually over the next 10 years, driven by expansion into new disease targets – particularly cancer, dengue fever, Alzheimer's disease, and tick-borne disease – and broader age groups vaccinated with current vaccines. ♦ The 2009 swine flu epidemic will spur even more investment in pandemic research. ♦ The major threats to the U.S. vaccine market are increasing regulatory safety requirements and a growing anti-vaccine movement. ♦ The U.S. economic stimulus package will add some short-term funds to pandemic vaccine manufacturers. ♦ Vaccine manufacturers are watching the possibility of a pathway for biosimilars in the U.S., but that is not discouraging them – yet. ♦ Manufacturers are confident there will be sufficient supply of pandemic and seasonal flu vaccines for the next flu season. ♦ GlaxoSmithKline was recognized as having the best vaccine pipeline; Sanofi Pasteur partners on almost everything, and Merck is doing more partnering; Novartis believes the future is vectors, adjuvants, and cell culture-based vaccines; Wyeth is waiting for FDA approval of a revised Prevnar vaccine. ♦ The outlook for the biologic market is good, although manufacturers worry about the high cost of research. ♦ New technologies to watch include reverse vaccinology, new administration methods such as nasal sprays and patches as well as new manufacturing processes.

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WORLD VACCINE CONFERENCE

Sterling, VA
April 21-23, 2009

Meeting only a few days before the swine flu (influenza A H1N1) hit, vaccine industry representatives were generally upbeat about the industry's direction, seeing growth in all areas. The recent epidemic may give vaccine makers a much needed shot in the arm, with money in the fiscal year 2009 supplemental appropriations bill currently in Congress designated for vaccine production and increased awareness of the need for better preparation for pandemic disease. Even without the appearance of swine flu, industry officials see enormous opportunities to expand existing vaccine use into broader populations. The industry is also working on new manufacturing and administration technologies, facilities, and prophylactic vaccines for cancer and other diseases.

Vaccine growth is expected in pediatrics, therapeutics, and new vaccines targeting cancer. Industry expects about an 8% annual growth rate over the next 10 years to about $96 billion in sales. The rate of growth will slightly decline as emerging countries' economies become more stable. Drivers for growth include:

- New disease target possibilities, i.e., Chlamydia, gonorrhea, cancer
- New administration methods
- Expanding targeted age groups
- An improving economy that will increase focus on preventative healthcare in the developing world
- New promising technology on the horizon

Dr. Peter Khoury, vice president of global marketing, vaccines, for Baxter Bioscience, gave an overview of the market, "The vaccine market is set to expand into new disease targets, broader age groups vaccinated with current vaccines, and vaccines coming to the market." Dr. Khoury said that the vaccine market has a growth rate projected at 8%-13% per year, "In 2009 we expect the market to be $23 billion worldwide, growing to almost $40 billion by 2013." Margie McGlynn, president of Merck's global vaccines and infectious diseases unit, estimated the market somewhat lower, projecting $30 billion by 2014.

Dr. Khoury said that smaller companies are working in the arena of potential blockbuster products such as nosocomial vaccines (Intercell and Novadyne Therapeutics have development programs).

- *Clostridum difficile* (*C. diff*). Sanofi just purchased Acambis, which is developing a vaccine.
- Human immunodeficiency virus (HIV). Cytel is using its DNA vaccine technology.

- Vector-borne diseases, Chikungunya virus, Lyme disease, West Nile virus, Hendra virus, and Nipah virus.

Additional infectious disease targets include mycobacterium tuberculosis, mycobacterium leprae (leprosy), Brugia malayi (elephantiasis), and *Schistosoma mansoni* (schistosomiasis).

Tick-borne encephalitis (TBE) is a vector-borne disease for which there is a vaccine (Baxter). (i) vector TBE is a serious, acute, central nervous system infection which is spreading throughout Western and Eastern Europe, with unknown rates of infection in the southeastern European areas. Dr. Khoury said, "It is a notifiable disease in 16 European countries and in three non-EU member states, Norway, Russia, and Switzerland. It is thought to be endemic in 27 European countries. Even outside of Europe it is endemic in Mongolia, China, Kazakhstan, Japan, and South Korea. 157,584 cases were documented between 1990 and 2007, and there has been a dramatic increase over 30 years." High vaccine rates in Austria are leading to a dramatic decrease in the disease there.

New Vaccines Targeting New Age Groups

Vaccine	Traditional target	New Target
Influenza	Infants and elderly	Universal coverage
Streptococcus pneumoniae	Infants and toddlers	Elderly
Meningococcal disease	---	Elderly
Rotavirus	---	Everyone
Human papillomavirus (HPV)	Girls	Boys
Herpes zoster	---	Adults 60+
Respiratory syncytial virus (RSV)	Infants	Children, women of reproductive age
Cytomegalovirus	---	Transplant patients, women of reproductive age
Chlamydia	---	Men and women

Opportunities and Challenges of the Vaccine Market

Category	Situation
U.S. market	
Strengths	Historic successes, innovative technologies, improved health cost savings
Weaknesses	Expensive and lengthy R&D process, high cost to entry, market consolidation
Opportunities	New disease targets, improvement of existing vaccines, changing demographics
Threats	Anti-vaccine movement, developing world accessibility, adequate preparedness
Developing world	
Strengths	Favorable demographics, increasing focus on preventative care, momentum of NGOs
Weaknesses	Developing business models, regulations/restrictions, distribution channels and access
Opportunities	Private/public cooperation, vaccine education, growing economies and disease targets
Threats	Misinformation/cultural beliefs, funding priorities, intellectual property protection

New Disease Targets for Vaccination

Disease	Annual cases	Manufacturer
Cancer	25 million	GSK, Merck, Dendreon, Geron, Chiron, others
Dengue fever	50 million	GSK, Sanofi Pasteur
Epstein-Barr	N/A	GSK, AstraZeneca
Stomach cancer	N/A	Novartis

What is causing increasing TBE rates?

- Improved surveillance, identification, and diagnosis of TBE in humans.
- Human population is increasing, and there is a migration to suburban areas.
- Changing leisure habits, with greater exposure to vectors and to an animal reservoir of ticks.
- Displacement of human populations (conflicts).
- Increased reforestation (greater deer population, greater tick population).
- Other potential contributing factors (global warming impacting distribution of vectors, increasing costs for fossil fuels, demand for native wood for heating).

Projected Vaccine Market Growth by 2013

Vaccine type	Annual growth rate	Value in 2013	Driven by	Most prevalent
Pediatric	~9.7%	$17 billion	Strong growth in emerging markets and in sales of new pediatric vaccines	Meningococcal vaccine as it gets approved for children as young as 2 months of age for the ACYW conjugate
Adult	~11%	$5.5 billion	New vaccines for the elderly	Alzheimer's, nosocomial vaccines
Influenza	~15%	$6.4 billion	Increased production, vero cell culture, expanding target groups, pandemic planning	Seasonal, pandemic
Prophylactic cancer	12%	$4 billion	Introduction of Gardasil (Merck) and Cervarix (GlaxoSmithKline) in new markets, increase in uptake due to the high efficacy and cost benefit	Cervical
Hepatitis	11%	~$2.7 billion	Improvement in efficacy, vaccination of traditional non-responders by a more efficacious vaccine	A and B
Therapeutic	60%	$3.3 billion	Targeting cancers and addiction	Prostate, pancreatic, leukemia, myeloma, abdominal, breast, brain, lung cancers, etc.; addiction: nicotine, cocaine

Dr. Khoury said that one of the biggest threats to the U.S. market is the anti-vaccine movement, "which led to much disinformation, not only on the side effects of vaccines, but also the association of autism with MMR (measles, mumps, rubella vaccine), the primarisol controversy, campaigns against cervical cancer vaccines – all hurt the industry." This was a theme throughout the conference, and industry reps blame the media for much of the trouble.

Vaccine administration. An estimated 12 billion injections are given worldwide each year, and problems include:

- Dangers of needle stick injuries, contamination, and disease transmission.
- Lack of proper training, accessibility, storage, cold chain, and patient compliance and convenience.
- Needle stick injury estimates for healthcare workers per year are 66,000 cases of Hepatitis B, 16,000 cases of Hepatitis C, and up to 5,000 cases of HIV.

Advances in vaccine administration:

- Oral vaccines.
- Intranasal vaccines.
- Microneedle technology. Sanofi will use this with its egg-based flu vaccine later this year.
- Transdermal patches. Intercell/Iomai is developing transdermal patch technology, and it should be launched in the next few years.
- Pulmonary administration and needle free injections.

Promising Vaccines

Vaccine type	Manufacturer
Alzheimer's	Wyeth
Cervical cancer	GSK, Merck
Clostridum difficile	Sanofi Pasteur/Acambis
Dengue fever	GSK, AstraZeneca
Epstein-Barr	GSK, AstraZeneca
Herpes simplex	GSK
HIV	Cytel
Influenza	CSL Biotherapies, Nabi, VaxInnate, Vaxin, Novartis
Malaria	GSK
Meningococcal	GSK, AstraZeneca, Novartis, Wyeth, Sanofi Pasteur
Multiple sclerosis	Bayhill
Nicotine addiction	Nabi
Non-small cell lung cancer	GSK
Non-typeable Haemophius influenza	GSK
Pneumococcal	GSK, Nabi
Rabies	Crucell
Rotavirus	Novartis
Stomach cancer	Novartis
Tick-borne encephalitis (TBE)	Baxter, Novartis
Tuberculosis	Sanofi Pasteur/Statens
Type I diabetes	Nabi

National Vaccine Plan Implementation

Stimulus package problems

Dean Mason, assistant vice president, global vaccine policy at Wyeth, said that it is very difficult to prepare 10-12 year immunization plans. He said that the stimulus package money awarded to the states will probably occur in September 2009 and should be spent by December 31, 2009, "We are not certain if any funds will be allowed to carry over after that date, and this is one of the questions for which the Centers for Disease Control and Prevention (CDC) will give further guidance. These funds are separate and distinct from the Section 317 grant awards, which was an increase of $30 million in fiscal year 2009 compared to fiscal year 2008. That (stimulus package) money will be primarily spent on vaccine purchases, but some will also be dedicated to innovative projects, perhaps to raise coverage among disparate populations. It will also go towards capital decisions that states may make for expending these monies, for example on computers or to enhance registries. You might think that the states were thrilled with the monies, but, indeed, while they welcome it, it raises a number of new problems for the states. It's a good example of unanticipated consequences reflected or not in the national vaccine advisory. States will be hesitant to hire personnel. When the money is gone, those personnel, because of obligations of the states, will be hesitant to do anything. It will be state dollar purchases after the federal government retreats from the stimulus. States may have policies in place and programs that don't have adequate funding, but no expansion will be done of that particular funding even though the need is there."

Questions for the government

Mason said that Wyeth is committed to development of a national strategic plan, but added, "We believe it would be further enhanced if the National Domestic Preparedness Organization (NDPO) also provided a rationale for vaccine prioritization…It would be helpful for Wyeth if the government described some of the incentives it envisions for R&D, especially for vaccines that have little market value, which might include collaborative research, guaranteed market contracts, and streamlining the regulatory process…The vaccine program has eroded the private market, yet there remains a private market, and as long as the balance remains, that is significant."

Mason added that vaccine safety is of paramount importance, but that no vaccine has zero risk, and Wyeth would like a better government definition of risks and safety signals, rather than automatic surveillance after adverse events. And he said that communication is important between vaccine manufacturers and the government, "We certainly do not point the finger at other manufacturers; we had a shortage of Prevnar in the early 2000s. We remain committed to that sort of cooperation with the federal government should we have supply shortages in the future."

Public fear of vaccines

A running theme throughout the conference was that of public skepticism and fear of vaccines. However, that fear may subside at the prospect of the new influenza A H1N1 strain returning in the fall.

Wyeth's Mason said that the rationale for requiring vaccines should be a state strategy, "Courts have agreed that the benefit to society outweighs the individual benefit when evaluating daycare and school level requirements. This has been one of the best public interventions – has increased school attendance – and we support the recommendations as established…We believe that an immunization schedule is essential."

He said that a major goal for his company is the introduction and use of its Pneumococcal 7 vaccine (Prevnar), especially in developing markets.

Private/public partnerships

Marguerite Baxter of Novartis Vaccines talked about private/public partnership needs:

- A policy framework sustains and rewards innovations.
- Innovation needs to be evidence-based.
- Framework must be flexible enough to respond to evolving health challenges.
- A litigious environment hurts incentive to manufacture vaccines and bring new vaccines to market.
- It is important to sustain a stockpile approach and policy.
- Only pediatric vaccines and childhood vaccines are included in the stockpile plan.
- The first meeting of the vaccine injury compensation table group went well.

Baxter said that two committees in Florida's state legislature have passed legislation which now goes to state senate committees that would make it a criminal act for a pediatrician to administer certain vaccines to children under the age of 6, despite proof that the vaccines are safe, and she warned that these types of actions might spread to other states.

Merck's Dr. Laura Efros said that the goals of the national vaccine plan include developing new and improved vaccines in the U.S. and worldwide, and the list of new vaccine targets "must be prioritized based on the health burden and shared overall relevant federal agencies. We also recommend that these priorities include vaccines for adult and immunocompromised populations."

Dr. Efros said that Merck is a founding member of the 317 Coalition, which she hopes will expand enough to cover the administration fee, "making sure providers are adequately reimbursed for providing services for Medicare. We support efforts for coverage of vaccines and to simplify reimbursement for providers. This is growing as there are more vaccines for (the Medicare) population." Challenges, she said, include providing and improving coverage rates for adults.

Merck has specific programs aimed at covering extended payment terms, reimbursement support services, cervical cancer, other HPV disease and is working to "reduce uncertainty and take away disincentives." Merck has the first vaccine patient-assistance program for adults and the industry. Any uninsured adult in a recommended population with income below 2% of the national poverty level is eligible for certain vaccines. In other countries, Merck is accelerating access to its new Gardasil and RotaTeq vaccines. In Nicaragua, more than 85% of infants have been vaccinated, and 3 million doses of Gardasil have been distributed in Global Alliance for Vaccines and Immunization (GAVI)-eligible countries.

Supply and Distribution

Phil Hosback, vice president of vaccine development for Sanofi Pasteur, said, "Ensuring vaccine supplies was originally going to be part of this panel. In terms of overarching comments on the national vaccine plan, it's great that we have an ambitious plan, and it should be ambitious, but in some sense we need to go back to the basics by using new tools (and learn) how best to educate and communicate in order to increase vaccine rates in all populations. We are stagnating a bit and backsliding, whether it's the economy or anti-vaccine movements…We have to get back to the basics, and we have to re-educate. If we bring new vaccines the same way it was done before, we're going to end up in the same place we are today. Goal No. 1 is to develop new vaccines. The easier ones we've already gotten, and the newer ones will be a lot more difficult. It would be very helpful to make sure that we have appropriate targets that we can all focus our resources and efforts on in order to develop new vaccines. I was happy to see some discussion of vaccines on nosocomial (hospital-acquired) infections, antibiotic resistant infections, such as methicillin-resistant *Staphylococcus aureus* (MRSA), or tuberculosis (TB), and I'd like to see these in the top 10 of any list."

As for vaccine supply, Hosback said, "Manufacturing vaccines is very complex, and it's my belief that having supply chains will always be challenging. They are much more complex than drugs, and they don't always grow and respond in relation to demand. If one manufacturer is having a problem, it does take time to respond and fill some of the gaps and needs…We sometimes have bumps in the road, and maybe we need to be rethinking in terms of validation and FDA approval." He said that Sanofi Pasteur's new facility is "out of the gate – that facility is up and running…The second component of ensuring vaccine supply is a return on investment. It costs $1,500 to immunize a child through 18 years of age, compared to $45 twenty years ago. Should we rethink how we value vaccines?"

Hosback talked about why manufacturers left the flu vaccine business, "A couple of manufacturers decided not to reinvest because then (9-10 years ago) flu vaccine was only $1.80 a dose. To get facilities back to speed involved gutting them, etc. Flip the switch a few years later, and the vaccine was $6 a dose in the early 2000s, and manufacturers are back on board. Fair valuing vaccines will encourage participation. Vaccines like shingles, rotavirus, MCV4 – they are all being made because the return on investment was clear for us as manufacturers."

Sanofi Pasteur has shortened or lowered the amount of vaccine it has in the supply chain. The CDC and other programs used to carry six months of product in various parts of the chain, but now it's down to four to six weeks. Hosback said, "We are in a situation today where we might be worse off than in the past…We have to rethink how we think about the supply chain."

Asked how manufacturers are going to handle legislation which would authorize the FDA to oversee biologics, Hosback said, "There exists a pathway for follow-on biologics…where they are quickly following competitors if they have the ability to invest." He said that there are potential competitors coming on line, including manufacturers in other countries, who "are scaling up and rushing to get into the vaccine market." Novartis's Baxter added, "The good manufacturing practice (GMP) standards that vaccine manufacturers are held to in the U.S. and in Europe are quite significant, and my colleagues would agree that if we took a snapshot of the past five years, the development pathway, the number of subjects required to bring a product to the market, particularly in the U.S. and in Europe…and the regulatory standards are significant and will pose significant challenges (to manufacturers outside the U.S.). It's our read, looking at the legislation on file, that they don't erode the GMP standards for our industry. They make some modifications of biologic regulatory pathways, but it doesn't change the standards of the manufacturing practice."

Asked how the manufacturers are working to avoid disruption in supply, Hosback said, "You see supply disruptions for a whole host of reasons…Certainly when you have a legacy product…it gets more difficult to reinvest. We reinvest anyway because we have to…There are multiple reasons (for problems); it's the nature of biologics. I don't think we're ever going to have a perfect supply chain." Dr. Efros added that Merck is making "a very significant investment in making whatever modifications are needed – upwards of a billion dollars in improved and new facilities. The manufacturers here plus some others have made $4 billion in investments in just influenza, and the bulk has been in our manufacturing capacity."

Pandemic and Seasonal Flu Vaccines

Dr. Beatrice De Vos, vice president, global scientific and medical affairs, at Sanofi Pasteur, said that adjuvants will give manufacturers a 10- or 20-fold increase in production. This year, Sanofi Pasteur set up five-year contracts with the companies that produce adjuvants and antigens.

Another part of Sanofi's program is cell-based technology. Dr. De Vos said, "We believe that we have moved the field forward and have been awarded six contracts to develop cell-based technology. We like egg-based and cell-based technology, and we are trying to stimulate both of these processes. Cell-based influenza vaccine provides some advantages, but so does the egg-based. The company has begun Phase III seasonal vaccine efficacy trials with the cell-based manufacturing process. It has completed a Phase II/III seasonal vaccine immunogenicity trial in children and completed two new seasonal vaccine Phase I trials.

One was filed in 2008, and a BLA will be filed soon. Three of its contractors have produced pandemic vaccine lots, four have access to proprietary adjuvant technologies, and three INDs have been filed. Six out of six projects are still active, and three contracts are under review at various stages to see if the company will go forward. Dr. De Vos said, "We knew in the beginning that there would be some winnowing down. We are in process of reviewing the six contracts."

Sanofi Pasteur also has a partnership with Novartis in Holly Springs NC which will be the first cell-based vaccine program facility in the U.S. The U.S. government funded 40% of the building's cost, and the company will get five years of commercial production. It will produce two commercial lots of its choice, and there are options for 20 years beyond that. The facility will be able to produce 150 million doses of pandemic vaccine. Sanofi also has an arrangement with Novartis so that if an emerging pathogen of interest comes up in the 25-year period, Sanofi will have negotiation rights to transition to a different kind of vaccine.

Obstacles/challenges to this new technology include:

- Comparison of egg- and cell-derived vaccines are complicated by the fact that vaccine seed is derived from eggs.
- FDA concerns persist about the safety of the vaccine (particularly a live vaccine) produced in permanent cell lines.
- Manufacturers concern about overcapacity.
- U.S. government policy – Congressional Budget Office (CBO) white paper – raised questions and concern about the value of cell-based strategy. Dr. De Vos said that this paper raised concerns that Sanofi Pasteur's $1.3 billion programs couldn't solve the problem for the world, "We have no opinion one way or another. It was a little challenging to see CBO take on our $1.3 billion program."

- Efficacy trials hampered by unpredictable influenza infection rate at the study sites.

On Sanofi Pasteur's pandemic flu program, she said, "We've been able to stimulate egg-based production, increase egg-based production with one of our partners – to the point where in a year or two, we will have production capacity of 150,000 eggs per day." The company has one pandemic inactivated split vaccine and three inactivated split vaccines in clinical development. Formulation is antigen only, but adjuvant formulations are in clinical development.

Sanofi Pasteur's seasonal vaccine supply "looks a little better. We have more inactivated split vaccines (five) and four inactivated split vaccines in clinical development." Dr. De Vos said that her company hopes to reach the goal of 40 million doses this year for the critical workforce.

The company has these contracts for infrastructure development:

- Retrofit MedImmune 2010 and Sanofi 2011.
- Cell-based facility NVD 2012.
- Egg supply – extend current contract, new award in 2010.
- Storage formulation and filling contracts.
- Planning a cell-based facility in the U.S. like Novartis's.

The future for advanced development of vaccines includes:

- Antigen-sparing
- Recombinant
- Universal vaccines
- New emerging disease targets

For 2012 and beyond, Dr. De Vos said, "We want recombinant vaccines and adjuvant production (two to three adjuvants) on U.S. soil by then as well as cell-based production."

Debbie Drane, senior vice president, R&D, and divisional manager at CSL Biotherapies, created a buzz when she said that results from a Phase II trial of her company's seasonal flu vaccine showed that it also gives protection against pandemic flu, "People vaccinated with seasonal vaccine were protected against pandemic flu. We were definitely not expecting it."

The Iscomatrix vaccine for influenza uses a saponin-based adjuvant. The vaccine uses *quillaia saponins*, which comes from the bark of a tree indigenous to Chile and Peru and which is cultivated in northern India. Crude *quillaia* is used in agriculture, cosmetics, food and beverages, and mining and has been used in veterinary vaccines since the 1950s. A number of companies use saponin-based adjuvants, and the most well known is Antigenic's QS21 saponin. QS21 is in late-stage development at Wyeth.

The Iscomatrix adjuvant is a complex of oscoprep saponin, cholesterol, and phospholipids. It provides some stability to the saponin and a good safety profile. Cross protection is rapid, persistent, and efficient with the Iscomatrix vaccine. Drane said, "What this means is that you get very strong antibody responses. You get increased magnitude, dose-sparing (less antigen, fewer doses), accelerated, long-lasting, and neutralizing." The company recently completed and will publish very soon studies in ferrets. It also has very broad cross protection.

The rationale for the company's flu vaccine, called CSL-412, is that immune systems peak around 18-years-old and then slowly decline. There have been studies showing that T-cells decline even more rapidly, "It is clear that antibodies are extremely important in preventing flu, but T-cells play a role, too. You need a combination of antibodies and T-cells…We can combine the two, and the idea is to make elderly immune systems behave like that of younger adults."

The Phase II study was done in the U.K. and contained four cohorts, with 180 patients age 18-45, 120 patients 60-75, 79 patients older than 75, and 104 patients 60 or older living in long-term facilities. Control was CSL's FDA-approved flu vaccines Enzira or Afluria. In adults ≥60, she said, "We are not convinced we got the assays right, so we continue to do more assays." Results showed "encouraging data…We believe Iscomatrix adjuvant augments antibody and cellular immune responses. The safety summary shows that it was well tolerated…So, saponin-based adjuvants are a potent group of adjuvants."

Asked about carcinogenicity in animal studies, she said, "In our ferret studies, both with seasonal and H5N1 vaccine, we showed substantial cross-reaction. We have to get back some comments from reviewers, and then it will be published."

Asked if it was a combination pandemic vaccine, she said, "With our seasonal vaccine we can get cross protection against pandemic. How that is mediated is the question – whether you are protected from death in a lethal challenge."

GLOBALIZATION OF THE VACCINE BUSINESS

Margie McGlynn, president of Merck's global vaccines and infectious diseases unit, said that normal business models do not apply to the vaccine industry due to GMP standards, differences in serotypes, and varying degrees of disease in the world. Merck divides the vaccine business into three segments:

1. Developed Markets

The value proposition: Significantly decreased morbidity, mortality, and healthcare costs through safe, effective, and convenient vaccines.

McGlynn said that higher development costs due to increased safety requirements are leading trials the size of which are unprecedented in vaccine history, such as the 70,000-person trial that Merck conducted for a rotavirus vaccine, "In today's economic crisis, there is a strong desire to ensure cost competitiveness and value. There is cost sensitivity at the payer level and the provider level, and rising patient level copays are also creating sensitivity in the marketplace. But if you take a step backward, you would still conclude that there is a supportive environment for bringing new vaccines with strong efficacy and safety profiles and that addresses unmet medical needs that will be successful across developed markets."

Developed Markets

Needs and opportunities	Challenges
Major advances in new vaccine technology	Changing regulatory environment
High level of broad-based support for vaccination	Increased GMP requirements
Clear paths to regulatory approval and recommendations	Higher development costs
Value-based pricing	Increased price sensitivity
Ability to differentiate broad funding through governments and private insurance	Changing growth perspective for vaccines as penetration rates grow
Legislative and judicial progress	Growing consumer concerns over safety
Low participation of generic manufacturers	

2. Emerging and middle-income markets (BRIC – Brazil, Russia, India, China; plus Turkey, Mexico, and South Korea)

The value proposition: Significantly decreased mortality and morbidity through safe, effective, and low cost vaccines. Some markets are focused on building in-country technological expertise.

McGlynn said, "You would conclude that this is a viable economic proposition for vaccine manufacturers to achieve success. I don't believe that you can be successful as a global player without being successful in these markets, but you have more risk built-in, and you need well thought through strategies."

Emerging and Middle-Income Markets

Needs and opportunities	Challenges
Rapidly growing and evolving healthcare markets	Requires high volume and low cost supply chain
Increased spending as a percent of GDP on healthcare	High burden for vaccine differentiation
Growing middle class, self-pay markets	Growing desire to control supply chain through local manufacturing
High burden of disease in vaccine preventable diseases	Changing regulatory and policy environments
Expected public market adoption of new vaccines	Variability around intellectual property protection
Large birth cohorts in key emerging markets	Uncertain demand due to rates and extent of adoption as well as tender dynamics
	Creates an increased risk for "reference pricing," parallel trade or diversion

Developing World Markets

Needs and opportunities	Challenges
Large birth cohort	Highest burden for vaccine differentiation
Highest need populations	Need for high volumes at low cost
High disease burden creates an increased urgency for broad vaccination	Traditional delayed introduction relative to other markets
Growing funding commitments by national governments, Gates foundation, other non-governmental organizations (NGOs)	Uncertain demand due to cohort dynamics, tender risks, and program approvals
Infrastructure now exists thru GAVI to implement vaccine programs	Vaccines may be lower priority vs. more basic needs (e.g., safe drinking water)
	Typically lack a national immunization policy or enforcement
	Weaker regulatory oversight
	Limited healthcare infrastructure/cold chain

3. Developing world markets (sub-Saharan Africa, Afghanistan, Cuba, Vietnam)

The value proposition: Decreased mortality through safe, effective, and very low cost vaccines.

McGlynn said that if a manufacturer brought a vaccine to market 20 to 30 years ago, there was no feasible way to get that vaccine broadly utilized in the developing world. However, GAVI is helping get needed vaccines to people who need them.

Vaccines are available for all four diseases. McGlynn said that a rotavirus program is underway in Phase I in Latin American markets and is expected to expand into Phase II.

Top 2 Million Annual Vaccine-Preventable Deaths

Disease	Annual deaths
Pneumococcal disease	716,000
Rotavirus gastroenteritis	611,000
Measles	454,000
Cervical cancer	240,000

Commercialization Models

Market	Model
Developed	50% comprehensive policy, sales, and marketing efforts
Emerging	Policy efforts and tendering capability required for many public markets
Developing	Policy and advocacy teams focused on UNICEF, GAVI, WHO, etc.

There is agreement at the GAVI level that cervical cancer is important to address, but that agreement came during the global recession, and increased funding is now a question. McGlynn said, "I do think that program will go forward as we work out a way through the global recession." New vaccines account for 74% of the dollars that GAVI allocates.

Research and development needs include:

- Innovation vs. higher costs
- Larger scale trials required in the developed world
- Variable IP production

McGlynn said that companies working in an emerging market need to secure policy recommendations but don't necessarily need a sales and marketing infrastructure unless a government program leads to a strong update by doctors. In the developing world, companies don't need any sales or marketing people but do need good strategists who help figure out how to work with the various stakeholders such as GAVI, WHO, and UNICEF, as well as local groups.

She said, "Putting it all together, as a multinational vaccine manufacturer with a strong desire to succeed on a global scale, it should be clear in addition to inherent complexities that already exist, that there is a high degree of complexity across these three market segments that you have to be able to navigate. It's key to have early planning in your development process, and to understand what's going to happen when you get to the end of the process. What will the cold chain need to be? What are the formulation needs? Will stakeholders need multi-dose vials? Where does thermostability come in? And breadth of coverage is an extremely important question. Will funders be willing to pay for a broader or different profile if it is deemed to be necessary? I know that debate rages on, and clearly we're seeing that with the pneumococcal program, which includes serotypes that are important in different parts of the world."

Planning for the manufacturing process includes asking whether ultimate demand is going to be more in the high income multimarket, where 30-40 million doses may be needed, or on a global scale, where tens of millions or hundreds of millions of doses will be needed. McGlynn said, "You have to think carefully about the uncertainty that exists in that demand profile, and managing that variability in demand and being able to be flexible."

Looking ahead, McGlynn said there will be:

- Increasing focus by multinational corporations (MNCs) in accessing global markets.
- Increasing investments by MNCs in eradicating vaccine preventable disease on a global scale (pneumococcal disease, tropical disease i.e., malaria).
- Higher degrees of partnership between MNCs and local companies (R&D commercial and supply chain).
- Increasing NGO funding for local market data through clinical trials and demonstration projects.
- Increased efforts to bring vaccines to the developing world through targeted funding and incentives (advanced market commitments, priority review voucher programs).

She said, "We have to see how things play out with the global recession, but when we are through with it, we will see increased funding, and incentives like advanced market commitments – e.g., priority review vouchers – will provide the economic incentives all of us need to go back to our companies and say go ahead with the program, even if the need only exists in the developing world."

Asked how the presence of low-cost Hepatitis B vaccine manufacturers in emerging markets affect large manufacturers, McGlynn said, "Hepatitis B vaccines are now available for about 20-30 cents…but measles is also available at those prices or lower, and the measles initiative is still needed. GAVI is making an impact beyond Hepatitis B; pentavalent is one example. Price is certainly a factor, but even with that you have to coordinate with the manufacturers to make it happen."

CHALLENGES AND OPPORTUNITIES FOR MANUFACTURERS

GLAXOSMITHKLINE (GSK)

Dr. Philippe Monteyne, senior vice president and head of global vaccine development, GSK Biologics, received three awards at the conference for the Best Pipeline, which he called "rich." He said that the biggest emerging technology is adju-

GSK Vaccine Trials

Phase I	Phase II	Phase III	Submitted to regulators
HIV	Mosquirix (malaria)	Simplirix (herpes simplex virus)	Cervarix (cervical cancer). Approved in Europe March 30, 2009. Also approved in Canada and Australia)
Streptococcus pneumoniae adult	TB	New generation seasonal flu	Synflorix (streptococcus pneumoniae)
Cytomegalovirus	Herpes zoster	MAGE-A3 ASCI (non-small cell lung cancer)	Non-typeable Haemophius influenzae
NTHi-pneumo	Dengue	Flu pre-pandemic (Quebec)	
WT1 (acute myelogenous leukemia)		Flu pandemic (Quebec)	
		Hib-MenCY-TT	
		MenACWY-TT	

vant systems, and the frontiers in vaccination are:

- Combination vaccines
- Recombinant vaccines
- Adjuvant systems
- Antigen-specific cancer immunotherapies (ASCIs)

All the vaccines in the pipeline except Dengue, Hib, MenACWY, and Synflorix contain a GSK proprietary adjuvant system. Cervarix has a C.E. Mark in Europe and is available in more than 90 countries. WT1, MAGE-A4 ASCI , and MAGE-A3 ASCI are ASCIs. The flu pre-pandemic and pandemic vaccines are in-licensed or other third-party alliances.

Dr. Monteyne gave an example of what GSK is trying to do that is new with its malaria vaccine, "There will be no marketing in richer countries; that can only be done in partnership (with developing countries)."

MERCK

Dr. Anthony Ford-Hutchinson, senior vice president and franchise head, vaccines and infectious disease, at Merck Research Laboratories, explained why Merck decided to get out of the flu vaccine business, "This is a highly commoditized market. The market doesn't pay for a novelty in the flu market. It's all about price."

He said that Merck is focusing on pathogens instead, "Merck set up an experimental epidemiology unit…to try to identify patients at risk for *Clostridium*, "We did a licensing deal with Medarex on monoclonal antibodies. The combination resulted in a 70% reduction in recurrent rates of the disease." The licensing agreement is for CDA-1 and CDB-1 (also known as MDX-066/MDX-1388 and MBL-CDA1/MBL-CDB1), an investigational fully-human monoclonal antibody combination developed to target and neutralize *C. diff* toxins A and B, for the treatment of *C. diff* infection (CDI). Merck has global rights to develop and commercialize CDA-1 and CDB-1. Medarex and co-developer Massachusetts Biologic Laboratories (MBL) will receive a $60 million cash payment with additional cash up to $165 million, dependent on completion of certain milestones. *C. diff* is associated with a serious and sometimes daily form of diarrhea called difficile-associated diarrhea. Dr. Ford-Hutchinson said, "We realized that a lot of vaccines needed for the U.S. market are very difficult to develop for some kinds of disease – not like measles – but RSV (respiratory syncytial virus) and CMV (cytomegalovirus), so we, as part of our strategy, had deep discussions of how we would develop the vaccine even before we started working on it."

Looking ahead, Dr. Ford-Hutchinson said that part of Merck's planning involves collaboration with other companies, for example Sanofi Pasteur, with which Merck is partnering in Europe. He added that Merck's strategy is to divide the global market into thirds – developed, emerging, and developing – leads to "the need to really understand about manufacturing. The way that we have been manufacturing in the past cannot be done if you're going to start playing in these markets. That led us to India, where we have strategic alliances with Indian manufacturers so that we can produce things in volumes that were unthinkable before and at costs that are also very different. As we get into the developing world, I hope that we'll have an announcement in two months on how we'll approach that. We will be working on a not-for-profit approach to put novel vaccines into the developing world."

NOVARTIS

Dr. Christian Mandl, head of research and global head of viral vaccine projects, Novartis vaccines and diagnostics, said that licensed vaccines are mostly based on antibody-mediated protection against pathogens with low antigenic variability. However, things get more challenging with increased involvement of T-cells. He said that a big advancement in recent years is reverse vaccinology, "We use…genomic data, and we can mine the genomes of bacteria mostly to find new antigens that can be used in vaccines. But we will need better and newer technologies. For example, HIV is still a huge problem in 2009. If you look at the evolution of vaccine research, in the early days it was an empirical approach, then to glycoconjugation (MenACWY, *S. pneumo*, Hib), and reverse vaccinology is the next step. So, the future is that we're looking at vectors and adjuvants."

On Meningococcus B, Dr. Mandl said, "We used the entire genome information to deduce several hundred potential surface-exposed proteins. We then went into animals to screen …and selected five which are now included in our vaccine, which is in Phase III trials against Meningococcus B. The next step after genome mining is information on the structure of proteins, and we believe that there is a possibility of specifically changing proteins in a way to make them immunodominant. Another way to tackle that is to express it *in vivo*, so we think that there is still a lot of room for alphavirus vectors. We're partnering with AlfaVax in a Phase II clinical development program to make this technology and take the next significant steps."

Dr. Mandl said that alphavirus replicon particles are a promising platform for vaccine applications:

- Single round infections, so no virus is spread
- Simple RNA genome
- Cytoplasmic life cycle
- Risk of integration
- High level, transient antigen expression
- Dendritic cell targeting

Adjuvants like NF59 increase the antibody titers and drive the response towards the protective regions. Dr. Mandl said that Novartis has developed a technology around MF59, "We are optimistic that this technology will help us tackle more antigens in the future."

Novartis is also moving toward cell culture flu vaccines, and Dr. Mandl said, "The future of flu vaccines will be in cell culture."

Dr. Mandl said that there is no mechanism in place to develop vaccines that are needed only in developing countries, and so in 2008 Novartis founded a non-profit initiative called Novartis Vaccines Institute for Global Health (NVIGH). The Italy-based group's task is to develop effective and affordable vaccines for neglected infectious diseases in developing countries.

SANOFI PASTEUR

Dr. Robert Ryall, R&D director at Sanofi Pasteur, said that the company has 10 production and R&D sites and a relationship with Wyeth. It manufacturers 20 vaccines that address 20 different diseases:

- **Viral:** Yellow fever, mumps, poliomyelitis, measles, rubella, influenza, Hepatitis A, Hepatitis B, rabies, Japanese encephalitis, and chickenpox.
- **Bacterial:** Petussis, diphtheria, *Haemophilus influenzae*, type b infections, meningococcal meningitis, pneumococcal infections, tetanus, TB, typhoid fever, cholera.

However, he said that more than 40 disease targets lack an existing vaccine. Areas of improvement in influenza vaccines include efficacy in the elderly, "It is not optimum, and we spent a lot of time trying to improve that."

Challenges in new vaccine development include:

- **Scientific/technical challenges of new vaccine targets.**
  - Antigenic diversity (e.g., HIV, HCV, rhinovirus). Rhinovirus is in the development program. A different strategy is needed to offer broader coverage.
  - Understanding of pathogen biology.
  - Limited natural immunity (e.g., HIV, chlamydia).
  - Immunopathology (e.g., RSV, SARS, dengue).
- **Meeting regulatory standards for licensure of new vaccines.**
  - Pre-licensure requirements.
  - Post-licensure commitments.
- **Developing processes to meet rigorous manufacturing requirements.**
  - Ensure consistent and adequate supply.
  - Cold storage requirements.
- **Escalating costs of R&D.** This requires a balance between Life Cycle Management projects and new vaccine development.

Dr. Ryall said, "You have to be sure you can produce consistently and maintain supply." Areas of therapeutic interest include:

- **Monoclonal antibodies** (complementary approach to vaccines include active therapy and passive prevention, for example, rabies post exposure). Sanofi is partnering with Crucell on this.
- **Vaccines for therapeutic applications**
  - Latent TB (partner with Statens Serum Institut)
  - Autoimmune disease
- **Novel research programs and technologies to drive future growth**
  - Collaborative research
  - Partnerships
  - Improve our understanding of the desired immune response
  - Identification of new antigens/vaccine targets/new adjuvants to achieve a desired immune response, new delivery systems such as transdermal delivery, use of genomics and proteomics, expression systems, downstream processing, *in vitro* and *in vivo* model development

Dr. Ryall said, "In exploratory and preclinical stages, these are the high-risk stages of development." 80%-90% of Sanofi Pasteur's projects in the area are partnered. Once the project enters Phase I, it is in Sanofi's new vaccine portfolio. Of those, about 40% are partnered and 50% are Life Cycle Management projects. Clinical development usually takes from four to eight years."

Sanofi set up about 20 partnerships over the last four years, and Dr. Ryall said that it will maintain that relative growth, "We need to introduce one or two new vaccines into our portfolio each year in order to sustain a good flow through our pipeline." The company has about 28 vaccine products in new vaccine development. Three of these have been submitted to the FDA, 14 are in Phase II and III, and 11 are in pre-clinical and Phase I trials. More than 40% of the projects are partnered. The company is working on more than 12 different targets, the majority of which are partnered in Internal Discovery. Dr. Ryall said, "In order to sustain growth, we recognize the need to partner. We feel that it is the most effective way to tap into the best technology in the area."

WYETH

Dr. Bruce Forrest, senior vice president of late phase vaccine development programs at Wyeth Vaccines, runs the development/analytical/downstream/upstream processing part of the company as well as the clinical group. He said, "One of the challenges we face is how to transfer to the reasonable manufacturing process…We were a flu vaccine business ($30 million a year), and we walked away from it when the market said we're not going to pay more than $5 (per dose). One of

the challenges we face is that this has to be driven by sound, good science. Also, we are desperate to have strong, sound epidemiology, which establishes the medical need and which is missing." Dr. Forrest said that it is difficult to make combination vaccines, "in part because intellectual property law prevents companies from working together."

He called Wyeth's Prevnar, "the most successful vaccine of all time…with the most public health impact," adding that it meets the needs of many developing countries, "but it has taken a long time." As more serotypes outside of the U.S. and Europe have been identified, "Serotype 19A is the one we all missed, and (it represents) 23% of invasive disease in South Korea. So, we decided to go back in, and we needed to (modify the vaccine). Right now, this has been submitted in the U.S. and Europe for approval…19A represents a significant unmet medical need. The incidence of invasive pneumococcal disease (IPD) due to serotype 19A started to emerge in 2000 and 2001, just as we started to roll out the vaccine in the U.S. One thing that we perhaps fail to recognize is that even if there are existing vaccines, there are many opportunities, including (expanding use into) older adults."

Dr. Forrest described the limits of 23vPS (a 23-valent pneumococcal conjugate) vaccine in adults:

- While serotype coverage is high (80%-90%), antibody titers and efficacy appears to wane after five years.
- 23vPS induces hyporesponsiveness to either another dose of 23vPS or to a dose of conjugate.
- Re-vaccinations cause more severe adverse events.

He said that PCV7 "does not induce hyporesponsiveness to a subsequent dose of PCV7, whereas pneumococcal polysaccharide vaccine (PPV) does. In fact, if you give it first you can still get a response." Dr. Forrest complained that efficacy trials are getting larger. Wyeth's Prevnar was tested in 38,000 children, and ongoing trials in the elderly in the Netherlands plans enrollment of 85,000 people.

Dr. Forrest then discussed Wyeth's rLP-2086 candidate for meningococcal B (MnB), "rLP-2086 was identified as a broadly protective component of an outer membrane fraction:

- It is surface expressed (98%)
- It is present in all MnB clinical isolates tested (n=2,404)
- Two subfamilies, A and B
- Sequence identity between subfamilies 60%-75%
- Sequence identity within subfamily >83%

Wyeth's bivalent rLP-2086 vaccine candidate will soon move to Phase II trials:

- One protein from each subfamily is both necessary and sufficient for broad coverage against MnB
- The rLp gene is present in all MnB clinical isolates tested and surface expressed in 98%
- Encouraging Phase I trial results

He summarized:

- Prevnar continues to address need globally
- Expanding through age groups (to older patients)
- rLP vaccine is designed for the unmet medical need of meningococcal B

Panel Questions

Asked about drugs in the pipeline, Sanofi's Dr. Ryall said, "On average we have one or two vaccines moving on to registrations. You want to sustain growth, but we recognize that there are still a number of unmet needs remaining. As for biosimilars, in some cases, like influenza vaccine, it's difficult for one supplier to supply the world, so we need to maintain a supply."

Asked what GSK envisions commercializing within its family of drugs, GSK's Dr. Monteyne said, "What is interesting with GSK is that the vaccine division has been the vaccine division of a bigger and bigger group. Initially the vaccine division started with a small Belgian company, but at some point it was obvious that we needed to grow. We can no longer work as an independent entity within GSK. It is not possible any more, and it would be a mistake because there is expertise in oncology (in other divisions of GSK) and expertise in putting oncology products on the market. We have built a sort of business unit, and there is a structure with a steering committee. The steering committee is co-chaired by my boss in the vaccine division and by the head of oncology within GSK, and we have people with all expertise working on building the strategy together, so we have expertise on the technology and immunology."

The presenters were asked how they determined which regulatory pathway new vaccines would go through. Merck's Dr. Ford-Hutchinson said, "Our oncology vaccines are in oncology, and the Alzheimer's vaccine is in the Alzheimer's franchise." Dr. Ryall said, "We have neuroscience for Alzheimer's therapy. Non-clinical management is done by my group, and the clinical is done by the neuroscience clinical group." An FDA official in the audience said, "It was an internal decision about how those vaccines would be regulated…What we decided was that all vaccines against infectious disease would get regulated within the office of vaccines, and that made sense, because that's where most of the expertise was. Then it got complicated in 1993, when therapeutics was transferred to CDER, but the vaccines stayed within CBER (Center for Biologics Evaluation and Research)."

Asked if he sees any other paradigms besides doing very large trials based on the incidence of disease, Dr. Ryall said, "I think we're seeing it with meningococcal C. It comes down to a partnership between good epidemiology, which is even more difficult for us to do, vs. a large trial. Sometimes you can do a large trial in four years. As the diseases become less common in developed countries, we're also chasing disease for which

there is no market, and the regulatory agencies are slowly catching up to what might be alternatives."

Asked about increasing requirements from regulatory agencies, Dr. Monteyne said, "HPV is an example. We were asked to demonstrate efficacy in two pre-cancer lesions. Everybody knows that with infectious HPV there is no cancer, so we all agreed that we wouldn't have to do that for first generation vaccines. We can hope that future generations will not be asked to show efficacy against pre-cancer lesions against any single virus covered by the vaccine, either through cross protection or through direct protection. It is simply impossible to demonstrate with statistical significance the efficacy of pre-cancer lesions due to rare HPV." Dr. Ford-Hutchinson said, "You can look at (a vaccine) for the prevention of genital warts, but you can't look at the transmission to females, which is probably the most important reason to vaccinate males. And for head and neck cancer in males, there is no intermediate between infection and actual cancer, so you do get caught in these situations."

Asked about so-called regulatory creep, Novartis's Dr. Mandl said that Novartis had to grapple with the prospect of "potentially extremely large safety databases…So, I think the safety database issues really do merit some consideration in terms of regulatory creep issues and trial size. Also, I see repeatedly in the manufacturing side that they are dealing with yet-to-be discovered agent detection, which seems to have caused significant challenges for folks with other cell-based manufacturing processes."

Asked about adjuvants, Dr. Monteyne said, "The adjuvant system for us is very important. It opens the door. We hope that we will have the first FDA-approved adjuvant vaccine… As for the question of safety; one answer is to build a strong safety database and initially concentrate on one or two adjuvant systems. But more than that, of course there will be post-marketing commitments, but the answer isn't there. It should not be in the big numbers. Numbers are never enough – that's the issue. If you want to look for any single autoimmune disease, you need to look for hundreds of thousands of subjects. The real answer is to understand the mechanism of action and build a very strong knowledge of the adjuvant system which is considered. That's important for any potential disease. If you have the understanding of the mechanisms of action, then the numbers will confirm." Dr. Mandl said that more basic research, such as the question of surrogate markers and how to differentiate autoimmune response and which antibodies mediate protection, would help companies escape the need for larger and larger clinical studies."

The FDA official in the audience said, "I want to go back to HPV and boys. If you immunize boys to prevent genital rubella, a trial to measure the efficacy of prevention is probably impossible. I can't think of a way to do it. But in the absence of being able to demonstrate efficacy, would Merck be willing to market a vaccine for boys for which no efficacy in preventing transmission of genital warts has been demonstrated?"

NOSOCOMIAL VACCINE DEVELOPMENT

The market for nosocomial vaccines is estimated to be in the millions of dollars because the consensus among key opinion leaders, including the CDC, say that a vaccine is needed instead of another antibiotic. Nabi Biopharmaceuticals is working on a multicomponent polysaccharide conjugate called Penta-Staph, and Merck, collaboration with Intercell, is working on a single antigen vaccine.

Nabi president/CEO Dr. Raafat Fahim discussed the vaccine his company is working on for pneumo-coccal disease, "Most people would agree that staphorious is one of the most notorious infections. Nosocomial infections are ranked number one and are certainly one of the biggest problems that we have. Not only are they very adaptable bacteria, but they are able to resist almost every antibiotic, including the last resort, vancomycin. We know that there are strains discovered in Japan and in the U.S. that have resistance to vancomycin. There are very adaptable bacteria which are able to develop resistance very quickly."

He said that almost 30% of the world's population carries staphylococcus bacteria, and 10%-20% are chronic carriers. Once there is a cut in the skin, staph quickly gains access and causes problems. It also produces many toxins, which attack the immune system. Staph produces two major infections – skin and soft tissue infections (cuts and bruises), but also bacterium, which can cause a lot of diseases, including necrotizing fasciitis, which kills otherwise healthy people.

Nabi has identified two vaccine candidates that cover at least three highly virulent toxins. One is produced by almost all clinical isolates, and the other is associated with severe skin and soft tissue infections caused by the newly emerging multi-drug resistant community acquired MRSA strains. The vaccine contains the two main capsular types, 5 and 8, which are found in the outer coating of more than 80% of *S. aureus* bacteria. Dr. Fahim said, "We have antigens, and they are not immunogenic on their own, so you have to conjugate them, and they are conjugated with recombinant exoprotein B. We wanted to move away from classical diptheria and tetanus, and it is a powerful immunogen, so you get a robust response with the carrier. Then, we have an antigen to the cell wall. Obviously, once you get beyond the capsule itself you have the cell wall – it doesn't always have the capsule. Some strains have lost the capsule. One of the most abundant strains is U.S. 336, which is unencapsulated. We chose the Type 336 wall antigen. It is also a polysaccharide and is conjugated with recombinant exoprotein A."

The two toxins used are the ubiquitous alpha toxin – a recombinantly detoxified protein antigen – and Panton-Valentine Leukociden, found mostly in community-acquired

methicillin-resistant *S. aureus* (MRSA). It is cross protective in animal models.

There are five total antigens, which Dr. Fahim said, "is a very good combination for a vaccine against *S. aureus*. We have been in the clinic previously with Types 5 and 8 in two previous Phase III clinical trials. One showed efficacy, and the other did not. We have corrected those issues of manufacturing, and now we think we have what should be a very good antigen in Types 5 and 8." He said that the 336 conjugate has shown to be safe in Phase I and II trials, and the antitoxins are in the final stages of preclinical toxicology. Nabi, in collaboration with the U.S. military, will test the vaccine for both skin and soft tissue infections. The other indication would be for bacterilemia, and Nabi will do those tests on its own. Dr. Fahim said, "We think that *S. aureus* could be a gold mine, and it is a much needed vaccine. There is no doubt that it is one of the vaccines that one would imagine needs to be developed rather rapidly, not the least of reasons because it is resisting every antibody."

Dr. Robert Goodwin, president/COO of Ligocyte Pharmaceuticals, said that his company is developing a number of applications. Its lead product is a norovirus vaccine. Norovirus is the most common cause of extreme vomiting, diarrhea, and dehydration in the U.S., Europe, and Japan. It strikes where people congregate, including nursing homes, hospitals, schools, the military, and cruise ships. The CDC estimates that there are 23 million cases a year in the U.S., 900,000 pediatric clinic visits in developed countries every year, and 200,000 deaths in children <age five worldwide.

Most gastroenteritis in adults is caused by the norovirus, and it is second to rotavirus in children in the developed world. Dr. Goodwin said, "People are good at growing norovirus in their body and as they vomit they can aerosolize the virus and distribute it to everyone around them. It can remain virulent for up to a month on surfaces, and you can shed for a month after symptoms subside…There is a significant potential role for norovirus vaccine in healthcare workers and infection control programs."

The problems of nosocomial vaccines include: Immunization of inpatients to prevent hospital infections is unlikely to be effective since most patients arrive on short notice. But it is very realistic in long-term care (LTC). Long-term care residents are sources of pathogens in hospitals, and lowering emergency room visits in general will have an impact on hospital outbreaks. The question is: Are healthcare workers the vector for nosocomial spread? There is evidential indications that a widespread immunization program for healthcare workers is likely to have an impact on disease burden.

Dr. Goodwin suggested immunizing communities, saying that his company has "a prophylactic approach." Dr. Fahib said, "The same thing (goes) for *Staph aureus*, but it wouldn't be universal. You'd vaccinate people being scheduled for surgery or going into long-term homes." Dr. Goodwin said that his company is planning to start a virus challenge study this summer, "immunizing people with the vaccine and then giving them the virus. We want to see if there is broad protection."

Asked what role functional biomarkers play, Dr. Goodwin said, "We have looked at other conjugate vaccines, and capsular polysaccharides have been the most effective vaccines as yet today. That is the standard approach. Having said that, it is hard to predict efficacy just on immune response."

HUMAN MONOCLONAL ANTIBODIES

Crucell's chief scientific officer, Dr. Jaap Goudsmit, said that Synergist has the only antibody available to be licensed and sold, and Crucell wants to be the second in the market. Crucell started its program five or six years ago with a severe acute respiratory syndrome (SARS) project, "The market then vanished, which made it not a profitable strategy to continue, but we learned a lot about SARS."

Rabies

Dr. Goudsmit said that the company is in Phase II trials with a rabies monoclonal mixture and is moving ahead aggressively, "It will be our first product based on two monoclonal antibodies, and we also have a new antibody mixture against influenza…We showed (with SARS) that we could reduce the cases and duration of the outbreak (with an antibody), and we are doing the same for flu. We found that mixing two non-competing antibodies extended the breadth of protection and quickly mapped them for flu, and we can go all the way with crystallography. What we learned was that speed in a monoclonal antibody (mAb) discovery program to combat a potential killer bug is essential, and the use of an immune library increased the success rate for mAb discovery."

Dr. Goudsmit said that the superiority of mixtures of mAbs compared to single mAbs was demonstrated, and the company licensed the first rabies antibody – a mAb CR57 sequence – from Thomas Jefferson University. The mAb CR57 neutralizes most but not all representative rabies street viruses, so a second antibody is required to obtain full neutralization of all viruses. The second mAb, CR4098, complements mAb CR57 for rabies neutralizing activity. In the Phase II trials, the company had to show continuous breadth of protection (>40 rabies viruses) with a mixture of two mAbs.

Influenza

Dr. Goudsmit said that infections with the H1 and H2 viruses subtypes are the main cause of flu, and in the last flu season there was a clear difference between the U.S. and European serotypes. He said that the resistance of H1N1 influenza viruses to Roche's Tamiflu (oseltamivir) "is almost universal, and Tamiflu resistance is related to the fitness of the virus… Almost all the European H1 strains are Tamiflu resistant, which leaves you only Relenza (GSK, zanamivir)…So we have to bridge all the different strains in subtype and outside

subtype…We identified cross-reactive strains, and from our SARS experience – and we've done the same in West Nile, which is coming out this month – we identified the immunoglobulin M (IgM) component, select high potency antibodies."

He said that the first antibody that company scientists identified was in the H1 class and very potent. The CR6261 antibody neutralizes multiple H1N1 strains. The mAb CR6261 recognizes A2, and its hydrophobic receptors fit into the pocket of the stem region. Dr. Goudsmit said, "The antibody CR6261 reacts directly to the region that is responsible for all the viruses to fuse through the membrane, and it blocks a post-fusion event."

Dr. Goudsmit said that mouse and ferret studies showed that therapy with mAb CR6261 three days after challenge blunts disease and prevents death, "mAb CR6261 outperforms Tamiflu in preventing disease and death, and we will publish that soon, and you don't have to give the antibody three times." He added that the company has other cross-reactive antibodies using the same IgM technology.

The company has its own PER.C6 technology platform, and it can grow the cell line to densities of 150 million cells per mL with high viability. Under those conditions, it can make concentrations of mAbs of 27 grams per liter, and the company thinks that it can go higher. The company is also planning to manufacture in a $25 million empty shell instead of a $150 million factory. Dr. Goudsmit said, "You can validate all the machines, boxes, everything at one factory site, move it into your box, and you're there."

He concluded:

- You can bridge a broad range of pathogens, even in flu
- We found a second set of antibodies
- It can be made in an affordable, viable range
- Protection data in ferrets and mice demonstrated the prophylactic and therapeutic effects of this new class of human mAbs and will be tested in humans next year

The first human trials will be using H1 and H3 strains, which are significantly weakened, but Dr. Goudsmit said that "at least we will get a bridgeable assessment of dosing compared to the ferret." Testing is underway in Europe. It is unknown whether there is any immunogenicity against the antibody. Dr. Goudsmit said, "In rabies we haven't seen any problems so far which hampered the clinical process." The antibodies are humanized, not from mice, "We get them from human libraries. As for doses, I can't answer, but we think that we can get them significantly lower (than Synergis)."

THERAPEUTIC VACCINES

Nicotine vaccine

Nabi's Dr. Fahim described his company's nicotine conjugate vaccine technology, which he said has blockbuster potential, "The market is young and growing and is expected to grow 16% per year and reach $4.6 billion by 2016." Pfizer's Chantix (varenicline) was a promising therapy until adverse reactions (suicidal ideations and actual suicides) caused a major drop in sales. Nabi's NicVAX is a therapeutic vaccine designed to support smoking cessation and prevent relapse. It uses the body's immune system to generate highly specific antibodies. It is a novel antibody mediated mechanism that provides long-term continuous protection, and it has a favorable safety profile. Dr. Fahim said, "We prevent nicotine from crossing the blood brain barrier, reducing the likelihood of central nervous system (CNS) mediated adverse events. Once you conjugate it, you can produce antibodies. We use recombinant exoprotein A…The next time you smoke, as it circulates in the blood system, the antibody captures the nicotine molecules and prevents them from crossing the blood brain barrier." Nabi believes that its vaccine injections wean the brain off of nicotine. At a certain point, the antibodies become high enough so that it lowers the threshold for someone to stop smoking. In animal models, all the nicotine goes to the brain and in the vaccinated group much of it stays in the serum.

Nabi's Phase II proof-of-concept study showed that the vaccine is safe, with excellent tolerability. It was equal to placebo but also to other vaccine elements used in adults. The higher antibody dose of 400 mg was "quite impressive vs. placebo… The higher the antibody, the better your chances are to quit smoking."

Dr. Fahim said that people who receive the vaccine do not "oversmoke" in order to receive pleasure from cigarettes, "People who continue to smoke are actually smoking less than in the placebo group, so there is a positive impact on those who continue to smoke, which was a favorable and unexpected result."

Key findings:

- Initial series of 400 mg dose induces high antibody levels relatively early on.
- An antibody effect threshold was identified, with an additional dose at Week 12 to increase antibody levels.
- Booster doses maintain long-term high antibody levels in circulation, and abstinence extends to 12 months.

Nabi is planning its Phase III trial, in which there will be a high antibody level as well as an additional injection at Week 12. Dr. Fahim said, "We can see that an additional injection at Week 12 has resulted in a very favorable antibody response at the time you want people to quit. Almost 83% will achieve the tare tab level that we think will be necessary for efficacy, and they will quit at Week 14."

Asked how much nicotine can be neutralized by the vaccine, Dr. Fahim said, "We do have the data, but I can't share it. I can tell you that we get reasonably high antibody levels compared to other conjugate vaccines. We get between 10 and 78 micrograms of antibodies per amount, which is a respectable amount when you think about conjugate vaccines. That's not bad at all."

Asked if he worries about autoimmune complex disease, he said, "No, you don't worry about that. There are vaccines with much higher antibodies." As for the relapse rate, he said, "Every drug licensed to date has only four weeks of abstinence rate, and you and I know that's not enough to predict long-term efficacy. In our trial we went out a year, and at least statistically speaking, those who stop smoking for six months to a year usually – they are stopped. Having said that, there is opportunity to actually boost them for a year. We've gone a year, which at least in our discussions with the regulatory authorities here and in Europe, would be sufficient to predict long term."

Autoimmune Disease and Diabetes Vaccines

Dr. Hideki Garren, co-founder and vice president of research at Bayhill Therapeutics, discussed primary endpoints for autoimmune vaccine studies. She said that more than 10% of the world's population has some sort of autoimmune disease. The market for multiple sclerosis (MS) drugs was more than $8 billion in 2008.

Bayhill's Genie vaccine for MS has completed two trials – a Phase I trial in 30 patients and a Phase II trial in 300 patients which was completed 1.5 years ago. The endpoint was MRI lesions, but Dr. Garren said that although they are commonly used in Phase II trials, "They don't correlate with clinical response, at least on a patient-by-patient basis. To simply count the number of relapses a patient has (doesn't work because) patients have less than one relapse per year. 2,000 patients are needed with a minimum of two years to get that endpoint."

Bayhill has another vaccine for Type I diabetes which is "designed to turn off the disease," according to Dr. Garren. There were 48 patients in the Phase I/II safety trial. Dr. Garren said, "A problem with endpoints is that to date there has not been a drug approved for Type I diabetes, so we don't know what the Phase III trials should look like. If you look at endpoints like blindness, then you're looking 10-15 years out. Then we measure C-peptide, a marker of pancreatic function. I'll tell you that in the current trial we are seeing tremendous preservation of C-peptide. That is our experience to date. The trials take a long time – two years or more – and they take a lot of patients. Those are some of the challenges we face."

Dr. Garren said that looking for decreased antibodies, decreased T-cells, is challenging, "Yes, (the patients) have autoimmune disease, and to find circulating cells is difficult – less than 0.01% – so it is almost impossible. Then, looking for a decrease has been very difficult. We have had some success in the MS trial, and we did see a dramatic reduction in MMP (matrix metalloproteinase). We have to go through heroic efforts of trying to get fresh samples from the patients…but that's all we can do today. There are no other surrogate markers available for autoimmune disease. So, autoimmune disease represents quite an opportunity, but the endpoints, the immunomonitoring, are very difficult. You might call (a DNA vaccine) a therapeutic vaccine. However, there is a chance that it could be used in early patients or patients predisposed to the disease."

Facilitating Vaccine Manufacturing, Evaluation, and Availability

Robert Becker, vice president of business development for VaxInnate, a company spun out from Yale University in 2002, said that his company's current influenza vaccines incorporate flagellin, a (toll-like receptor) TLR45 ligand. Becker said, "These are key molecular patterns expressed by microbes, and we distinguish them in an immunological way – mixing with antigens isn't enough. We've looked at a number of TLR agonists, and the flagellin molecule is the one best suited for manufacturing. Flagellin sits within this repertoire. All the rest are lipid-based or nucleotide-based as structures, so if we have to associate the agonist to the antigen, having a protein-based agonist is beneficial. We know that we have a molecule that contains both agonist and the protein, so we're applying this to any number of targets." Becker said that his company can induce immunoresponses even as low as 39 ng, "which is unheard of. These are soluble. They are highly potent vaccine formulations in their own right."

Becker said that the other approach is to look at hemagglutinin (HA), "We take the HA globular head (HA1-2) and express protein and get properly folded HA globulated heads associated with flagellin. Compared to standard flu vaccines, in our Phase I trials we got comparable response at doses of a ten-fold lower concentration than what one sees with current vaccines. We intend…to take this product forward and be able to show, as we did in the human study, comparable types of potency and efficacy." He said that a single 100 liter fermentation run at one microgram dose produces 40 million doses per lot. It can be readily transferred, made at sites, and the projected total manufacturing time per lot is 10 days.

Vaxin CEO Bill Enright discussed nasal and patch delivered technology. His company's pipeline is focused on influenza, and it has done a small Phase I study with a seasonal flu vaccine "with good safety results and very high immunogenicity." The company is working on a seasonal pandemic H5N1 vaccine and poultry (in ovo). The seasonal vaccine has completed a Phase I trial and the poultry vaccine is two-thirds completed Phase II. An anthrax vaccine has finished its preclinical trial. It is a molecular based vaccine – the HA gene is

synthesized and cloned into the adenovirus. The adenovirus is replicated (using Crucell's technology) and then administered nasally in a single dose. Enright said, "This avoids some of the issues long associated with adenovirus-based vaccines. We are able to stimulate pretty broad multifaceted immune response." He said that the company can manufacture 150 million doses per year (1000L Bioractor), with a 21 day production cycle time (cell substrate to DSP-disposable technologies) and single reduction in COGS (decreased facility costs and decreased operational costs).

NanoBio CEO/chief scientific officer Dr. James Baker said that his company's technology uses a high energy emulsion – a nanoemulsion-based intranasal vaccine adjuvant platform. He said that manufacturing is safe. They have scaled up to 4,000 kilos. The emulsions are oil and water. The product is stable and immunogenic at 40° for six weeks. He said, "We could avoid the need for a cold chain during a pandemic event. It improves antibody titers and up to forty times higher HAI (hemagglutination inhibition) titers were achieved using only one-sixth of the commercial antigen dose with NE (nano-emulsion). We not only augment the immune response, we improve it (in animals), and we can achieve titers with a lower dose and without causing nasal inflammation." Four cohorts are being dosed in the current human trial.

Dr. Baker said that his company can produce enough antigens in a short period of time, "Nanoemulsion can be produced in 48 hours – enough for the U.S. population. He said that he has seen enough protection against anthrax with a single dose, "We see in animal models with flu and anthrax – and the response has lasted for as long as we've tested for as long as a year, where the animals are still 100% protected. Also, we've done multiple doses over a period of time, looking at HA and not seeing issues with repeat injections of a vaccine over a several month period, but that hasn't been done in humans to date."

Dr. Baker said that capacity is a two-edged sword, "You have to build the capacity to get a pandemic product out when it is needed, and then the market becomes oversaturated." He said that new nasal vaccines are not easily approved, "The easiest thing would be to take a traditional vaccine where there is a niche need for improvement, like in the elderly…You have an easier regulatory route compared to using a new antigen."

Regulatory pathways to approval

Dr. Karen Midthun, deputy director of the FDA's Center for Biologics Evaluation and Research (CBER), said that pandemic flu initiatives include:

- Building review and testing capacity, including for surge and new vaccine technologies.
  - Influenza virus strain and reagent preparation needed for vaccine manufacturing and testing.
  - Improved assays for evaluating vaccine potency, immune response, etc.
  - Support HDDS (hazards data distribution system) planning and vaccine development, enhance emergency vaccine emergency preparedness.
- Pathways to speed development.
  - Licensure of H5N1 vaccine for certain populations.
  - Fast track/priority review.
  - Available for emergency use under the Emergency Use Authorization (EUA).

The FDA is proactively facilitating developing of licensure and the availability of new vaccines and developing pathways to speed development and enhance assessment of safety in global collaboration with WHO and other entities.

Fast track designation is reserved for products which are for serious or life-threatening conditions and which demonstrate the potential to address an unmet medical need. A product is eligible if it provides design improvement in safety or effectiveness of treatment, diagnosis, or prevention of serious or life-threatening disease. Most counterterrorism products are expected to qualify.

The FDA has a lab called the Division of Product Quality which is moving to get ISO certification for some laboratories. Dr. Midthun said, "There is a lot of interest in cell substrates using adjuvants. There are new rapid sterility methods and animal models for vaccine efficacy for bioterrorism agents and other emerging threats."

As for WHO and UN purchases, WHO prequalifies vaccines for purchase by the UN. The agency relies in part on a National Regulatory Authority (NRA) to provide ongoing oversight for the vaccine, such as inspections, post-marketing surveillance, and lot release. The FDA serves as a reference for NRA for the rotavirus vaccine that Merck manufactures called RotaTeq.

Dr. Midthun said that there is confusion about whether the FDA can license vaccines for diseases that are not endemic to the U.S., "That is not true. There is a typhoid vaccine and a Hepatitis A vaccine, a pivotal study of that was done in Thailand…There is guidance recently issued that speaks to the tropical disease priority review vouchers and which authorizes the FDA to award priority review vouchers to sponsors of certain tropical disease product applications. It encourages the development of new drugs and biological products for the prevention and treatment of certain tropical diseases."

Dr. William Egan, vice president of PharmaNet Consulting, discussed vaccine approval pathway barriers. He said, "You only have to prove that it is safe, pure, and potent and that you can make it consistently. The rest is in the details, and there are many details, at least for vaccines." He mentioned the recent Chinese heparin scandal, saying, "Trust is fragile, and, once broken, it is very difficult to gain back." Regarding flu vaccines, he said, "For seasonal vaccines, seroconversion rates

and HI antibody titers that are >1.40 are not surrogate markers for efficacy. As a result, one needs to conduct a clinical trial using a disease endpoint for licensure (traditional approval or following accelerated approval). The efficacy of each component should be demonstrated in clinical studies."

Dr. Egan said that the use of adjuvants (other than aluminum salts) will be necessary. However, there are many potential problems, for which CBER's December 2009 adjuvant workshop will be a needed beginning.

Dr. Ken Surowitz, senior director of regulatory affairs, infectious disease & vaccines/biologics for Merck, discussed strategies for novel vaccine development in North America. In some parts of the world, certification of a pharmaceutical product (CPP) is required. It is issued by a regulatory agency which states that the product is approved in the U.S., and some countries want the CPP as part of the licensing application.

There are other reasons for sequential filings, and the reason is capacity. A company may not be able to respond to various agencies simultaneously or be able to produce launch quantities sufficiently:

- **Identify product or profile differences among markets**
  - For multi-valent vaccines with different antigens/ serotypes
  - Immune
  - Concomitant use with different vaccines (e.g., OPV, BCG)
  - Formulation (e.g., single dose, multi-dose)
  - Cold chain requirements
  - Delivery systems
- **Develop a global development plan**
  - Pay attention to GMP standards (HVAC classifications and requirements, pharmacopedial standards, raw materials, test specifications, lot release, product testing, pharmacology/toxicology studies)
  - Plan to address common or global needs
  - Plan to address local needs or differing requirements
- **Clinical development**
  - Ability to extrapolate study populations and need for separate/special studies, including intrinsic and extrinsic ethnic differences, standard of care/diagnosis
  - Concomitant vaccine use
  - Differing immunization schedules

Dr. Surowitz said, "Typically, regulatory agencies are reluctant to provide guidance at investigational new drug application (IND) meetings. A lot of programs won't survive the first-in-man trial…but it's necessary to have early (discussions) with the agency. Generally, the most important meeting and the place where we gain the most understanding of the ultimate requirements for registration is the so-called end-of-Phase II meeting. Frequently, there is a separate discussion with the regulatory agencies to discuss chemistry, manufacturing, and control (CMC) quality issues apart from the clinical issues…The main purpose is to review Phase II results and discuss whether it is appropriate to move into Phase III. It is a data driven meeting and looks at:

- Need for any further safety assessment (e.g., toxicology) studies
- CMC quality
- Review Phase II results
- Intended label claims
- Agreement on Phase III design and endpoints – this is almost like a pre-trial contract
- Safety database
- Data analysis plan
- Special protocol assessment

Dr. Surowitz explained, "The pre-authorization meeting is the last meeting – a data meeting to review Phase III results and talk about whether the endpoints were met, as well as further talk about requirements for BLA filing. This is also the time to finalize the plans for process validation if it is not completed by now…Regulatory agencies are autonomous, so it is appropriate to discuss a plan for harmonizing requirements that could result in approvals throughout the world. But at the end of the day, agencies make the decisions independently, and harmonization is not always possible."

Strategies to develop harmonized product filing:

- Single agency guidance – Seek guidance from the agency you believe to have special expertise in the matter at hand – or the most conservative based on past experiences. This is a streamlined approach but should not be used if you want to develop the vaccine broadly.
- Parallel scientific advice – This is a program between the FDA and EMEA in Europe developed in 2004 with the pilot program beginning in 2005. The procedure is requested by the sponsor and is focused on "important breakthrough products," which means that it should be a fast track eligible vaccine. The goal is increased dialogue between the two agencies and sponsors, facilitating a deeper understanding of the basis of scientific advice, and to try to optimize product development process.
- Simultaneous advice allows the ability to contact multiple agencies simultaneously, provides a common documentation package, obtains input from multiple agencies, and thoroughly evaluates guidance received.
- Sequential advice.

Typically, the FDA will set up a teleconference or video-conference for a single session. CBER will meet internally and then meet with the Committee for Medicinal Products for Human Use (CHMP), the Scientific Advice Working Party (SAWP), and then with the sponsor. A third session will include the sponsor and SAWP.

Some pros and cons:

- Limited experience with vaccines so far
- Can be efficient, resource-sparing process to develop harmonized development path
- Simultaneous FDA-SAWP input may reduce ability for sponsor to digest and consider input
- Receiving simultaneously differing advice from FDA and SAWP may lead to complicated discussion
- Simultaneous meeting venues limit face to face interactions

Clinical Trial Evaluation for Vaccines

Dr. Karen Near, medical director, vaccine and immunologic products, Baxter Bioscience, said that "Vaccine Phase I trials are simple…With adjuvants, at best you are going to double your work because you're going to compare with and without the adjuvant. Another complication is the fact that vaccine research is a high-risk endeavor. You're dealing with a healthy population, so if you have a problem with one subject, it can undo your whole program, or at least jeopardize it." She said that while everyone wants faster clinical trials, "How can you really expect to do faster trials? You have to wait for immunity to take place, and that can take some time. For flu vaccines you do safety trials for six months. The actual data that you collect may be within the first 21-42 days, but you still have to wait. Immunity can take a while, and reactions you see may take a while as well. The FDA knows all this and is rightly cautious, and we are, too."

Dr. Luwy Musey, director of clinical research at Merck Research Laboratories, said, "I usually do a Phase I trial in adults to evaluate safety. Usually after the Phase I trial in adults, in about 20 or 30 individuals, we go to another phase to find the dose. You can do a dose-ranging study…Then, you go to Phase II to provide proof-of-principle for a new vaccine or, if there is another vaccine, a non-inferiority trial. Also, you could combine Phase I and II and do a staggered design. If the first study is in a small group of infants, you open up enrollment to a larger population, and that is agreed to with the regulatory agency. Phase III is a pivotal study, and you can do a bridging study or clinical efficacy study. Phase III is a cumbersome process for a preventive vaccine. Do you do a consistency lot or evaluate the performance of 20 lots? You need to evaluate against all the different vaccines and with blood samples from babies. Phase IV will be assessing the effectiveness. You might do a bridging study – bridging antigens into one combination vaccine. Or maybe an immuno-bridging study – sometimes using that protection to extend to other age groups. Overall, it's about speed vs. addressing unknown safety issues. So, what we do is take advantage of various opportunities. We may have to interact with regulators to discuss our clinical plans and evaluate issues. You need to outline a development strategy, and an efficacy endpoint will be discussed, as well as the collections of safety data and discussion of any safety concerns."

He said that large studies in babies are difficult because you need 2,000 subjects, so companies have to go to Europe, where there are some challenges, and to other countries.

Planning is everything, and Merck scientists try to regularly draft a shell study, including different components with mock tables and mock figures "so it can be approved prior to time results. Then, plug in the data, and that can be done quickly."

Keeping the layers down to two for review also helps speed up the process. Tackling differences in regulatory requirements early is also important and avoids problems later on. Good interaction with regulators and all the stakeholders early and often, a good plan, and consensus on what has been done saves time and will help reduce the number of last minute requests from agencies.

Dr. Barry Holtz of Holtz BioPharma Consulting said that when it comes to cancer vaccines, "We communicate with the FDA almost on a patient-by-patient basis. We enter the data-base with our review committee as the study is going, and we don't wait for milestones or endpoints. The (FDA) cancer group has been good about that. We get a lot of feedback and are able to move ahead quickly, especially if something works, especially in the unmet need area."

James Wong, manufacturing collaborator, vaccines, at MedImmune, discussed manufacturing the influenza vaccine. Most work is done in Type A (which infects humans, horses, swine, and birds) and Type B (which infects only humans). There are 16 HA subtypes of Type A and 9 NA subtypes of Type B.

To produce the master virus seed, MedImmune receives circulating wild-type candidates from WHO affiliates. It takes them and uses them in its plasmid rescue process (also known as reverse genetics technology) for the production of the 6:2 reassortant, which is then expanded to a master virus seed and frozen. Vero cells were electroporated from the master donor virus plasmids and the new wild-type strain plasmids. There is only one possible combination, and that's the master strain 6:2.

The 6:2 reassortant process is a defined and predictable process:

- MedImmune starts receiving wild-type strains as early as October or November for the following flu season, and it works on a library of potential vaccine candidates.

- Once the 6:2 reassortant is obtained, antigenic and process characteristics are evaluated.
- Once the northern hemisphere strains are selected in February, the plasmid rescue process shortens the lead time to begin bulk manufacturing.
- One challenge is when a late strain breaks and the WHO decides that it wants to take the new epidemics and utilize them as the vaccine candidate.

Monovalent bulk process (FluMist):

- Wash and candle eggs, primary incubation
- Additional candling, inoculation using automated inoculation
- Secondary incubation, candling, and manual harvesting
- Pooling and clarification using ultracentrifugation
- Pool and dilute using sterile filtration

The company had a manufacturing initiative to process the virus under 2-8° C conditions and to process the material as quickly as possible to minimize losses, so it implemented disposable bag and bottle technology. It is in the process of replacing stainless steel mixing tanks with disposable bags, which can be placed at 2-8° C. It also implemented an automated collection system into disposable bags for collecting concentrated virus off of the centrifuge, which can be placed onto cooling plates. All buffers are received into disposable bags. The final drug substance is converted to a closed system using C-Flex tubing and Terumo welding technology. The process is basically closed to the environment.

Production steps include: Receive and thaw monovalent bulks, calculate blend formula, blending, filling, packaging, and storage.

MedImmune's Tacteveo product is a live cold-adapted temperature sensitive attenuated virus vaccine. It is a trivalent A/H1N1, A/H3N2, B vaccine which is produced on an annual basis to WHO strain recommendations. It is a 0.2 ml nasal spray with no preservatives and is provided in single-dose sprayers. After it is filled, it's kept at -5°, so doctors and pharmacists need to keep it refrigerated.

Wong said that the company is saving money both by not having to buy stainless steel tanks and by being able to increase capacity and shorten turnaround time. He said that it has not run into any regulatory issues by switching to plastic, "All the plastics we use are short-term temporary exposures to our product. We still have challenges to look at plastics in the long term."

As far as the impact on the environment, he said, "It's probably somewhat of a tradeoff because we don't use a lot of water during our introduction of stainless steel – it's a little bit less energy used at the plant because we don't have to go through autoclaving and CIP (cold isostatic pressing). We do limit our purchases by buying as needed, so we're trying to stay as green as possible."

How the Biotech World is Changing

Dr. Gavin Zealey, executive director of corporate development at Sanofi Pasteur, said that there have been no biotech IPOs since February 2008, and the IPO exit strategy is closed for vaccine companies. 2008 financing was $10 billion, the lowest since 1998, and decreased investor risk tolerance means concentration on existing portfolios. There is increasing reliance on mergers and acquisitions (M&A) and licensing with big pharma.

The challenges:

- Small biotech companies need cash. 38% of 370 U.S. biotech companies have <one year cash, so they are seeking near-term revenues.
- Big pharma and big biotech need to fill pipelines.

However, 1Q09 pharma deals accounted for almost 50% more than all of the industry's transactions announced in 2008 – 29 deals worth $4.9 billion.

Trends in the evolving vaccine industry:

- Today's vaccines are directed against the prevention of infectious diseases.
- Many vaccines have already been successfully developed.
- Many technology platforms have been successfully employed, including:
  - Killed vaccines
  - Live, attenuated vaccines
  - Protein subunit vaccines (recombinant subunit vaccines)
  - Conjugate vaccines
  - Vectored vaccines
  - Adjuvanted vaccines
- Many infectious diseases still exist for which vaccines are not currently available (i.e., Meningitis B, herpes, and *C. difficile*)

The vaccine industry is trending in two different areas:

1. **Vaccines against infectious disease.** There are many infectious diseases for which vaccines are not available such as meningitis B, herpes, and *C. difficile.*
2. **Vaccines against non-infectious disease** (primarily therapeutic focus): cancer vaccines – augmenting immune response, melanoma, prostate, colorectal – and non-cancer therapeutic vaccines, including Alzheimer's and Type I diabetes.

Common areas of partnership include new products, new technologies, and technology platforms, such as antigen identification/expression systems, adjuvants and immunomodulators, and delivery systems.

What makes a partnership attractive?

- Meeting a significant unmet medical need, such as TB, HIV, Meningitis B, *Staph aureus*, flu, *S. pneumoniae*, dengue, cancer, *C. difficile*
- Innovative product or unique product development approach
- Competitive advantage (strong IP position, development stage ahead of competitors, opportunity to leverage complementary strengths)
- Potential for significant return on investment
- Large market, short projected product development time lines, high probability of success
- Favorable risk reward profile
- Partner compatibility – synergy

Dr. Zealey said that Sanofi is working on new antigens and "those pathogens which are different, identifying important antigens. We have strep pneumonia protein-based vaccine approaches and are relying on a number of collaborations there. We are also working with partners on alternative routes of vaccine administration and delivery; agents to enhance immune responses, including eight adjuvants; manufacturing technologies, including cell culturing, expression systems, downstream purification/processing; and *in vitro*/*in vivo* models that are in some way predictive of vaccine potency or are used as potency release tests in manufacturing."

Sanofi Partnerships

Partner	Project
Becton Dickinson	Approved delivery system – late stage
Crucell	Rabies monoclonal antibody – mid stage
Eisai	Adjuvant – early stage
Institut Pasteur	Malaria vaccine – early stage
Intercell	Bacterial vaccine – early stage
Novartis	Chiron's CMV vaccine – mid stage
Provalis	Bacterial vaccine – early stage
Statens	TB – mid stage
Vivalis	Cell culture manufacture – early stage

Dr. Zealey said that Sanofi Pasteur sells half of the world's supply of influenza vaccine. Developments include:

- Fluzone HD (increased dosage of Fluzone)
- Intraderma delivery (in collaboration with Becton Dickinson, approved in Europe February 2009)
- Improved manufacturing technologies with Crucell and Acambis (Acam-Flu-A)
- Cell based in Per.C 6 cells (Crucell) has a contract with the U.S. government for scale-ip
- Adjuvanted flu vaccines
- Acam-Flu-A in collaboration with Acambis targets the ion channel M2E

He summarized:

- Partnerships are the most common source of new products, technology platforms, and support technologies in the vaccine industry.
- Primary areas for R&D partnerships include novel antigens, immune-enhancing agents, alternative delivery routes, and tools for improving product development and manufacturing process.
- A broad spectrum of possible partnership business structures exist.
- 80% of alliances will fail, but 20%-40% would have been more successful with alliance management.

Asked if Sanofi is looking to develop a protein-based vaccine for streptococcus pneumonia, he said, "The goal of a strep pneumonia protein-based vaccine is to identify a minimum number of protein antigens – three or four – so it will be able to address all serotypes of strep pneumonia. That is one part. The other part is how are you going to test that? There are countries in which Prevnar has eradicated strep pneumonia. We can't test there, but there are countries that don't use Prevnar at present."

Dr. Clement Lewin, head of strategic immunization planning at Novartis Vaccines and Diagnostics, described how something like his company's meningitis franchise can grow organically, "Novartis recently expanded its portfolio through acquisition of Chiron's business. The old Chiron vaccines and diagnostics business was a stand-alone business, and vaccines are divided into three franchises focused on unmet medical needs: meningococcal, seasonal and pandemic influenza, and pediatric and specialty."

- **Seasonal flu** – Fluviron, Fluid, Agrippal, Begrivac, Optalflu, Focetria, Aflunov is in development
- **Pediatric and specialty** – Encepur (targeted primarily in Europe for tick-borne encephalitis), Rabipur/RabAvert (rabies), Ixiaro (Japanese encephalitis), Quinvaxem (partnership with Crucell for DTP, hepatitis B, and Hib)
- **Meningococcal**

Meningococcal Vaccines

Vaccine	Status
MenC-CRM	Registered
MenACWY-CRM	Adolescent: registration
MenACWY-CRM	Infant: Phase III
MenB Infant	Early Phase III in 2009

Dr. Lewin said that meningococcal disease progresses rapidly and can kill a child in 24 hours. It is also difficult to diagnose. It is very susceptible to antibiotics if treated early enough, but even treatment with antibiotics can harm the patient. There are five primary serogroups, and the incidence of disease and serogroup distribution are dynamic and unpredictable over geography and time. The highest rates of disease are in infants across all serogroups, and currently licensed vaccines are effective but have age limitations.

He also said that the key to success is the conjugation of polysaccharide-proteins, which provides significant immunological improvements over other vaccines, "The advantage of conjugate vaccines is that they are effective in infants, induce immune memory, have prolonged duration of protection, a booster effect, reduction of carriage, contribute to the herd effect, and show hyporesponsiveness with repeated dosing. Conjugate vaccines have had remarkable success. The Hib vaccine eliminated *haemophilus influenzae*, and pneumococcal disease was dramatically reduced, but neisseria meningitis is a primary cause of bacterial meningitis and septicemia. It is the next target for vaccine prevention of pediatric bacterial meningitis…Our goal is to provide protection against all major disease-causing serogroups and all ranges."

Dr. Zealey described reverse vaccinology, "We worked on the genome sequences of the organism, identified open reading frames, expressed and codified them, put them in mice, and identified novel protein antigens with bactericidal activity. You are actually sequencing the genome, identifying proteins that are immunogenic, and developing the vaccines as opposed to working on known antigens…The conventional approach didn't work. Reverse vaccinology facilitated selection of immunogenic proteins capable of generating coverage against a broad array of serogroup B strains. The candidate is now in Phase II trials and has elicited robust immune responses and is well tolerated."

He said that the launch of adolescent MenACWY-CRM vaccine "will be a key driver for creation of a U.S. pediatric sales force for Chiron and Novartis, which have had a relatively small presence in the U.S. with flu and rabies vaccines that don't necessarily require large sales forces."

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