

COLLABORATIVE INNOVATION IN ACTION

A Two-Part Forum on:

- Vaccines
- CNS Disorders through the Lens of Personalized Medicine

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CBI Consortium White Paper:

Vaccines: Opportunities and
Barriers Across The Value Chain



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Vaccines: Opportunities and Barriers Across The Value Chain

A CBI Consortium White Paper

I. Transformational Challenge Statement.

The CBI Vaccines TRP seeks to advance the transformation of vaccine development, manufacturing and delivery to enable manufacturers to meet global healthcare needs for safe, effective, affordable preventive care.

II. Background

Vaccine Marketplace

The U.S. vaccines market is a small segment of the overall pharmaceutical marketplace and is highly concentrated amongst 5 manufacturers (Sanofi-Aventis, Wyeth, GSK, Merck, and Chiron/Novartis). Of twelve vaccines routinely recommended for infants and young children, seven are made by only one company, and only one is made by more than two companies. For 2004, vaccines account for only 3% of total US pharmaceutical revenues –for the four largest US vaccine manufacturers, vaccines account for less than 10% of revenues (1).

The patient segments in the preventive vaccine marketplace include healthy infants, children and adults. The therapeutic targets include traditional childhood infectious diseases, annual influenza strains, new vaccines aimed at adolescent and adult segments, such as the human papilloma virus (HPV) vaccine against cervical cancer, vaccines to prevent global pandemics – SARS, avian flu, Bioterrorism agents – BioShield, and third world-focused diseases – malaria, rotavirus.

The payor mix in these segments varies considerably from that for therapeutic drugs, where a free market continues to exist at least in the U.S. Public health needs and bioterrorism, as well as the global risks of infectious disease have created a market in which government and global agencies are heavily involved in the policy-making and price setting aspects of these products in the U.S., as well as globally. The limits on pricing flexibility for these products add to the marketplace issues for manufacturers.

There is a long history of purchasers wanting prices that result in net cost savings, dismissing “value pricing” that recognizes health benefits and avoidance of suffering, but may raise total costs. Third party payment (private, government) for adult vaccinations often does not fully compensate providers for costs of acquisition and administration.

Liability Issues

The widespread, nearly universal immunization of healthy children has left vaccine manufacturers accountable for risks based on very rare but serious health outcomes,

despite conducting clinical trials involving >50,000 subjects. By way of example, Wyeth's rotavirus vaccine, Rotashield, licensed in 1998, was withdrawn in 1999 when it was found to have caused a rare (≤ 1 in 10,000 recipients) but serious intestinal obstruction. Moreover, there has been a long history of protests to compulsory vaccination laws, and highly publicized litigation alleging that pertussis vaccines cause brain damage and thimerosal preservative causes autism. In 1999, a decision by the FDA, US Public Health Service & American Academy of Pediatrics to cease licensing for thimerosal led to subsequent diphtheria, tetanus, and pertussis vaccine shortages. Understandably, currently developers are loath to consider any vaccine taken by pregnant women. In reaction to the vaccine liability issues, in 1986, Congress established the Vaccine Injury Compensation Program allowing science-based no-fault compensation to claimants (75¢ excise tax per vaccine dose). This has reduced the litigation burden, but it covers only childhood vaccines, not all vaccines for adolescents and adults, and it contains increasingly utilized opt-out provisions for unsatisfied claimants.

Manufacturing Issues

Current consolidated vaccine manufacturing capacity can be compared with prior years, in which 26 manufacturers existed in 1967 and 17 manufacturers in 1980. Since the year 2000, nationwide shortages of six recommended childhood vaccines have occurred and influenza vaccine supplies have not kept pace with demand during several seasons. Reasons for the shortages vary, but an exacerbating factor is the limited number of manufacturers. Supplies are vulnerable to manufacturing problems – since 2000, vaccines for 9 of 12 preventable diseases have required supply rationing (2-3).

The existence of a limited number of manufacturers is in part due to a long history of troubled and distrustful interactions among vaccine developers, government purchasers, private and public providers, parents, and plaintiffs' litigiousness, but is also due to other marketplace factors. Vaccine demand is concentrated – not just due to government buying power, but also because the Advisory Committee on Immunization Practices (ACIP) recommendations are typically followed by private as well as public purchasers. The vaccine marketplace has evolved to become a “winner take all” market... undifferentiated products, supported by economies of scale, priced at close to marginal cost has lead ultimately to exit of all but one producer. The cost of entry and a risk-averse regulatory environment committed to ensuring that vaccines do no harm to healthy patients act as barriers to entry, but existing single suppliers are unlikely to exit unless their offering is replaced by a superior product, or after having experienced safety or manufacturing problems.

The cost of entry to the vaccine marketplace is heavily influenced by the production needs. Vaccine production is costly, in part because of the rigid processes established in facilities to meet cGMP standards. Plants are built for a particular vaccine, with design determined by the production processes involved. Since the resultant vaccine cannot be assessed through chemical analysis with precision, rigid monitoring of processes is critical to meet specifications. Moreover, there is little incentive for a sole supplier to

maintain excess capacity or redundant production capacity to prevent supply disruption (1,4).

The issues with threatening pandemics are even more formidable. Scale up of adequate manufacturing capacity for avian flu vaccine and the infrastructure to reach populations affected is a significant challenge for manufacturers. Innovations in manufacturing and vaccine development will be needed to effectively deal with these challenges.

Development Issues

For manufacturers choosing to develop new vaccine products, many issues must be considered in the decision-making process. The cost and time associated with development vary according to the potential safety issues, the immunogenicity of the product which affects manufacturing requirements, and regulatory uncertainties, which are particularly problematic for new types of vaccines. For small companies, financing the development of new vaccines must consider the challenges of raising funding, establishing and managing partnerships, as well as asserting and defending intellectual property rights, both in the US and globally during the lengthy development process. Moreover, the previously noted liability issues for administration of vaccines to healthy patients create unique challenges to clinical trial design to address safety concerns.

Global Distribution and Economic Challenges

In many cases, particularly with vaccines for infectious diseases, the healthcare delivery systems in underdeveloped countries pose significant challenges to the effective distribution of vaccines to patients. For non-oral products, infrastructure issues and sanitary conditions are particularly difficult. Innovation in new types of vaccines and vaccine delivery may provide opportunity to address these issues. Even more problematic is the issue of how to pay for vaccines in underdeveloped countries where the cost of treatment in an economically developed country far exceeds the affordability ceiling.

III. Stakeholder Perspective.

As part of the 5th annual Celebration of Biotechnology at the Massachusetts Institute of Technology (MIT) in August, 2006, the Center for Biomedical Innovation (CBI) hosted a program titled “Collaborative Innovation in Action”, including a forum on Vaccines.

“Vaccines: Opportunities and Barriers Across the Value Chain,” comprised two case studies and a panel discussion which addressed the perspectives of key stakeholders in vaccine development and manufacturing. The first case study was presented by Dr. Una Ryan, CEO of Avant Immunotherapeutics, on the commercialization of a vaccine against diarrheal disease, Rotarix®. The second case study was presented by Dr. John Pena, President of Ancora Pharmaceuticals, on a new anti-toxin polysaccharide approach to a malaria vaccine.

Rotarix® is an attenuated live virus vaccine based on a single human rotavirus strain isolated from an infant in Cincinnati during the 1988 season. Rotavirus is highly contagious and causes diarrhea which can lead to severe dehydration. Infection is extremely common and most people will be infected in their lifetimes, however, in developing countries, diarrheal disease is the leading cause of childhood mortality, killing approximately two million children per year.

Rotarix® faced a particularly arduous licensure process due to the introduction in 1998 and withdrawal in 1999 of a vaccine, Rotashield, by Wyeth. The withdrawal was due to a suspected link between the administration of the vaccine and intussusception, a painful condition where the bowel telescopes into itself leading to a bowel obstruction. The emotional nature of the side effect and the fact that vaccines are given to healthy children led to congressional involvement which mandated that no approvals would be given unless it was proven that the rate of intussusception was no higher than the basal rate. This decision would have tremendous consequences on the commercialization of Rotarix®, which at the time was just completing Phase II studies which showed 89% protection against any infection and complete prevention of severe illness. Because the basal rate of intussusception was not well known, but suspected to be very small (~1 in 1000) in the target population, an extremely large Phase III study was required, upwards of 80,000 subjects at a tremendous expense of more than \$500 million. This would impact the launch strategy, financing of Avant, and ultimate cost of the vaccine.

Avant had already anticipated the expense of a smaller (3-5 thousand subjects) Phase III study and the manufacturing and marketing resources needed for global distribution of Rotarix and had signed on GlaxoSmithKline as a partner. Due to the stringent requirements for licensure in the United States, GSK's launch strategy involved introducing Rotarix into developing world markets where the need would be higher, but revenues lower. This decision would significantly impact the timing of the manufacturing capacity required to supply the large developing world markets. In addition, it would postpone royalty revenue to Avant and disrupt its financial structure which assumed a conventional initial launch into US markets. To overcome this problem, Avant sold rights to its future royalty revenue, a strategy also adopted by the academic partner, the Cincinnati Children's Hospital.

The Rotarix® story provided an excellent backdrop for the ensuing stakeholder panel discussion on the interplay between biotech and big pharma and the impact of safety regulations on manufacturing and pricing of vaccines.

The Ancora story provided a different perspective on how scientific innovation in both understanding disease processes and also in carbohydrate synthesis is leading to a new approach to malaria vaccination.

Malaria is caused by infection by a Plasmodium parasite that is endemic to many tropical and subtropical regions. Its life cycle includes transmission through the blood by mosquitoes. Current treatments attempt to disrupt the parasite life cycle within its human host, with limited success and offer no long term protection against malaria. Children

under five years old are most at risk of death from malarial disease, however the peak parasite load in the population is in 10 year old children and most people develop a resistance to the parasite over time. These factors suggest a toxin is involved in the disease process. The Ancora approach is to vaccinate against malarial disease caused by this toxic effect to prevent death and allow the natural resistance to the parasite develop over time. This approach is based on over 10 years of work to isolate the potential malaria toxin which was found to be a glycolipid molecule called GPI. This native GPI isolated from parasites cultured in red blood cells was shown to provide 50% protection from malarial disease. In order to rule out the presence of a highly potent impurity, the GPI molecule was synthesized using a novel carbohydrate synthesis process and showed 80% protection against malarial disease, validating GPI as an immunogenic toxin. At this point, Ancora began commercial development of the malaria vaccine including optimization of the lead antigen candidate, defining the appropriate adjuvants and other drug product components, and establishing the critical development path to the clinic. These activities all required the GPI molecule and the scale up of a synthetic carbohydrate manufacturing process. Ancora is now capable of producing tens of grams or even 100 grams of GPI and is aiming to have a vaccine product that can be integrated into the expanded program of immunization, potentially preventing millions of deaths from malaria in the developing world.

Academia-Biotech-Pharma Partnership

The first topic of discussion was the challenge associated with moving vaccine development from academia to biotech to big pharma. In particular, understanding what each partner contributes. The panel concluded that Academia serves to reduce the scientific risk, Biotech serves to reduce the technology risk, and Big Pharma bears the majority of the remaining regulatory, manufacturing, and marketing risk. The scientific risk includes determining the basic approach to developing the vaccine and demonstrating its potential in animal models or humans. The technology risk includes demonstration of manufacturability and producing materials to complete a phase II clinical trial. And the regulatory, manufacturing, and marketing risk includes funding pivotal phase III trials, scale up to commercial production, and acceptance by government and private customers. An important point that came out of the discussion was that each partner should be aware of the roles and constraints of the others. In particular, for academics, research should be conducted using cell lines cleared by the FDA for eventual manufacturing to smooth the transition to biotech. Also biotechs must understand the marketing needs and financial pressures of their big pharma partner. The start of manufacturing for phase III trials is often a stumbling point that is rarely properly timed and budgeted.

Vaccine Development Issues

The next topic of discussion was how do safety issues affect the cost and timeline of vaccine development. The key message was that safety is not absolute, which is unfortunately a common misperception. Rather, safety should be assessed in the context of a cost benefit analysis of potential outcomes with and without vaccine administration

and be specific to the population of interest. For the case of Wyeth's Rotashield, which was withdrawn in the United States due to a 1 in 10,000 increased risk of intussusception, the decision by developing countries not to use the vaccine, where the risk of death from rotavirus infection is 1 in 500, was unfortunate. Safety should also be evaluated in the context of the safety study itself. Results from safety studies are in fact very specific to the population that is studied and even the mechanics of how the study is conducted. Variables that impact whether study results can be applied include the age of the population, access to health care, wealth, environment, behavior, and genetic makeup. For example, in general, oral vaccines shown to work well in wealthy countries do not work as well in poor countries. This could be due to differences in maternal antibodies, interference from other pathogens, or differences in how the vaccine is metabolized. As a consequence, clinical trials to assess safety necessitate larger and larger studies, requiring a balance between confidence in the safety assessment, cost, and time to market. Critical questions include, how can some clinical trial data be re-used, or how can studies be designed to account for previously acquired data, especially with respect to background incidences of adverse conditions.

The anti-toxin nature of the Ancora approach to malaria presents special challenges for conducting clinical trials. A lot of things can confound study results and increase the uncertainty when applying results more generally. For example, insecticide use, or the degree of bed net usage, which impacts the frequency of mosquito bites and opportunities for transmission can skew results. Also, what is the degree of compliance and how will the study itself impact the effectiveness of the vaccine? For example, if the study requires a drastic change in behavior, such as visiting a clinic once a week with reminders to take the proper doses, will the results be representative when the study is not being conducted? All of these issues must be carefully considered when ascertaining the true safety and efficacy of the vaccine. For the specific case of the Ancora anti-toxin vaccine, an interesting consideration is whether the treatment will increase the infected population since the vaccine prevents death, but not infection.

Manufacturing Issues

The third topic of discussion was what can be learned from Rotarix case study which might be helpful for planning manufacturing for pandemics or bioterrorism. The main lesson is the importance of preparation due to the long time between a vaccine concept and an approved product. While the preparation of materials for vaccine development can be performed ahead of time, the last step, scale-up for commercial manufacturing of the vaccine, is a significant hurdle due to the expense of conducting manufacturing scale experiments and the specialized facilities that are required. This problem is exacerbated by industry wide manufacturing capacity constraints, which further restricts opportunities to prepare for the acute manufacturing demands of a pandemic or bioterrorist event. A way to do production scale process development without capital intensive experiments would be of tremendous value and could be an opportunity for the CBI to engage the broader engineering community at MIT to develop systems capable of modeling production scale reactors. An example noted was microfluidic bioreactor arrays that are

under development. Also, designing vaccines that are more temperature stable, with longer shelf-life would help alleviate the need for urgent production of vaccines.

As opposed to the live virus based Rotarix vaccine, the synthetic nature of the Ancora malaria vaccine brings up interesting issues with product characterization. For the Ancora product, based on a carbohydrate, characterization questions include the purity of the carbohydrate, verification of the stereochemistry, and the specific binding of the carbohydrate to the protein component, characterization of carbohydrate. A good role for Academia would be to develop tools and analytical methods for product characterization.

Because of the unique chemical synthesis approach to a product that is traditionally manufactured using bioenzymatic pathways, the Ancora story provides the background for an interesting discussion on the challenges and opportunities for chemical synthesis of biologicals. One challenge discussed was establishing equivalency between the natural compound on which the vaccine is based and the synthesized product. Mimicking nature in general requires equivalency more so than open synthesis and screening of small molecule drug compounds. Efficient production of the specific molecule with the proper stereochemistry is also a challenge, however synthesis does allow for rapid production and optimization of drug candidates through modifications of natural compounds. A synthetic approach can therefore lead to a shorter time to market and still leave open the option of developing a biosynthetic process which is potentially more efficient.

Economic Policy Issues

The fourth topic of discussion was the major policy issues that impact differential pricing and economic incentives for vaccine development. The panel opened with an impassioned declaration that there was a huge misconception that patents increase costs and prevent people in developing countries from getting vaccines. This idea is dead wrong and that patents are required to incent manufacturers who take on significant risk. They need to know that the long investment that is made to develop and manufacture a vaccine will have a pay off. Tiered pricing plays a role in the outcome and requires a charitable payer for developing countries, tiered pricing for middle class countries, and full pricing for the developed world. Indemnification is also critical for manufacturers, including protections during clinical trials, which are in fact research efforts where uncertainty is a given. Overall regulatory predictability is important and a refined understanding of safety. Post marketing surveillance of safety should replace large and expensive phase III trials. This would have the advantage of surveying the intended population and making the vaccine available much sooner to populations that need it most. Placing post marketing surveillance requirements on top of large phase III trials would surely kill new vaccine development.

As with Rotarix, because the malaria vaccine is targeted at the developing world, the subsequent panel opened with a discussion of affordability and access to vaccines. Having a market that includes healthy, wealthy travelers, the military and government employees is helpful, however driving the cost per dose below \$2/dose would be required to allow satisfying world demand through charitable payers. To put the \$2/dose objective

in context, the Merck rotavirus vaccine costs \$60/dose in the developed world. The CBI can foster the public/private partnerships to increase public funding and also establish partnerships between donor and scientific communities to reduce the long time lag between vaccine conception and commercialization.

IV. Transformational Opportunities.

Innovation in the vaccine marketplace creates an opportunity to advance a broader model of preventive care for medicine which has been growing for the last decade as an alternative to the traditional treatment of disease and symptoms. In response to the issues raised herein, CBI proposes that there are a number of areas of opportunity for the consortium of stakeholders to address, as described below.

Vaccine Marketplace

Educational Outreach Programs. For new types of preventive vaccines currently in development or recently approved, there is a need to inform, educate, and promote, as well as deliver to the market. Direct-to-consumer and physician promotion will be costly for manufacturers but critical, as will be the case for all new preventive care treatments. These programs will be needed to influence policy in an environment which shifts from disease ‘repair’ to disease ‘prevention.’ Helping the marketplace to understand and recognize the benefits from the newest generation of vaccines will be key to patient access to products in this transformation. Collaborative research and development of pre-competitive programs in this space will benefit all stakeholders.

Proposed Key Stakeholders: Pharma, Biotech, Patient Advocacy groups, Provider groups, Payors (Private, Government)

Anticipated time frame: Short (18 months) to Mid-term (2-4 years) Impact

Development Issues

Preventive Vaccine Clinical Trial Design Improvement. Issues specific to the development of preventive vaccines can be addressed through improved clinical trial designs and processes, as well as resolving key regulatory uncertainties. The goal for this opportunity area is to reduce the time and cost of clinical development, while maintaining appropriate confidence in efficacy and safety issues for providers, regulators and patients. Areas to pursue include clarification of standards of safety for licensure v. post-marketing surveillance, development of new clinical trials based upon innovative design, fully leveraging Phase I and II data for Phase III trial design, identifying markers for sensitivity and safety of vaccine, as well as others to be further defined by the stakeholders.

Proposed Key Stakeholders: Pharma, Biotech, FDA, Academia

Anticipated time frame: Short (18 months) to Mid-term (2-4 years) Impact

Academic-Biotech-Pharma Partnerships. Financing the development of new vaccines must consider the challenges of raising funding, establishing and managing partnerships, as well as asserting and defending intellectual property rights, both in the US and globally during the lengthy development process. Areas for consideration within this opportunity are policy issues which impact global commercialization, optimizing the models and processes for relationships of partners, potential novel ways to finance vaccine development, as well as others to be further defined by the stakeholders.

Proposed Key Stakeholders: Pharma, Biotech, Academia, others TBD

Anticipated time frame: Short (18 months) to Mid-term (2-4 years) Impact

Manufacturing and Global Distribution Issues

Manufacturing Process Technology Improvement. Reducing investments and speeding development of manufacturing capacity through process and technology improvement will have dramatic impact on patient access to new preventive vaccines. Innovations in manufacturing and vaccine manufacturing development will be needed to effectively meet this challenge. Areas of opportunity to be examined include new cell lines, early integration of manufacturing process development with the vaccine development process, regulatory improvements, purification methods, innovative process technology (microfluidics), product quality innovation, batch operations and reproducibility, new tools and analytical procedures, innovation in molecular biology, as well as others to be defined by stakeholders.

Proposed Key Stakeholders: Pharma, Biotech, Academia, FDA

Anticipated time frame: Short (18 months) Mid-term (2-4 years) and Long-term (5-10 year) Impact

Economic Models for Policy and Pricing:

Influence US and Global Policy for Impact on Pricing and Liability. Issues specific to the economics of preventive vaccines can be addressed through collaborative participation in the processes which influence related policy-making. The goal for this opportunity area is to remove hurdles which inhibit manufacturer incentives to innovate and deliver new, safe and effective vaccines to meet global healthcare needs. Areas to pursue include vaccine liability reforms, support for innovation in new types of vaccines and vaccine delivery to address infrastructure issues and sanitary conditions in underdeveloped countries, how to pay for vaccines in countries where the cost of treatment far exceeds the affordability ceiling, new models for evaluation of health benefits for preventive treatments, new pricing models to address global economic disparity, as well as others to be further defined by the stakeholders.

Proposed Key Stakeholders: Pharma, Biotech, Academia, WHO, CDC

Anticipated time frame: Short (18 months) to Mid-term (2-4 years) Impact

V. Transformational Outlook.

Achieving the goals of this CBI Vaccines TRP to “advance the transformation of vaccine development, manufacturing and delivery to enable manufacturers to meet global healthcare needs for safe, effective, affordable preventive care” provides the promise of dramatic improvements in overall healthcare. All of the specific transformational opportunities previously articulated are technically possible, given adequate time, as described. Reducing the time from vaccine concept to commercial production is a fundamental goal and could be achieved through several of the initiatives outlined above, including a better understanding of the entire commercialization process by academics when developing new concepts, reducing the time for manufacturing scale up to produce phase III trial materials, reducing the length of phase III clinical trials through improved study design and incorporation of improved background data.

As with any challenge of this magnitude, its success is highly dependent on the integrated efforts of many parties who have divergent incentives in their day to day roles and responsibilities within their organizations. From helping to establish the relationship between academia, biotechs, and big pharma through licensing agreements; navigating regulatory requirements and establishing a reasonable safety record; scaling up manufacturing to supply world markets; and understanding the incentives and barriers for undertaking vaccine development, there are many opportunities for the CBI to make contributions to bring more life saving vaccines to market.

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