WTEC Panel Report on

INTERNATIONAL ASSESSMENT OF RESEARCH AND DEVELOPMENT IN RAPID VACCINE MANUFACTURING

PART TWO: AUSTRALIA, CHINA, INDIA, JAPAN, SOUTH KOREA

Joseph Bielitzki (Chair)
Stephen W. Drew
Sheldon H. Jacobson
Terrance Leighton
Mary Ritchey
WTEC PANEL ON RAPID VACCINE MANUFACTURING

Sponsored by the National Science Foundation (NSF), Department of Health and Human Services (HHS), and the U.S. Department of Agriculture (USDA).

Dr. Joseph Bielitzki (Chair)  
University of Central Florida  
Office of Research and Commercialization  
12201 Research Parkway  
Orlando, FL 32826

Dr. Terrance Leighton  
Senior Staff Scientist  
Children's Hospital Oakland Research Institute  
5700 Martin Luther King Jr. Way  
Oakland, CA 94609

Dr. Stephen W. Drew  
Drew Solutions LLC  
126 Mountain Avenue  
Summit, NJ 07901

Dr. Mary Ritchey  
Ritchey Associates, Inc  
206 Somerset Road  
Norwood, NJ 07648

Dr. Sheldon H. Jacobson  
Professor, Willett Faculty Scholar  
Director, Simulation & Optimization Lab  
Department of Computer Science  
University of Illinois  
201 N. Goodwin Avenue (MC258)  
Urbana, IL 61801-2302

Sponsor Representatives with WTEC Panel

Cyril Gerard Gay, DVM, PhD  
Senior National Program Leader  
Animal Production and Protection  
Agricultural Research Service (ARS)  
Research, Education, and Economics  
United States Department of Agriculture  
5601 Sunnyside Avenue  
Beltsville, MD 20705-5148

Dr. Narayan Iyer  
Division of Chemical, Biological, Radiological, and Nuclear (CBRN) Countermeasures  
Biomedical Advanced Research and Development Authority (BARDA)  
Office of the Assistant Secretary for Preparedness and Response  
Department of Health and Human Services  
330 Independence Avenue, S.W.  
Washington, DC 20201

Dr. Frederick Heineken  
Program Director (retired)  
National Science Foundation  
1701 Carissa Way  
Carlsbad, California 92011

WTEC Mission

WTEC provides assessments of international research and development in selected technologies under awards from the National Science Foundation (NSF), the Office of Naval Research (ONR), and other agencies. Formerly part of Loyola College, WTEC is now a separate nonprofit research institute. The Deputy Assistant Director for Engineering is NSF Program Director for WTEC. Sponsors interested in international technology assessments and related studies can provide support for the program through NSF or directly through separate grants or GSA task orders to WTEC.

WTEC’s mission is to inform U.S. scientists, engineers, and policymakers of global trends in science and technology. WTEC assessments cover basic research, advanced development, and applications. Panels of typically six technical experts conduct WTEC assessments. Panelists are leading authorities in their field, technically active, and knowledgeable about U.S. and foreign research programs. As part of the assessment process, panels visit and carry out extensive discussions with foreign scientists and engineers in their labs.

The WTEC staff helps select topics, recruits expert panelists, arranges study visits to foreign laboratories, organizes workshop presentations, and finally, edits and publishes the final reports. Dr. R.D. Shelton, President, is the WTEC point of contact: telephone 410-467-9832 or email Shelton@ScienceUS.org.
WTEC Panel Report on

INTERNATIONAL ASSESSMENT OF RESEARCH AND DEVELOPMENT IN RAPID VACCINE MANUFACTURING

PART TWO: AUSTRALIA, CHINA, INDIA, JAPAN, SOUTH KOREA

FINAL REPORT

July 2011

Joseph Bielitzki (Chair)
Stephen W. Drew
Sheldon H. Jacobson
Terrance Leighton
Mary Ritchey

This document was sponsored by the National Science Foundation (NSF) and other agencies of the U.S. Government under an NSF cooperative agreement (ENG 0844639) with the World Technology Evaluation Center (WTEC). The Government has certain rights in this material. Any opinions, findings, and conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of the United States Government, the authors’ parent institutions, or WTEC.
ABSTRACT

The unanticipated pandemic that emerged in the spring of 2009, caused by a novel triple reassortant virus (H1N1pan), renewed focus on the world's capability to produce effective vaccines quickly and deploy them in large volume. In 2007, WTEC completed a Rapid Vaccine Manufacturing study in North America and Europe. The H1N1 pandemic reinstituted interest in broadening this study to include Asia and Australia. The present report complements the 2007 report, updating the state of vaccinology research, development and policy in Asia and Australia. How the nations of Australasia coped with the H1N1 pandemic, when contrasted with the actions of North America and Europe, provided valuable insight into national policies, research strategies, and relationships among academic, government, and commercial entities.

Vaccines are the most cost-effective and enduring medical countermeasures yet developed; their efficacy has dramatically reduced illness, death, and epidemics worldwide. Nevertheless, emerging and accelerating public health threats require accelerated development and deployment of a new generation of vaccines. However, traditional vaccine production and integration into public health practice is slow and often cumbersome. The vaccine community has an unmet need to embrace innovation and become significantly more agile, adaptive, and responsive. Manufacturers urgently need new engineering approaches that can rapidly and safely incorporate the latest scientific discoveries into scalable, modular vaccine manufacturing processes. Regulators need greater awareness of new and emerging technologies so that differences from established practice can be incorporated into frameworks that support timely approval and distribution of advanced vaccines.

The first WTEC rapid vaccine manufacturing study evaluated vaccinology status and trends in the North America and Europe through workshops and site visits with the goal of identifying new areas of scientific and engineering opportunity and reward. The current study used the same approach to study rapid vaccine manufacturing in Asia, specifically in Australia, China, India, Japan, and South Korea. The WTEC study team visited 29 sites, exploring new research and production approaches, particularly as they relate to mitigation of a major pandemic threat. Because many innovative techniques of vaccine production have been developed first for animal vaccines, veterinary product manufacturing was a particular focus. In addition, the WTEC panel gathered information on the approaches and strategies used by Asian and Australian manufacturers to deliver vaccines at low per-dose costs.

This report considers vaccine policies, developing markets for vaccines, response to the H1N1 pandemic, and emerging manufacturing platforms. Based on the information gathered, key policy recommendations are made and research needs are identified. Major topics covered in the report are (1) government policies and controls on vaccines, including policy recommendations; (2) technology platform advances for rapid vaccine manufacturing, with a discussion of new ways of creating vaccines, controlling immune response, and reducing business risk, such as through public/private partnerships; and (3) vaccine economics, distribution, and supply chain management, with emphasis on economic factors impacting pediatric vaccines, influenza vaccine production, and pandemic influenza response and production issues.
ACKNOWLEDGMENTS

We at WTEC wish to acknowledge and thank all the panelists for their valuable insights and their dedicated work in conducting this international benchmarking study of rapid vaccine manufacturing R&D, and also to thank all the site visit hosts for so generously sharing their time, expertise, and facilities with us. For their sponsorship of this important study, our sincere thanks go to the National Science Foundation, the Department of Health and Human Services, and the Department of Agriculture. The subject of this study is of intimate concern to people everywhere; we believe this report provides a valuable overview of the field that can help citizens and policymakers around the world better understand and more effectively address requirements for new vaccine manufacturing technologies and systems so as to more rapidly produce effective vaccines that are reliable, affordable, and available as needed.

R. D. Shelton
President, WTEC
# Table of Contents

**Executive Summary** ........................................................................................................... xiii

- Vaccine Policies ....................................................................................................................... xiii
- Developing Markets for Vaccines .............................................................................................. xiii
- International Cooperation for Vaccines ................................................................................... xiv
- Response to the H1N1 Pandemic ............................................................................................... xiv
- Advancing Technology Platforms ............................................................................................ xiv
- Ten Key Policy Recommendations .......................................................................................... xv
- Research Needs ......................................................................................................................... xvi

**Perspectives** ............................................................................................................................. 1

- Background ................................................................................................................................. 1
- Vaccine Manufacturing Considerations ....................................................................................... 2
- Research Needs ............................................................................................................................ 3
- Process and Regulatory Needs ...................................................................................................... 5
- Scope of the Present Study ........................................................................................................... 6
- Overview of the Report ............................................................................................................... 10
- Acknowledgments ....................................................................................................................... 10

**Government Policies and Controls on Vaccines for Disease Prevention** ............................... 13

- Background ................................................................................................................................. 13
- Australia ....................................................................................................................................... 14
- China ........................................................................................................................................... 17
- India ........................................................................................................................................... 20
- Japan ........................................................................................................................................... 22
- Korea .......................................................................................................................................... 26
- Summary .................................................................................................................................... 27
- Recommendations ....................................................................................................................... 27

**Technology Platform Advances for Rapid Vaccine Manufacturing** ......................................... 31

- Understanding Immune Response ............................................................................................... 31
- Reducing Business Risk ............................................................................................................... 36
- Technology Platforms ................................................................................................................ 39

**Vaccine Economics, Distribution, and Supply Chain Management** ........................................... 43

- Background: Immunization and Vaccines .................................................................................. 43
- Routine Pediatric Immunization .................................................................................................. 44
- Pediatric Combination Vaccines and Pricing .............................................................................. 45
- Pediatric Vaccine Shortages and Stockpiling ............................................................................. 46
- Influenza Vaccine Production and Demand ................................................................................. 48
- Vaccine Distribution, Pandemic Influenza Response and Production Issues ............................ 50
- Questions and Challenges: The Future ......................................................................................... 55
- Research Opportunities ............................................................................................................... 58

**Appendix A. Delegation Biographies** ...................................................................................... 63

- Panel .......................................................................................................................................... 63
- Other Delegation Members ........................................................................................................... 66

**Appendix B. Site Reports** .......................................................................................................... 68
List of Figures

Figure 2.1. Relationship of the Gene Technology Regulator with other agencies. (OTGR website)...... 15
Figure 2.2. Application and approval procedure for clinical trials (from http://eng.sfda.gov.cn/cmsweb/webportal/W43879537/index.html).......................... 19
Figure 2.3. Japanese product development process: flow of drugs and medical devices from development to marketing. (from http://www.pmda.go.jp/english/service/outline_s.html)...... 23
Figure 2.4. Timeline for vaccine development (presentation to panelists, Feb 26, 2010). ............... 26
Figure 3.1. Use of simple synthetic lipid structures for targeting different vaccine cargos to dendritic cells (from Jackson 2009).......................... 33
Figure 3.2. The simplest immunogen consists of a helper T cell (Th) epitope and a pathogen target epitope (from Jackson 2009). .................................................. 33
Figure 3.3. Dendritic cell targeted cancer vaccine (courtesy of C. Parish)........................... 35
Figure 3.4. The role of technology platforms on the critical path to safe, effective vaccine. ............... 39
Figure B.1. General properties of liposomes used by Parish/Altin as a vaccine technology. .......... 73
Figure B.2. (Left) 3-Nitritriacetic acid di-tetradecylamine (3-NTA-DTDA) chelates metal ions (Ni2+) and binds multiple histidine residues in proteins (i.e., 6 His tags); (Right) Dendritic cell targeted liposome with engrafted His-tagged scFv or dAb specific for DC surface antigens and encapsulated tumor antigen and/or cytokines (Courtesy of Australian National University). .... 73
Figure B.3. Dendritic cell targeted cancer vaccine: contains membrane vesicles derived from tumor cells (courtesy of Australian National University). .................................................. 74
Figure B.4. Potent tumor protection is induced by DC targeted tumor antigens (B16-OVA Tumor). TMV = Tumor membrane vesicles from B16-OVA melanoma, L2 is a 6 His tagged peptide with no affinity for DCs, CD11c and DEC-205 refers to scFv specific for these antigens on mouse DCs and engrafted on the liposome-TMV vaccine construct (courtesy of Australian National University).................................................. 75
Figure B.5. Schematic representation of Lipovaxin. The vaccine construct is prepared by fusing 3NTA-DTDA liposomes with tumor membrane vesicles from the human melanoma cell line MM200, incorporation of IFNγ as a DC activator, addition of nickel and engrafting, via Ni-3NTA, a dAb specific for human DC-SIGN on DCs (Courtesy of Australian National University). ............... 76
Figure B.6. Vaccine development outline for Bioproperties Pty Ltd. ........................................ 83
Figure B.7. Development of recombinant influenza VLP vaccines (courtesy of Cadila Pharmaceuticals Limited). .................................................. 90
Figure B.8. Disposable manufacturing set-up (courtesy of Cadila Pharmaceuticals Limited). ............... 91
Figure B.9. The IIL veterinary vaccine plant, part of the 213 acre Hyderabad site, is one of the largest plants in the world with the state-of-the-art technology, WHO-GMP and ISO-9002 certified (courtesy of Indian Immunologicals Ltd.). .................................................. 102
Figure B.10. Annual production of vaccines in Japan (from a survey by the Association of Biologicals Manufacturers of Japan, Saikin Seizai Kyoukai; courtesy of the Ministry of Health, Labour, and Welfare of Japan). .................................................. 123
Figure B.11. WTEC Team at Serum Institute (left to right: F. Heineken, M. DeHaemer, M. Ritchey, J. Bielitzki, Exec. Dir. S.V. Kapre, Senior Dir. S. M. Dodwadkar).................................................. 149
Figure B.12. Steps involved in the development and approval of southern hemisphere inter-pandemic and pandemic influenza vaccines (from Grohmann 2009). .................................................. 153
Figure B.13. Technologies chosen by six WHO grantees (red) to build in-country influenza vaccine production capacity, in addition to technologies being deployed by other manufacturers (black), with relative time and investment projections for the technologies (from Grohmann 2009). ............... 155
Figure B.14. What else is attractive to dendritic cells apart from geometry? (from Zeng et al. 2002.). ....... 157
Figure B.15. Time and concentration dependence of lipopeptide uptake (courtesy D.F. Jackson). ............... 157
Figure B.16. What branched lipopeptides do to dendritic cells (courtesy of D.F. Jackson). ............... 158
Figure B.17. Secretory IgA is elicited by lipopeptide vaccines (from Batzloff et l. 2006). ............... 158
Figure B.18. Lipopeptides vaccination with Group A streptococcal (GAS) lipopeptide vaccine recuces bacterial load and allows survival (from Batzloff et al. 2006). .................................................. 159
Figure B.19. Novel intravaginal human papilloma virus (HPV) challenge using a fluorescent reporter (from Alphs et al. 2008).

Figure B.20. (Right) Lipopeptides induce strong anti-‘flu CD8+ T cell-mediated viral clearing responses; (Bottom left) … and prevent death following lethal challenge (from Jackson et. al. 2004).

Figure B.21. Antigen-specific CD8+ T cell responses after lipopeptide vaccination (from Day et al. 2007).
List of Tables

Table 1.1. Research Needs of the Vaccine Enterprise ................................................................. 4
Table 1.2. Uncertainties in Vaccine Production and Delivery ......................................................... 5
Table 1.3. Australian and Asian Sites Visited by WTEC Panelists* ................................................. 8
Table 1.4. Australia, China, Japan, South Korea Workshop (May 5, 2010) Presentations ................. 9
Table 5.1. History of Review Time for Product Applications (PMDA website) ........................... 24
Table B.1. Local cutaneous reaction to LC16m0, LC16m8, and conventional vaccinia vaccines (1968-
1974) ........................................................................................................................................ 111
EXECUTIVE SUMMARY

In April 2009, an unanticipated influenza outbreak occurred in central Mexico. The similarity of the H1N1 strain responsible for the historic outbreaks of “swine flu” during the early 20th century raised significant public health concerns. The infection spread rapidly among human populations with outbreaks occurring in the United States within weeks of the initial report. Unlike seasonal influenza that usually has the greatest impact on the very young and older populations, the most severe H1N1 cases occurred in children, young adults and pregnant women. In the United States, it is estimated that 59 million individuals became ill, with about 250,000 hospitalizations, and 12,000 deaths.

VACCINE POLICIES

In April and May of 2009, vaccine manufacturers were faced with the challenge of rapid response to an unanticipated antigenic variant of influenza that had sufficient similarity to previous swine flu outbreaks to elicit public health concerns and elevate risk perceptions. During the 2009 pandemic, vaccine manufacturing was accomplished within 6 months using methods and approval processes identical to those used for the production of annual influenza vaccines. The United States made a number of vaccine format and delivery decisions that possibly delayed vaccine availability; these included: single dose vials, no preservative, no adjuvant and poorly adapted models for vaccine distribution with limiting supplies. Several nations, notably Australia (population 22.3 million) and China (population 1.34 billion), were able to produce and release vaccine before distribution in the United States began.

The estimated global population is at 6.91 billion people. Of this number, 1.34 billion reside in China and another 1.16 billion in India. Currently, China has over 160 cities with populations exceeding one million people; and India has 43 million-plus cities. In a pandemic, these populations are at greater risk of disease transmission due to: their high pediatric (superspreader) density and the concentration of populations within cities. Failure to respond to disease emergence can and will result in significant morbidity and mortality while contributing to a global state of public health emergency.

DEVELOPING MARKETS FOR VACCINES

Populations with the highest number of individuals less than 18 years of age are found in Central Africa where school age children would benefit significantly from vaccination against the most common of childhood illnesses. In a pandemic, this large unvaccinated population represents a significant reservoir of infection, disease spread and probable mortality. Many Central African nations lack vaccine production capability and consequently must seek contracted or surplus vaccine as available.

African markets are of interest to both India and China for economic reasons and also political reasons that create opportunities for vaccine diplomacy. Asian countries are focused on the global engagement of disease risks, vaccinology capability and capacity, and regulatory conformity. The large populations of China and India are drivers for those governments to encourage development of vaccines that are can be produced in high volumes and low cost. Vaccine companies in China and India noted that countries in Africa, South America, and Southeast Asia are important markets for them, and that they would not compete in North America, Europe and Japan.
INTERNATIONAL COOPERATION FOR VACCINES

The World Health Organization (WHO) recently reached an agreement on sharing influenza viruses among nations during pandemics. The negotiations took four years to complete and the generated document does not have universal participation, and even with the best of intentions may fail to provide redress for the inevitable shortage of vaccines early in an outbreak. Issues of intellectual property, production costs, decision making, and distribution of product to third world nations slowed the agreement. Pandemic preparedness is, and will continue to be, a global health concern limited by geopolitical and legal issues divorced from the immediacy of public health concern, research funding and technology development.

RESPONSE TO THE H1N1 PANDEMIC

This WTEC study of rapid vaccine manufacturing in Australia and Asia was undertaken partly in order to identify effective immunization practices, policies, and regulatory strategies. The study revealed that in Australia and the Asian countries visited, the social context for development of vaccines, vaccine policices and regulation had common, but varying emphases among themselves, the United States, and the European countries studied in the 2007 report.

All the countries we visited understood the need to act rapidly to protect the population, but with care to ensure a safe and effective vaccine. Japan was most like the United States in concern for individual safety and the need for compensation programs to pave the way for the pandemic H1N1pandemic vaccine program. China, on the other hand, was more focused on information sharing among H1N1pandemic vaccine producers and rapid deployment of the program.

Australia and China had the most rapid responses and these countries used entirely domestic supplies of vaccine. Japan and Korea used internationally procured vaccine to supplement their supplies. Pre-planning for these immunization programs, which involved well established development and production methods, resulted in time savings of 1-3 months from a typical influenza vaccine seasonal program.

Several key differences stand out in each nation’s policy approach to pandemic flu. China’s centralized system allows for rapid deployment of programs. Australia’s extensive communication network and partnerships allow for programs to proceed quickly. Japan has a program in place to assure that it has sufficient domestic capacity to deliver pandemic vaccines quickly.

ADVANCING TECHNOLOGY PLATFORMS

The study also examined the state of the science and technology of vaccine discovery, development, antigen expression, scale-up, and manufacture in Australia and Asia and identified research opportunities. As was reported by the 2007 WTEC study on rapid vaccine manufacturing, technology platforms continue to be the foundation of rapid development of vaccines and play critical roles at each stage of progression to licensed vaccines. Some of the trends that were observed in 2007 have continued to grow in importance around the world, and the foundational science has strengthened. Exciting technical advances are occurring in the areas of molecular design of vaccines, the control and integration of immune response to vaccination and the fundamental interaction of innate and adaptive immunity. These advances in the science of immunology and microbiology and the technology of vaccine production could lead to more efficient and effective vaccines as well as shorten the time from discovery to manufacturing.
At Osaka University in Japan, Professor Shizuo Akira’s work with Toll-Like Receptors has shown that activation of the innate immune system is a prerequisite for the induction of acquired immunity involving T- and B-cell mediation and T Helper-cell response. Professor Akira’s work has mapped the functional genes of immune response in mice, and he predicts that the next frontier in immunology will be at the crosstalk interface of innate immunity and adaptive immunity.

In Australia at Melbourne University, Professor David C. Jackson has created synthetic self-adjuvanting vaccines that target dendritic cells through the endocytic toll like receptor TLR-2. His studies have shown that this new class of vaccines is effective against viruses, bacteria and tumors in test animals. Dr. Jackson’s results have demonstrated an innovative influenza vaccine modality, utilizing conserved viral epitopes, that might bypass the necessity of having prior availability of emergent pandemic or seasonal strains to achieve vaccine protection.

At Australian National University, Professor Christopher Parish in collaboration with Dr. Paul Foster’s group has developed a new approach to cancer immunotherapy. This innovative strategy for cancer vaccine development utilizes liposome-based vaccine constructs that target multiple tumor antigens (pan-epitopes) to DCs in vivo. This work has resulted in a complex and unique human melanoma vaccine formulation (Lipovaxin), which is undergoing clinical trials.

**TEN KEY POLICY RECOMMENDATIONS**

Innovations such as the above that arise in academic, government, or small company laboratories face daunting hurdles on the path to product license for clinical application. Oftentimes legal issues and economics are the largest obstacles to developing new vaccines and introducing them into the marketplace. Our studies in Australia and Japan identified two very successful examples of public/private partnerships that share intellectual and physical resources, manage economic risk, and reduce business uncertainty.

Current vaccine production is slow and meticulous, and lacks the agility, rapidity and modularity to meet the rising tide of global disease pressure. If the 2009-2010 pandemic had been caused by a more virulent influenza strain than H1N1pan, and vaccine production had proceeded at the same rates, uncontrolled morbidity and mortality could have resulted. Therefore, based on recent experiences with both H1N1pan and H5N1, the unmet needs for accelerated vaccine production are salient and require:

- Proactive enhancement of the regulatory process for approval of new vaccine production modalities and the repurposing of manufacturing facilities.
- Improved dissemination of information to the public with a greater emphasis on public health outreach, education about the value and safety of vaccines, their manufacturing process, and the time course for availability.
- Improvement to the regulatory process for and elimination of litigation barriers to the approval and adoption of new vaccine production methods.
- Encouragement of public/private partnerships to bridge the “valley of death” between vaccine and immunology discovery and clinical translation.
- Developing a funding mechanism that rewards proven scientific leadership and track records rather than project-specific proposals, also encouraging links to researchers outside of vaccinology, and limits reporting and reviews to multi-year cycles.
• U.S. government/industry partnership around a facility dedicated to developing and producing vaccines on an emergency basis.

• Routine review of rapid response policies at the Departments of Health and Human Services and Homeland Security.

• Continued focus on regulatory harmonization and guideline development for emerging technologies would allow more transparency in developing vaccines and facilitate quicker reviews.

• Investment more in technology platforms in the arenas of pre-clinical and clinical assessment of vaccine safety and efficacy. This will shorten, augment or eliminate animal and human studies and reduce the time required to bring new vaccines to market.

• Promotion of research into novel, more flexible paradigms for the delivery of public health services that can accommodate both existing and pandemic influenza outbreak vaccine and medical supply distribution requirements and needs.

RESEARCH NEEDS
The need for agile, adaptive and responsive vaccine development is obvious at all levels of the enterprise from basic science through the fill and finish process, as summarized below.

Basic Research Needs
Basic research investments are needed to understand:

• mechanisms of antibody protection
• mechanisms of non-antibody cellular protection
• the interplay between cell- and antibody-based protection
• mechanisms of adjuvant immune system programming
• pathogen strategies for immune system evasion

Discovery of new immunization strategies are necessary to:

• program the type and differentiation state of the immune response desired
• optimize the efficacy of effector mechanisms against pathogen vulnerabilities
• establish protective capacity at vulnerable body surfaces
• optimize pathogen fitness costs for vaccine resistance
• avoid immune system exhaustion, and establish system-wide synergistic capacity
• enhance capability for immune response at all relevant sites

Applied Research Needs
There would be substantial benefits from applied research that focuses on:

• aligning immunization modes and routes with the natural routes of disease infection
• dendritic cell targeting strategies
• technologies for multiantigen presentation
• strategies for induction of multiple arms of the immune system
• self-adjuvanting vaccines
**Bioengineering Research Needs**

Engineering research investments are required in:

- production module standardization, systems for embedded validation
- decreases in process scale
- development of production system replicability, transferability, and integration

There is also a need for further advances in:

- standardized interfaces
- in-line cell separation
- product isolation, and formulation, combined with end-to-end integration of components into macrosystems

The WTEC Panel on Rapid Vaccine Manufacturing

June 2011
CHAPTER 1

PERSPECTIVES

Joseph Bielitzki and Terrance Leighton

BACKGROUND

Vaccines are the most cost-effective and enduring medical countermeasures that science has developed. They have dramatically reduced global epidemics, death, and illness. Emerging and accelerating public health threats require new vaccine technologies to address a broad range of challenging diseases. Current vaccine production is slow and meticulous, and lacks the agility, rapidity, and modularity needed to meet the rising tide of global disease pressure. Vaccine manufacturers are in urgent need of innovative architectures that can rapidly and safely incorporate scientific discoveries into scalable and adaptive manufacturing infrastructures.

The initial WTEC study of vaccine manufacturing, conducted in 2007, evaluated the vaccine manufacturing processes in the United States and Europe. At that time serious consideration was given to the possibility that a global influenza pandemic could be caused by the avian H5N1 virus. Periodic human clusters of this infection had occurred globally with high levels of morbidity and mortality but low levels of transmissibility. In April 2009, an unanticipated influenza outbreak in central Mexico was associated with a triple reassortant H1N1 variant of influenza. The similarity of this strain to the historic outbreaks of “swine flu” during the 20th century raised significant concerns. The infection spread rapidly among human populations, with outbreaks occurring in the United States within weeks of the initial report. Unlike seasonal influenza, which usually has the greatest impact on the very young and older populations, the most severe H1N1pan cases occurred in children, young adults, and pregnant women. The World Health Organization declared a pandemic in June 2009 as the virus spread globally. In the United States, it is estimated that 59 million individuals became ill, with about 250,000 hospitalizations and 12,000 deaths. During the primary spread of this pandemic, no vaccine was available and existing vaccines provided little, if any, cross protection. By November 2009, vaccination against H1N1pan had been provided to about 65 million individuals globally as the infection rate showed signs of diminishing. H1N1pan continued to circulate in 2010 with evolution of new genotypes, antiviral resistance, and the potential for 2009 vaccine resistance. Although H1N1pan is highly transmissible, morbidity and mortality have been comparable to seasonal influenza levels.

In April and May of 2009, vaccine manufacturers were faced with the challenge of rapid response to an unanticipated antigenic variant of influenza that had sufficient similarity to previous swine flu outbreaks to elicit public health concerns and elevate risk perceptions. The World Health Organization (WHO) provided international leadership in the rapid development, production, and distribution of vaccine. The virus, originating in Veracruz, Mexico, resulted in severe disease and death in an unanticipated segment of the population.
The news media quickly focused on the spread of the disease and the public health risks created by previous pandemics. Governments were equally concerned with the potential of a devastating global pandemic with high mortality rates and economic impacts in the clear absence of a protective vaccine or adequate amounts of antiviral compounds.

**VACCINE MANUFACTURING CONSIDERATIONS**

Vaccine manufacturing in the United States and Western Europe resides within a small number of large multinational producers, whose production capacity is based on historic population trends, birth rates, and mandatory government requirements for vaccination. Traditional vaccine development and production for newly emergent pathogens is a slow and expensive, step-wise process requiring from 9 to 23 years. During the 2009 pandemic, vaccine manufacturing was accomplished within 6 months using methods and approval processes identical to those used for the production of annual influenza vaccines. Vaccine distribution—which required the identification of the H1N1pan strain, strain release for vaccine production, production optimization, large-scale production, and product release—was limited. Adequate numbers of doses become available only as the pandemic began to diminish.

The United States relies on some domestic influenza vaccine production, but much is produced in Europe. The United States made a number of vaccine format and delivery decisions that possibly delayed vaccine availability (e.g., single dose vials, no preservative, no adjuvant and poorly adapted models for vaccine distribution when confronted with limiting supplies). The use of single dose vials greatly reduces the possibility of contamination compared to multiple dose vials, but it increases the fill and finish time and packaging requirements for the product. Single dose vials allow the product to be released without preservatives. At the time of the pandemic, public opinion was concerned that the preservative or even the vaccine itself could be associated with autism, reducing its acceptability among parents of young children. The decision not to use an adjuvant increased antigen production times, since more antigen is required in the absence of an adjuvant to induce a protective level of immunity. Several nations, notably Australia (population 22.3 million) and China (population 1.34 billion), were able to produce and release vaccine before distribution in the United States began.

The need for vaccine production is determined to a large extent by the size of the population, the population at risk, environmental risk factors, and the public health infrastructure of the country. Many nations lack resident capacity to meet annual vaccine needs and are dependent on imported vaccines. Asia represents a region that diverges from vaccine production needs and philosophies seen in the United States and Western Europe. The large populations of India and China require a significantly greater investment in vaccine production at a scale that is not seen in the West. In addition to population requirements, other drivers impact these countries' vaccine infrastructure, such as political uncertainty; proximity to a major migratory route for wild bird virus hosts that links much of Eastern and South Asia with other population centers, such as Japan, South Korea, Australia, Indonesia, the Philippines and Malaysia; intensity of regional disease emergence and spread; political alliances; and altruistic public health programs in less developed nations.

The populations in India and China comprise one third of the total global population. These population sizes necessitate modifications in vaccine production if nations are to meet their responsibilities to global public health protection. The estimated global population is at 6.907 billion people, of this number, 1.34 billion reside in China and another 1.16 billion in India. Currently, China has over 160 cities with populations exceeding one million people and India
has 43 million-plus cities. In a pandemic, these populations are at greater risk of disease transmission due to: their high pediatric (superspreader) density and the concentration of populations within cities—driving shorter response times for the development and release of suitable vaccines. In addition, authorities recognize that failure to respond to disease emergence can and will result in significant morbidity and mortality while contributing to a global state of public health emergency. By comparison, the United States population approximates 311 million, and the European Union approximates 501 million people.

In most developed nations the average age is increasing and birth rates are declining. Populations with the highest number of individuals less than 18 years of age are found in Central Africa where school age children would benefit significantly from vaccination against the most common of childhood illnesses. In a pandemic, this large unvaccinated population represents a significant reservoir of infection, disease spread, and probable mortality. Many Central African nations lack vaccine production capability and consequently must seek contracted or surplus vaccine as available. African markets are of interest to both India and China for both economic and political reasons that create opportunities for vaccine diplomacy. Asian countries are focused on the global engagement of disease risks, scientific communities, vaccinology capability and capacity, and regulatory conformity. The United States cannot afford to ignore these geopolitical forces and trends.

The unmet need for accelerated vaccine production is evident based on recent experiences with both H1N1pan and H5N1. Vaccine production at current developmental rates for unknown (e.g., Severe Acute Respiratory Syndrome, or SARS) or emerging viruses could have cascading and devastating consequences. Fortunately SARS, a coronavirus, had low transmissibility and H1N1pan had high transmissibility combined with modest mortality. SARS represents a challenge for traditional vaccine development. SARS emerged in China and rapidly became a global public health issue when cases were reported in 43 other nations. No vaccine existed for SARS and no existing vaccine provided cross protection. Following the initial wave of infections and resolution of the initial outbreak, Chinese investigators developed a SARS vaccine within four years. The vaccine completed early Phase 1 clinical trials and further development stopped at this point. Additional trials would have prepared the vaccine for release, but in the absence of disease an economic rationale could not be developed or justified for further investment. Given the endemic nature of coronaviruses in bats, the multirecombination origins of these viruses, and their potential for species jumps, further development and testing of a coronavirus vaccine could be prudent.

**RESEARCH NEEDS**

The need for agile, adaptive, and responsive vaccine development is obvious at all levels of the enterprise from basic science through the fill and finish process (Table 1.1).
Table 1.1. Research Needs of the Vaccine Enterprise

**Basic Research**
Investments are required to understand:
- Mechanisms of antibody protection
- Mechanisms of non-antibody cellular protection
- The interplay between cell- and antibody-based protection
- Mechanisms of adjuvant immune system programming
- Pathogen strategies for immune system evasion
- Antibody responses that are not protective

Discovery of new immunization strategies is necessary to:
- Program the type and differentiation state of the immune response desired
- Optimize the efficacy of effector mechanisms against pathogen vulnerabilities
- Establish protective capacity at vulnerable body surfaces
- Optimize pathogen fitness costs for vaccine resistance
- Avoid immune system exhaustion, and establish system-wide synergistic capacity
- Ensure capability for immune response at all relevant sites
- Uniformly generate protective immunity with a single dose of vaccine

**Applied Research**
There would be substantial benefits from research focused on:
- Aligning immunization modes and routes with the natural routes of disease infection
- Dendritic cell targeting strategies
- Technologies for multiantigen presentation
- Strategies for induction of multiple arms of the immune system
- Self-adjuvanting vaccines
- Stimulation of natural adjuvants

**Bioengineering Research**
Research investments are required in:
- Production module standardization, including systems for embedded validation
- Decreases in process scale
- Development of production system replicability, transferability and integration

There is also a need for further advances in:
- Standardized interfaces
- In-line cell separation
- Product isolation and formulation
- End-to-end integration of components into macrosystems

A range of process oriented questions impact pandemic or emerging virus decision trees (Table 1.2). Many of these uncertainties have been engaged in scenarios, but how these plans will perform in an actual pandemic is unknown.
Table 1.2. Uncertainties in Vaccine Production and Delivery

- Which agency or department is best equipped to identify the pathogen?
- How long will it take to make this identification with existing capabilities and what methodologies are required to make such identification in near real-time?
- How will samples be handled and transported nationally and if necessary internationally?
- How will information be shared among agencies, departments, and nations?
- How will the public be informed and kept informed during the pandemic as to the nature of the outbreak, disease spread and risk, treatment options, and the efficacy of prophylactic measures?
- What role will local health authorities have in establishing needs and priorities?
- What are the safety considerations for vaccines in a pandemic emergency?
- Which agency will make the decision on critical antigenic characteristics necessary to optimize an immune response?
- How will government activate industry and academia to respond to the crisis?
- Will international agreements be used to optimize production, formulation, and distribution priorities?
- Will these agreements be in place or determined ad hoc?
- Will nations with significant vaccine manufacturing capacity make vaccines available to nations with lesser or no vaccine production capability?
- Can the United States with its existing vaccine infrastructure meet the demands of the population for vaccines in a timely and efficient manner?
- Who will produce vaccine for the United States population if domestic production is inadequate?
- Under what form of agreement will such non-domestic production occur?

PROCESS AND REGULATORY NEEDS

New adjuvants are needed to improve immune responses and reduce response times. Single dose vaccines with immune response take rates approaching 100% are required to quickly extinguish outbreaks. Improved bio-surveillance and rapid methods for identifying protective antigens in emerging viruses are critical to the ability to respond to a pandemic. Our ability to repurpose existing facilities to produce a new vaccine in a timely manner is limited by design and regulation. The regulatory process employs antiquated metrics and clinical trial methodologies for validation and verification of vaccine efficacy and safety. Investment in new production modalities with improved bioengineering controls would shorten production times and improve product uniformity. Proactive enhancement of the regulatory pipeline in advance of an emergency situation, to mitigate rate limiting steps while maintaining safety controls, could reduce approval time without increasing risk. Information dissemination to the public during the H1N1 pandemic focused on the nature of the virus, symptomology, new case identification, and locations, with little content regarding vaccine availability or efficacy. Greater emphasis on public health outreach, education about the value and safety of vaccines, their manufacturing process, and the time course for availability are necessary.

Technologically, it is evident that development of new adjuvants, production systems, engineering controls, and distribution modeling are not progressing at optimal levels. Economic drivers are and will continue to limit progress in vaccine manufacturing. Regulatory constraints reduce innovation. The validation process is a barrier to innovation and technical progress. Innovative manufacturing paradigms, strategies, and partnerships must be encouraged and validated. New production modalities are costly to the vaccine developer. Every change in production increases the potential for liability and litigation, further reducing the drive for innovative change.
How innovation occurs and how the United States contributes to developing new technologies is unclear. Advanced vaccine production technologies capable of lowering production costs and time to product were developed in the United States but acquired by corporations outside the United States because of regulatory approval and litigation barriers to adoption of new production methods. Public/private partnerships could bridge the gap between vaccine discovery and clinical translation while enabling tighter coupling between infectious disease protection and public/private consortia supported by forward leaning investments. Basic research funding mechanisms are not optimal for fostering innovations in vaccine discovery, providing long-term multidisciplinary commitment, or encouraging links with industry. A funding mechanism that rewards proven scientific leadership and track records rather than project-specific proposals, encourages links to researchers outside of vaccinology, and limits reporting and reviews to multi-year cycles could overcome many of the current gaps in United States translation vaccinology. These strategies are already well established in several Asian countries.

The World Health Organization (WHO) recently reached an agreement on sharing influenza viruses among nations during pandemics (World Health Organization 2010, 2011). The negotiations took four years to complete and the generated document does not have universal participation, and even with the best of intentions may fail to provide redress for the inevitable shortage of vaccines early in an outbreak (see Enserink 2011). Issues of intellectual property, production costs, decision making, and distribution of product to third world nations slowed the completion of the agreement. Pandemic preparedness is and will continue to be a global health concern limited by geopolitical and legal issues divorced from the immediacy of public health concern, research funding and technology development.

SCOPE OF THE PRESENT STUDY

In 2007 WTEC conducted an assessment in this field. The final report and workshop presentations are posted at http://www.wtec.org/vaccmfg/. However, the available funds limited the scope to Western Europe combined with some study of R&D in North America. The expert panel and several of the sponsors wanted to extend the scope to Asia, where it was known that innovative techniques were being developed to deal with the endemic avian flu. When interest was rekindled by the swine flu pandemic in the spring of 2009, WTEC prepared a study to include Australia and Asia to complete the assessment of the field worldwide.

This WTEC assessment informs with respect to future research initiatives that address bottlenecks in the R&D and production chain which cause problems for the rapid development, large-scale manufacturing, and distribution of new vaccines. The results provide insight to R&D program managers worldwide, including those in the U.S. National Science Foundation and National Institutes of Health, as well as other agencies of the Department of Health and Human Services (e.g., FDA, BARDA, CDC), the Department of Homeland Security, and the Department of Defense. The information also will be available to international organizations concerned with public health.

Key questions that are addressed in this evaluation include the following:

- What is the status of international R&D on rapid vaccine manufacturing and the development-deployment systems chain?
- How do U.S. activities in this area compare to those of other countries?
- What ideas from overseas are worth exploring in U.S. R&D programs, and vice versa?
• What technologies will pay off, and what are the needs for government promotion of
general progress in vaccine manufacturing?
• What opportunities exist for international collaboration?

The study focus was an assessment of engineering R&D for flexible, scalable, modular vaccine
manufacturing that could provide rapid response to the needs of both the general public and
to smaller regional outbreaks of disease. Agricultural vaccines were considered as well
because of the demands for massive inoculation of domestic fowl and animals from which
applicable lessons may be learned. In addition, the supply chain issues of storage, shelf-life,
and delivery were examined.

The panel met as many leading researchers in vaccine manufacturing as possible and visited
representative production facilities in Asia, India, and Australia. Discussion of public policy
concerning vaccine production and distribution, including national responses to the recent
H1N1 pandemic, informed an understanding of national strategies for vaccine development
and distribution.

The Study Team

WTEC assembled a team of experts in the field of vaccinology to conduct the study, drawing
from academia, private business, and government. Five members of the team are authors of
the report. All of them had served previously as the panel of experts and authors for the
similar assessment in Europe that was reported in 2007. In addition three representatives of
sponsoring government agencies accompanied the principal authors on various legs of the
assessment in Australia and Asia.

Authors:
• Joseph Bielitzki (Panel Chair), University of Central Florida
• Stephen W. Drew, Drew Solutions, LLC
• Sheldon H. Jacobson, Professor, Department of Computer Science, University of Illinois at
  Urbana Champaign (UIUC), and Director, UIUC Simulation Optimization Laboratory
• Terrance Leighton, Senior Staff Scientist, Children's Hospital Oakland Research Institute
• Mary Ritchey, Ritchey Associates, Inc.

Sponsor Representatives:
• Cyril Gerard Gay, National Program Leader, Animal Health, Animal Production and
  Protection, Agricultural Research Service, United States Department of Agriculture
• Frederick G. Heineken, Program Director Bioengineering, U.S. National Science
  Foundation (retired)
• Narayan Iyer, Project Officer in the Chemical, Radiation, and Nuclear Section of the
  Division of CBRN Countermeasures in the Office of the Biomedical Advanced Research
  and Development Authority (BARDA) within the Department of Health and Human
  Services Office of the Assistant Secretary for Preparedness and Response.

WTEC participants in the Australia-Asian tour and site visits were Michael J. DeHaemer,
WTEC Executive Vice President; Remi Kumagai, advance contractor for China, Japan, and
South Korea; Juyan Zhang, guide-interpreter for China; Mohan Tilak, Anchortek, and Asmita
Damle, Le Cadeau, advance contractors for India.
Study Elements and Chronology

Kickoff (October 28, 2009)

After gaining the agreement of the European study panelists to participate, the assessment of rapid vaccine in Asia and Australia was begun at a meeting held at the National Science Foundation on October 28, 2009. Representatives of the sponsoring agencies charged the panelists to prepare for and conduct the assessment. Immediately with WTEC support, the panel members began the process of identifying the leading sites for rapid vaccine manufacturing R&D in Australia, China, Japan and South Korea.

Site visits in Australia and East Asia (February and March 2010) and India (October 2010)

Accordingly itineraries were formulated to visit the target countries in three subgroups of the panel, during the periods of February 21-26, March 1-5, and October 17-22, 2010. Table 1.3 shows the sites the WTEC team visited.

<table>
<thead>
<tr>
<th>Site</th>
<th>Country</th>
<th>Date in 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Department of Microbiology and Immunology</td>
<td>Australia</td>
<td>Feb. 21</td>
</tr>
<tr>
<td>Faculty of Medicine, Dentistry &amp; Health Sciences University of Melbourne</td>
<td></td>
<td></td>
</tr>
<tr>
<td>John Curtin School of Medical Research (JCSMR)</td>
<td>Australia</td>
<td>Feb. 22</td>
</tr>
<tr>
<td>Australian National University (ANU)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Royal Melbourne Institute of Technology (RMIT)</td>
<td>Australia</td>
<td>Feb. 22 &amp; 23</td>
</tr>
<tr>
<td>Bioproperties Pty Ltd</td>
<td>Australia</td>
<td>Feb. 22 &amp; 23</td>
</tr>
<tr>
<td>Therapeutic Goods Authority (TGA)</td>
<td>Australia</td>
<td>Feb. 23</td>
</tr>
<tr>
<td>Australian Government, Department of Health and Aging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ministry of Agriculture, Peoples Republic of China</td>
<td>China</td>
<td>Mar. 2</td>
</tr>
<tr>
<td>Ministry of Health, Peoples Republic of China</td>
<td>China</td>
<td>Mar. 1</td>
</tr>
<tr>
<td>National Institute for the Control of Pharmaceutical and Biological Products (NICPBP)</td>
<td>China</td>
<td>Mar. 2</td>
</tr>
<tr>
<td>PATH China</td>
<td>China</td>
<td>Mar. 3</td>
</tr>
<tr>
<td>Sinovac</td>
<td>China</td>
<td>Mar. 1</td>
</tr>
<tr>
<td>Tianyuan Bio-Pharmaceuticals</td>
<td>China</td>
<td>Mar. 2</td>
</tr>
<tr>
<td>Biken</td>
<td>Japan</td>
<td>Feb. 25</td>
</tr>
<tr>
<td>The Research Foundation for Microbial Diseases of Osaka University Kanonji Institute</td>
<td>Japan</td>
<td></td>
</tr>
<tr>
<td>Kaketsuken</td>
<td>Japan</td>
<td>Feb. 26</td>
</tr>
<tr>
<td>The Chemo-Sero-Therapeutic Research Institute</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kitasato University</td>
<td>Japan</td>
<td>Feb. 26</td>
</tr>
<tr>
<td>National Institute of Infectious Diseases(NIID)</td>
<td>Japan</td>
<td>Feb. 26</td>
</tr>
<tr>
<td>Osaka University</td>
<td>Japan</td>
<td>Feb. 26</td>
</tr>
<tr>
<td>Ministry of Health, Labour and Welfare</td>
<td>Japan</td>
<td>Feb. 26</td>
</tr>
<tr>
<td>Green Cross Veterinary Products Co., Ltd.</td>
<td>South Korea</td>
<td>Mar. 5</td>
</tr>
<tr>
<td>Mogan Biotechnology Research Institute</td>
<td>South Korea</td>
<td>Mar. 5</td>
</tr>
</tbody>
</table>

*See Appendix B for site reports on the WTEC Panel’s visits to these organizations.
Table 1.3, continued+

<table>
<thead>
<tr>
<th>Site</th>
<th>Country</th>
<th>Date in 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>All India Institute of Medical Science</td>
<td>India</td>
<td>Oct. 17</td>
</tr>
<tr>
<td>Hilleman Labs</td>
<td>India</td>
<td>Oct. 18</td>
</tr>
<tr>
<td>PATH India</td>
<td>India</td>
<td>Oct. 18</td>
</tr>
<tr>
<td>Department of Biotechnology, Ministry of Science &amp; Technology</td>
<td>India</td>
<td>Oct. 18</td>
</tr>
<tr>
<td>Panacea Biotec</td>
<td>India</td>
<td>Oct. 19</td>
</tr>
<tr>
<td>Cadila Pharmaceuticals Ltd</td>
<td>India</td>
<td>Oct. 20</td>
</tr>
<tr>
<td>Zydus Cadila Healthcare Limited</td>
<td>India</td>
<td>Oct. 20</td>
</tr>
<tr>
<td>Indian Immunologicals Ltd.</td>
<td>India</td>
<td>Oct. 21</td>
</tr>
<tr>
<td>Bharat Biotech International Limited</td>
<td>India</td>
<td>Oct. 21</td>
</tr>
<tr>
<td>Biological E Limited</td>
<td>India</td>
<td>Oct. 21</td>
</tr>
<tr>
<td>Serum Institute of India Ltd.</td>
<td>India</td>
<td>Oct. 22</td>
</tr>
</tbody>
</table>

*See Appendix B for site reports on the WTEC Panel's visits to these organizations.

**Australia, China, Japan, South Korea Workshop (May 5, 2010)**

The panelists conducted a workshop at the National Science Foundation on May 5, 2010 to discuss results of their assessment of the countries that were visited in February and March 2010. The presentations at the workshop are listed in Table 1.4.

**Table 1.4. Australia, China, Japan, South Korea Workshop (May 5, 2010) Presentations**

1. **Introduction**, Joe Bielitzki
   a. The Biogeography of Eastern Asia and Australia
   b. Vaccine Production in China and South Korea
   c. The Critical Path to H1N1 Vaccine Supply
2. **Manufacturing Highlights (Australia and Japan)**, Steve Drew
3. **Vaccinology Science and Technology in Australia**, Terry Leighton
4. **Vaccinology Science and Technology in Japan**, Steve Drew
5. **Government Policies and Controls on Vaccines in Disease Prevention**, Mary Ritchey
6. **Economics of Vaccines, National Goals, and National Investments**, Sheldon Jacobson
7. **Veterinary Vaccines**, Joe Bielitzki
8. **Trends, Needs and Gaps in Vaccine Science and Manufacturing (Where is Louis Pasteur When we Need Him?)**, Terry Leighton

Note: View the workshop proceedings at: [http://www.wtec.org/vaccine2/workshop/Vaccines2proceedings.pdf](http://www.wtec.org/vaccine2/workshop/Vaccines2proceedings.pdf)

**Site visits in India (October 2010)**

When further funding became available in the summer of 2010, a subgroup of the study panel was able to visit important sites in India, giving a further perspective for another populous nation with different needs and vaccination policies.
OVERVIEW OF THE REPORT

- Chapter 2 by Mary Ritchey focuses on public policies in Australia and Asia for vaccine approval and production with special interest in processes for handling the H1N1 pandemic.
- Chapter 3 by Steve Drew reviews important technology advances and trends that were noted to improve vaccine manufacturing in Australia and Asia, and, in fact, the rest of the world since 2007.
- Chapter 4 by Sheldon Jacobson compares the different practices for vaccine economics among the recently visited countries in Australasia, Europe, and North America. The chapter concludes with suggestions for future areas of research for improvement of the economics and logistics of vaccines.
- Appendixes
  A. Biographies of the study team members
  B. Site reports on the institutions visited
  C. Glossary of acronyms used in this report
  D. Definitions of terms used in this report

ACKNOWLEDGMENTS

The panelists wish to extend our gratitude and appreciation to all presenters and hosts for their generous sharing of time, expertise, insights, and facilities with us, and for the stimulating discussions that informed the preparation of this report. We also wish to thank WTEC staff members and advance contractors for the excellence of their support and arrangements, researching sites of interest, overcoming logistic and communication challenges, and completing very worthwhile itineraries. We thank the sponsors who made the study possible: the National Science Foundation, the Department of Health and Human Services, and the United States Department of Agriculture. We hope that the process of conducting the study and the resulting report will serve to extend mutual cooperation among practitioners in the field and contribute to advancing the science, technology, and associated systems of rapid vaccine manufacturing for the benefit of the world’s population.

REFERENCES AND SUGGESTED READING

President’s Council of Advisors on Science and Technology. 2009. Report to the President on U.S. Preparations for 2009 – H1N1 Influenza. August 7:www.ostp.gov/cs/pcast.


World Health Organization. 2010. Pandemic influenza preparedness: sharing of influenza viruses and access to vaccines and other benefits; outcome of the process to finalize remaining elements under the pandemic influenza preparedness framework for the sharing of influenza viruses and access to vaccines and other benefits Report by the Secretariat. 63rd World Health Assembly, A63/4: Provisional Agenda Item 11.1, 15 April 2010. 13 pp.

CHAPTER 2

GOVERNMENT POLICIES AND CONTROLS ON VACCINES FOR DISEASE PREVENTION

Mary B. Ritchey

Chapter 2 of the first WTEC report on rapid vaccine manufacturing (Bielitzki et al. 2007) described the context and background for regulating the development and commercialization of vaccines for disease prevention in addition to the general regulatory process. The status of regulation and control in the United States and Europe was described along with plans to control future viral influenza pandemics. In addition, selected elements of quality control testing technology were discussed.

This chapter will focus on the regulatory systems and policies that are in place for Australia, China, India, Japan and Korea and their experience with the process for regulating the recent pandemic H1N1 vaccine. Examples and opportunities for a more rapid response will be included. Specific technologies that could improve quality control testing were not highlighted by any of our hosts, but exciting immunological research that is being applied to vaccine development has potential to improve this area as well.

BACKGROUND

The insights into government policies and regulations in Australia and the Asian countries that we visited were derived from conversations with representatives of various government agencies and companies and university employees who were regulated by these agencies (see Appendix B. Site Reports). Websites of the various agencies were also reviewed.

The social context for development of vaccines, vaccine policies, and regulation had common, but somewhat different, emphases when compared among the different countries we visited in Europe and the United States. All the countries we visited understood the need to act rapidly to protect their populations, but with time needed to ensure a safe and effective vaccine. Japan was most like the United States in concern for individual safety and the need for compensation programs to pave the way for the pandemic H1N1 vaccine program. China, on the other hand, was more focused on information sharing among H1N1 vaccine producers and rapid deployment of the program.

The information presented in this chapter represents what the panel was able to gather from the various sites visited, noting that time was limited at each site and only a limited, although hopefully representative, sampling of sites was visited.
AUSTRALIA

Key Government Agencies

Human Vaccines

Human vaccines are regulated by the Therapeutic Goods Authority (TGA) of the Department of Health and Aging. This agency is responsible for pre-marketing assessments of vaccines, audits and assessment of manufacturing quality and post-marketing monitoring of compliance with standards. The regulations and guidelines are generally consistent with those found in the European Union or the United States. Applications for registration of products written in the Common Technical Document (CTD) format of the EU regulations are accepted. EU guidelines are used to determine acceptable practices and quality. Expert committees are employed to review data. Although the timing for review of applications is not specified, historical review indicates that review timelines are in the ranges generally found in the United States and Europe. Accelerated reviews are possible for life saving drugs, for example, review of Glivec, an anti-cancer agent was achieved in 5 months. Regulations allow for use of medicines with Phase 2 clinical data only in situations where alternatives do not exist.

The agency is small, without a research component, with about 25 core members to accomplish its mission. It is a "Cost Recovery Organization" meaning that it must obtain operating expenses from fees to companies that require its services. Because of its small size and geographic location, TGA relies on extensive collaborative and communication networks, especially with the World Health Organization (WHO) in order to be effective in its role. Individuals within TGA participate in many WHO committees and programs that help them optimize regulation in Australia, but also make contributions to the advancement of vaccine regulation and technical expertise in developing countries around the world.

Animal Vaccines

Animal vaccines are regulated by the Australian Pesticides and Veterinary Medicines Authority (APVMA). This agency is responsible for the registration of new products, monitoring the field performance of existing products, and conducting investigations when safety or efficacy concerns are raised. The regulations themselves consist of key principles rather than detailed requirements. A series of guidelines is available that describes appropriate practices and quality. Timelines for product registration vary with the complexity or newness of the medicine being evaluated. In general review times range from 3 to 15 months.

Vaccine manufacturers contract with an independent group of auditors to inspect their plants for compliance. Any individual inspector must not inspect the same establishment more than 3 times. Companies that are inspected bear the costs.

The Department of Primary Industries, an agency within the states rather than the national government, plays a key role in the development of autogenous vaccines. This organization has the capability to isolate organisms involved in local disease outbreaks and prepare vaccine seed stocks. These seed stocks then can be used by a vaccine producer to prepare small amounts of vaccine for control of a specific outbreak. The Department of Primary Industries issues permits for this process to be carried out.

An overview of sourcing of vaccines for responses to emergency animal diseases has been prepared by the Australian Animal Health Council and updated (Tweddle 2009).
Office of the Gene Technology Regulator (OTGR)

This agency is responsible for providing oversight for any activity that employs gene technology or genetically modified organisms (GMOs). It interfaces with TGA and other regulatory bodies to provide guidance and regulation for both human and animal medicines. Figure 2.1 highlights the interrelationships.

Establishments that work with GMOs must conduct activities in specifically designated areas that are licensed to do this work and are subject to inspections.

The Australian Quarantine and Inspection Service (AQIS)

This agency is responsible for controlling materials and goods that are imported into Australia to ensure that new diseases are not allowed within its borders. Regulations are applicable to both human and animal vaccines. Vaccine manufacturing procedures may require the use of animal derived ingredients which could potentially carry trace amounts of infectious disease agents, e.g., mad cow disease from beef. This agency oversees the regulations for importing and testing these materials to ensure that they are free from potential disease causing agents. Establishments that import such materials need a designated area to quarantine and test them before use and must be licensed by AQIS to perform these procedures. These establishments are subject to inspections by this agency.
Examples and Opportunities for More Rapid Response to Emerging Infectious Diseases

Cross Utilization of Human and Animal Vaccine Facilities

Different agencies regulate most of the activities involved in control, but OTGR and AQIS are common. We did not see examples of common use of facilities, but the regulatory principles appear to be similar. In discussions with TGA and Bioproperties, PTY, it was noted that filling of vaccines was a potential cross-utilization with the caveat that container sizes tend to be different, but change parts can be purchased to accomplish this.

Bioproperties is planning to enter some of its veterinary products into the European market where animal and human vaccines are regulated by the same agency. This will require that they undergo an inspection by the TGA as a substitute for inspection by the European authorities. A successful inspection can help pave the way for common use of these facilities.

Collaborations Among Public and Private Enterprises

TGA has developed extensive collaborations with WHO and other regulatory agencies in the United States and Europe that facilitate their receipt of information and materials in a timely manner. In addition, there is continual focus on communication with companies that they regulate. There is an agreement to accept regulatory documents from other agencies, notably the EU.

Partnerships can be formed between universities and private enterprises to facilitate the development of vaccines, production of clinical lots or small batch sizes. The collaboration between the Royal Melbourne Institute of Technology and Bioproperties is an excellent example of a partnership that results in rapid development of animal vaccines (see Bioproperties site report). This partnership involves developing goals that embrace the practical applications for vaccine manufacturing and protection of intellectual property for the companies, along with the advancement of science and publication goals of academia.

The formation of virtual organizations to conduct clinical studies is also possible. Dr. Parish at the Australian National University was able to find resources to prepare clinical trial materials and conduct the first study by employing the services of a knowledgeable individual.

Pandemic H1N1 Influenza Vaccine

An overview of the production steps for influenza vaccine and approximate timelines was provided to us by TGA (see Figure B.13 in the TGA site report). The basic steps described would apply for influenza vaccines made anywhere in the world for any population.

As observed in the figure, the typical timeframe for seasonal influenza vaccine development and release for Australia, in the Southern Hemisphere, begins with the strain selection during September and October and ends with the testing and release of vaccine from January through April of the following year. Vaccine for the H1N1 strain represented an out-of-season effort for Australia. The TGA currently does not have the capability of making the initial recombinant seed strains and needed to procure this from outside of Australia. They were able to obtain the strain developed for the United States in June of 2009 and had vaccine approved at the beginning of September with distribution occurring a few days later. Australia was one of the first nations to have vaccine available for its population. They were able to have vaccine on the market in approximately 3 months from strain selection when a typical seasonal vaccine averages 5-6 months to prepare. They attributed their success and speed to the following key activities: excellent communication and coordination among all of the groups involved, advance decision making regarding dose, adjuvant, and vial presentation
size with limited information, and advance regulatory planning with agreement on acceptance of data from other sources, for example, the European Union.

A total of 22 million doses were made available, but only around 10 percent was used. This low usage rate highlights the importance of communication with and education of the public with respect to the safety of the vaccine and the importance of getting vaccinated. Australia plans to incorporate the H1N1 pandemic vaccine in the seasonal vaccine for 2010 as this strain is the one causing the most disease.

In reviewing bottlenecks with TGA staff, it was noted that receipt of field isolates for analysis was very time-consuming and rate limiting to the process. There are gaps in worldwide surveillance, with not every area covered. In addition, they recommended that more attention be paid to looking at strains with the H2 component. Strains with this component have not been in circulation for many years and thus pose a high risk to individuals under 50.

CHINA

Key Government Agencies

Human Vaccines

The Ministry of Health is responsible for drafting laws, regulations, and policies regarding use of drugs and vaccines, and implementing the policy of “Prevention First.” They are involved in drafting national development programs on medical science and organizing national research efforts. They are responsible for supervising the programs for preventing and treating communicable diseases.

The Ministry of Science and Technology is the organization that establishes the science priorities to be funded at the universities and at government laboratories.

The State Food and Drug Administration, P.R. China (SFDA) is the agency with the main oversight for vaccines. Their role includes formulation of policies and programs for administration of vaccines, participation with other agencies in the development of relevant laws, regulations, normative documents, and good practices. They draw up national standards and publish the decrees that describe the processes, regulations, and Chinese Good Manufacturing Practices (GMPs). They are responsible for supervising the registration of products and then monitoring adverse events post use in the population.

The Center for Drug Evaluation works in concert with the SFDA and is responsible for implementing the drug regulations at the technical level. It is the main agency that conducts the technical evaluation of applications for performing clinical studies and applications to market products. This group convenes expert panel reviews as needed. It evaluates registration information using both WHO standards and Chinese protocols. An overview of the technical evaluation of biological products prepared by Chang Weihong, SFDA, in April of 2009 was presented at the EU-China Workshop on Registration and Clinical Trials.

The National Institute for the Control of Pharmaceutical and Biological Products (NICPBP) carries out the activities associated with ongoing vaccine development and production. They are responsible for drug testing and retesting to support the registration of drugs and vaccines and ongoing surveillance. They manage and calibrate a set of national reference standards, including seed stocks and are responsible for batch release for biological products. They provide technical assistance and guidance to other laboratories and inspect licensed establishments. A number of their affiliated centers and laboratories are part of the WHO collaborative network and are ISO (International Organization for Standardization).
accredited. As of 2008, this organization is a part of the USP (United States Pharmacopoeia) conference.

The Center for Disease Control and Prevention is an organized hierarchy of centers that includes a national center with provincial and local organizations. The responsibilities include management of stockpiles and distribution of vaccine, design and execution of clinical studies, maintenance of a database on disease statistics and monitoring of vaccine usage and performance in the field. This centrally managed organization has the capability to rapidly organize and execute large clinical studies and rapidly distribute vaccine to the population of China.

The group of agencies under and affiliated with the SFDA that regulate drugs and biologicals operate under specific guidelines and regulations, including a requirement to complete reviews and inspections with specific timeframes for normal and fast track reviews. Figure 2.2 shows the steps and timelines required for initiating clinical studies as published on the SFDA website. Similar step diagrams and timelines are available on the SFDA website for the other steps in product registration and approval, including imported drugs.

Other Organizations

In addition to the regulatory agencies there are state owned enterprises that conduct research and sell essential products to the state. Sinopharm/CNBG is the largest, producing both vaccines and pharmaceuticals.

Animal Vaccines

The Ministry of Agriculture is responsible for drafting laws and provisions for disease prevention and developing technical standards. These include a set of Good Manufacturing Practices for vaccines. China recognizes the importance of animal health in contributing to the health of the human population.

Examples and Opportunities for More Rapid Response to Emerging Infectious Diseases

China's system allows priorities for vaccine developers and manufacturers to be set by the central governing agencies, resulting in immediate focus on disease threats when required. During periods of urgency, extension of the work day and work week are employed to shorten cycle times. The well established and coordinated role of the central, provincial and CDC units allows for rapid execution of clinical studies and distribution of vaccine. It was reported to us that the CDC was able to organize a clinical study of 100,000 for a hepatitis B vaccine.

Regulations

China has had a fast track procedure in place since 2005 that speeds up the regulatory process beyond the normal fast track timelines. This procedure requires that key decisions be made rapidly, for example, only 24 hours to make a decision on accepting an application for review. It also allows exceptions to the general processes, for example, parallel testing of a product by the applicant and the government.

Harmonization

China currently uses WHO references to build its own internal standards. The various organizations are working toward WHO certification and are participating in various harmonization initiatives. The Chinese GMP guidelines are undergoing revisions with a view toward more similarity with European type standards. These efforts will allow more export opportunities for Chinese vaccines.
The EU-China Trade Project was initiated in 2003 and completed in December of 2009. One of the initiatives in the effort revolved around exchanging information and facilitating the trade of pharmaceuticals and biologicals between the EU and China. In April of 2009 this organization sponsored a workshop on EU-China Registration and Clinical Trials. Presentations from both industry and government on the systems used in EU and China were
given. These kinds of efforts will facilitate the ability to evaluate and use products from either region in the other to fulfill unmet needs.

Technology Priorities

In selecting areas for more focus, our Chinese hosts had consistent themes that we heard in Europe, Australia, and Asia. Animal based testing for potency needs to be replaced with in vitro models that are more rapid and in vitro models for efficacy need to be developed. New adjuvants should be employed to lessen antigen requirements and improve responses.

Pandemic H1N1 Influenza Vaccine

China was among the first nations to be able to deliver a vaccine to its population. This was accomplished by directing 10 companies to produce the vaccine and facilitating the sharing of data on vaccine development among all of the participating companies. With strain availability in June, two manufacturers, Sinovac and Hualan were able to have their vaccine registered on September 2 and September 4, respectively. Zhejiang Tianyuan was able to have its vaccine available in about 3 ½ months. NICPBP played a key role in the H1N1 pan vaccine launch.

INDIA

Key Government Agencies

Human Vaccines

Central Drugs Standard Control Organization (CDSCO). This agency is within the Ministry of Health and Family Welfare of the Government of India and works in concert with state governments to regulate drugs, cosmetics, diagnostics, and devices. Its main functions include: lay down standards and regulatory measures and amendments to acts and rules; regulate the market authorization for new drugs and clinical research; approve licenses to manufacture certain categories of drugs, including vaccines and sera; regulate the standards of imported drugs; testing of drugs within the Central Drug Labs; and publish the Indian Pharmacopoeia. Other functions include coordination of activities of the State Drug Control Organizations to achieve uniform administration of the act; policy and technical guidance, monitoring adverse drug reactions, and participation in the WHO GMP certification program.

Central Drugs Laboratory (CDL). This agency is within the Central Drugs Standard Control Organization. Its main functions include analytical quality control of most of the imported drugs and drugs and cosmetics manufactured within India on behalf of both the Central and State Drug Controller Administrations. Other functions include the storage and distribution of international reference preparations; preparation and maintenance of national reference standards, including biological cultures; training of analysts and WHO fellows on methods of analysis; advising the Central Drug Control Administration on the quality and toxicity of drugs awaiting licensure.

State Drug Control Organizations (State FDAs). Each state within India has an organization which has the following functions: licensing of the drug manufacturing and sales establishments; licensing of drug testing laboratories; approval of drug formulations for manufacture; monitoring the quality of drugs and cosmetics manufactured by respective state units and those marketed in the state; investigation and prosecution related to legal provisions; pre and post licensing inspections; and recall of sub-standard drugs.

Department of Biotechnology (DBT). This agency is within the Ministry of Science and Technology of the Government of India. Its mandate includes the promotion and use of
biotechnology; support of R&D and manufacturing; responsibility for autonomous institutions, e.g., the Indian National Science Academy; evolution of biosafety guidelines; manufacture and application of cell based vaccines; and acting as the nodal point for international collaboration and the collection and dissemination of information relating to biotechnology.

This agency along with others in the Ministry and Science and Technology has funds available for research activities related to vaccine-preventable diseases and "soft loans" for manufacturers to get started on a program. The agency also offers scientific advice through meetings with staff and open office hours.

There are three committees that have responsibilities related to genetically modified organisms. The Genetic Engineering Approval Committee (GEAC) within the ministry of Environment and Forests is the group that approves large scale use of any genetically engineered or classified microorganisms in industrial production and applications. The Recombinant DNA Advisory Committee (RDAC) evolves long term policy in rDNA research, formulates safety guidelines for research, and recommends training programs. The Review Committee on Genetic Manipulation (RCGM) develops manuals and guidelines; reviews rDNA projects involving high risk categories and field experiments; provides permits for work and lays out restrictions; regulates imports for research purposes; reviews data related to the preparation of cell banks and research approaches; and advises the GEAC on containment at research and production sites.

Examples and Opportunities for More Rapid Response to Emerging Infectious Diseases

Technology

Over the past several years, there has been an intensive effort on the part of Indian vaccine manufacturers to invest in new technologies and facilities. Most of the facilities we observed during our site visits were as technologically advanced as any that we observed in other parts of the world. Companies are also developing their own innovative products using in house developed technology or by active collaborations with companies around the world.

Emphasis is being placed on research and development of vaccines for prevention of diseases and improvements that will make vaccine delivery easier, e.g., more multivalent formulations using antigens relevant to the region. Cost is also a factor making research into thermostable formulations that do not require mixing in the field and automated injection devices important.

Regulations

The system within India is complex, involving both central and local authorities and other agencies. There are not as many detailed guidelines available nor are there separate defined pathways and organizational structures to handle different types of products. This situation is evolving as evidenced by publication of new guidance for preparation of a common technical document and target timelines for review of certain submissions (see the CDSCO website, http://www.cdsco.nic.in) The acquisition of WHO GMP certification by a number of companies for their products also provides a basis for further harmonization of standards between India and other regulatory authorities.

Pandemic H1N1. India did not provide a vaccine during 2009, but did provide Tamiflu. Several companies have since developed vaccines using egg based or tissue culture methods for both inactivated and live vaccines. This will provide the technology base for vaccines against future pandemic strains.
JAPAN

Key Government Agencies

Human Vaccines

The Ministry of Health, Labor and Welfare (MHLW) describes its scope of activities “from cradle to the grave” with respect to the well-being of the Japanese. It is the overarching agency with respect to regulation. Two of its bureaus, the Health Services Bureau and the Bureau of Pharmaceutical and Food Safety are directly involved with vaccines. The MHLW has oversight for the registration of vaccines, and is responsible for ensuring supply. In 2007 they completed an analysis of the vaccine industry within Japan in comparison to other parts of the world and developed recommendations to ensure adequate supply of both routine and new vaccines.

The Pharmaceutical and Medical Devices Agency (PMDA) is an independent agency that is funded by fees from those companies that register and market drugs, including vaccines and medical devices. It reviews license applications for compliance with laws and provides guidance for drug development. It is responsible for facility inspections, post-marketing surveillance, and the implementing of safety measures when needed. It also administers a program to compensate vaccine recipients for adverse events. Figure 2.3 gives an overview of the development and approval process for pharmaceuticals and medical devices.

The National Institute of Infectious Diseases (NIID) is an organization comprised of a large number of departments that conduct basic and applied research on all types of disease causing organisms. There are approximately 1000 employees, with around a third having advanced degrees in science or medicine. It provides reference services that include supplying organisms and reagents for diagnosis and surveillance and conducts surveillance for infectious diseases throughout Japan. It acts as the National Control Laboratory for lot testing and release of vaccines and the development of reference reagents and standards. At the request of PMDA, members participate in registration application reviews and inspections. There are laboratories within NIID that are part of the WHO collaborative system and this organization participates in international collaborative programs. They provide training programs for both domestic and international participants.
Figure 2.3. Japanese product development process: flow of drugs and medical devices from development to marketing. (from http://www.pmda.go.jp/english/service/outline_s.html).
With respect to timing, Table 5.1 provides a four year history from 2004-2008. It includes normal and priority reviews. Priority reviews are used for orphan drugs and drugs whose need is determined to be a priority based on clinical usefulness or seriousness of disease.

<table>
<thead>
<tr>
<th>Table 5.1. History of Review Time for Product Applications (PMDA website)</th>
</tr>
</thead>
<tbody>
<tr>
<td>----------------------------------</td>
</tr>
<tr>
<td>Applications submitted in and after April 2004**</td>
</tr>
<tr>
<td>No. of approvals</td>
</tr>
<tr>
<td>Regulatory Review Time (median)</td>
</tr>
<tr>
<td>Median Total Review Time</td>
</tr>
</tbody>
</table>

Note: Percentages in ( ) indicate the proportions of reviews completed within 12 months (9 months for priority review items.)

*Also includes applications filed in and before March 2004, which are excluded from targets in the Mid-term plan

**The values indicate the data for applications filed in and after April 2004 among those approved from FY 2005 to FY 2008

Animal Vaccines

The Ministry of Agriculture, Forestry and Fisheries (MAFF) is responsible for registration of vaccines. This agency performs required testing and post-marketing surveillance.

Examples and Opportunities for More Rapid Response to Emerging Infectious Diseases

Regulations

Although human and animal vaccines are regulated by different agencies, the standards are such that it is feasible to manufacture both human and animal vaccines in the same facility, in the same area. We saw an example of one area at Biken in Japan where vaccines for an animal and a human vaccine were made in alternating campaigns. At present, Japanese regulations and guidelines are not published at the level of detail as those found in the United States and Europe. The MOH is working toward fostering the development and publication of guidelines to make the process of applying for registration more transparent. Development of guidelines, especially if they are similar to those used outside Japan would also help facilitate the export of Japanese vaccines to other nations.

The MOH has expressed concern over the time that it takes for Japan to introduce new vaccines when compared to the United States or Europe. Part of the plan to remedy this is to add more staff to PMDA, the organization that is primarily responsible for review and analysis of data prior to registration.
Japanese Vaccine Industry Analysis

This report concluded with a number of recommendations that over time would strengthen the vaccine industry, thus facilitating more rapid introduction of new vaccines in Japan. These recommendations included: provide centers for human clinical studies, so that government shares the burden with manufacturers; subsidize orphan drugs and vaccine stockpiles; encourage domestic manufacturers (who are generally small companies) to form alliances with multinational, large foreign manufacturers; foster more rapid uptake of new vaccines via more rapid pre-registration reviews; provide education and communication for both the medical community and the public; and increase international collaboration.

Japanese International Cooperation Agency (JICA)

The Japanese International Cooperation Agency exists to facilitate the solving of development issues that other nations face. As part of this program, both government and private enterprises conduct training programs in technology and good practices regarding infectious disease prevention that are open to both domestic and foreign participants. Some companies, e.g., Biken, also send teams to other nations in Asia to transfer vaccine technology and help establish manufacturing operations. These types of programs facilitate worldwide efforts to combat pandemic diseases such as influenza.

Pandemic H1N1 Influenza Vaccines

Japan does not currently have the capacity for production of all of its vaccine needs in the event of a pandemic. They procured vaccine both domestically and internationally and used an “exceptional” system in order to speed up the process. This meant that they accepted European data to support the registration of European made vaccine into Japan, minimizing the amount of Japanese clinical data required. They put in place a program to procure about 50 million doses domestically and 100 million from outside Japan. They were able to initiate the immunization program mid-October with domestic vaccine.

The Japanese public is similar to the United States public in its concerns for individual safety in any public immunization program. Japan put in place an additional compensation law to assist individuals with adverse vaccine reactions in addition to a manufacturing indemnity program in order to facilitate the H1N1 pan immunization program. Despite these efforts, only a small portion of the population was immunized. This again points to the importance of communication with and education of both the medical community and the public when implementing an immunization program.

Other Influenza Pandemics

Japan developed its pandemic influenza plan in 2005. This ongoing effort is focused on ensuring enough domestic capability to produce the total national requirement for immunization against a pandemic in a six month period. An investment of $1 billion along with the partnership of the influenza manufacturers has been allocated for this program. The money will be used for development of technologies, such as cell culture, clinical studies, and the construction of a large cell culture facility. Manufacturers will establish and fund the initial development programs and then depending upon their success, will be selected to participate with the government in the larger venture. The draft timeline shown in Figure 2.4 describes a typical timeline for developing a vaccine with known parameters, but using new technology.
## Schedule of development of vaccine (Draft)

<table>
<thead>
<tr>
<th>year</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Adoption</td>
<td>Adoption of projects</td>
<td>monitor progress as needed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Non-clinical trial</td>
<td>Non-clinical, quality test, development of manufacturing method etc.</td>
<td>Additional examination of quality test, development of manufacturing method etc.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Clinical trial</td>
<td>Protocol development etc.</td>
<td>Phase I, II/Phase III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Construction of plants</td>
<td>Pilot plant construction / proliferative examinations</td>
<td>Design or construction of factory / validation etc.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Consultation / examination</td>
<td>prior consultation / development guidance</td>
<td>Approval application → rapid examination</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* As progress would differ among companies, this list merely shows a standard schedule.

---

**Figure 2.4.** Timeline for vaccine development (presentation to panelists, Feb 26, 2010).

### KOREA

#### Key Government Agencies

**Human Vaccines**

The Korean Food and Drug Administration has oversight for vaccines in Korea. The Pharmaceutical Safety Bureau, Biopharmaceuticals and Herbal Medicines Bureau, and the Drug Evaluation Department are under the umbrella of the Korean FDA and take responsibility for approval of both domestic and imported products. The National Institute of Toxicological Research performs testing and review of safety and efficacy data. The National Institute of Food and Drug Safety Evaluation conducts its own research on safety and efficacy and performs risk assessments. They are responsible for lot release. They also participate international collaborative programs.

**Animal Vaccines**

The National Veterinary Research and Quarantine Service (NVRQS), under the Ministry of Agriculture and Forestry is responsible for the registration of drugs and vaccines. They conduct disease surveillance, perform diagnosis and are involved in prevention programs. They are responsible for inspection of animal products. The agency serves as a national reference laboratory for many exotic diseases and is the primary government animal research institute. Many of the livestock and poultry vaccine manufactured in Korea were developed by the NVRQS and transferred to Korean animal health companies.

Veterinary vaccines for new pathogens require a minimum of 3 years to move from pathogen identification through approval. Mean times vary from 3 to 5 years.
Examples and Opportunities for More Rapid Response to Emerging Infectious Diseases

Harmonization

There is participation in the WHO collaborative network, and some organizations have ISO certification. Design of production systems is targeted to meet ICH (International Conference on Harmonization) and FDA-like standards. Korea companies are able to export products to other Asian countries and have developed partnerships with European nations. An increase in international collaboration is planned. There is also a goal to increase domestic capability for vaccine production.

Regulations

Autogenous animal vaccines have very flexible guidelines leading to rapid production and approval, especially for vaccines for E. coli, Acentiobacillus pleuropneumoniae, and Pasteurella sp.

Pandemic H1N1 Influenza Vaccine

A fast track program and both domestic and international sourcing were used to supply the needed amount of vaccines. Seed viruses were received in June and the program to develop, clinically test, and register vaccines was completed in October. Vaccines with and without adjuvant were used in the program.

SUMMARY

All of the countries we visited have a regulatory structure in place to deal with the registration, use, and monitoring of vaccines. Some systems are more complex than others, but all had systems in place to deal with the H1N1 pandemic influenza strain, except for India, where vaccine was not used for the 2009-10 seasons.

The time that it took to deliver vaccine to the population ranged from early September of 2009 to the third week of October, the shortest time frame from receipt of seed stock at about 3 months. Australia and China had the most rapid response and these countries used entirely domestic supplies of vaccine. Japan and Korea used internationally procured vaccine to supplement their supplies. The pre-planning for these immunization programs, which involved development and production methods that were well established, resulted in a time savings of 1-3 months from a typical influenza vaccine seasonal program.

All countries had some collaboration with WHO and all had ongoing efforts to engage in international collaboration with other organizations or countries. All recognized the importance of harmonization as a means of exchanging information and receiving/exporting products. Revision of existing regulation is toward EU and FDA like standards. These types of activities can facilitate rapid deployment of vaccine around the world.

Domestic vaccine capacity for a potential pandemic is considered very important and increasing capability is a focus in India, Japan, and Korea.

RECOMMENDATIONS

The most rapid response to a disease threat requires advanced planning and focused effort of all the organizations involved. Government policies and regulations can go a long way toward facilitating that response. China’s centralized system allows for rapid deployment of programs and Australia’s extensive communication network and partnerships allow for programs to proceed quickly. Japan has a program in place to assure that it has sufficient domestic capacity available to make pandemic vaccines available quickly.
In the United States, more rapid development of vaccines for an emerging threat could be facilitated by a United States government/industry partnership around a facility dedicated to developing and producing vaccines on an emergency basis. The facility could be kept as a warm base by producing non-routine vaccines, e.g., for the military and developing vaccines for potential threats. Government/industry contracts could also be developed to procure emergency use of capacity in commercial facilities, e.g., for filling/packing/distribution type activities.

Another action that could facilitate rapid response is to ensure that policies currently in place at HHS, Homeland Security to provide rapid responses undergo routine reviews and are updated appropriately. Continued focus on regulatory harmonization and guideline development for emerging technologies would allow more transparency in developing vaccines and facilitate quicker reviews. Pre-approval for interchange of animal and human vaccine production facilities can also assist in providing rapid response.

A review of the deployment of vaccine for the pandemic H1N1 strain this season would facilitate identifying opportunities to ensure that vaccine distribution is as rapid as possible.

Communications by government agencies for both the medical community and the public are key to an effective program and so must be coordinated and updated as needed.

REFERENCES


Central Drugs Standard Control Organization: http://www.cdsco.nic.in.

Department of Biotechnology, India: http://www.dbtindia.nic.in.


Development, Manufacture and Distribution of Vaccine in Japan. Presentation of the Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare (Japan) to WTEC panelists, February 26, 2010

EU-China Trade Project – EU-China Workshop on Registration and Clinical Trials, 2-3 April 2009.


National Veterinary Research and Quarantine Service, Korea home page: http://www.nvrqs.go.kr/eng/.


Pharmaceuticals and Medical Devices Agency, Japan home page: http://www.pmda.go.jp.


CHAPTER 3

TECHNOLOGY PLATFORM ADVANCES FOR RAPID VACCINE MANUFACTURING

Stephen W. Drew

The pathway from conceptualization of a vaccine to its ultimate clinical application to prevent or modulate disease advances through many interdependent stages. Figure 3.2 in the International Assessment of Research and Development in Rapid Vaccine Manufacture (Leighton and Bielitzki 2007) outlines the major steps in this progression and Chapter 4 of that analysis expands some of the interconnected networks of decision required to reach license approval of a new vaccine. During the study in 2007, we saw the beginning of new initiatives aimed at more rapid discovery, development, expression, scale-up, and manufacture of vaccines in Europe. In the intervening time leading to our assessment in Asia in 2010, further advances have strengthened worldwide ability to respond to impending disease threat. Technology platforms continue to be the foundation of rapid development of vaccines and play roles at each stage of progression to licensed vaccines. Some of the trends that we observed in 2007 have continued to grow in importance around the world; the foundation science has strengthened.

UNDERSTANDING IMMUNE RESPONSE

We observed exciting technical advances in the areas of molecular design of vaccines, the control and integration of immune response to vaccination, and the fundamental interaction of innate and adaptive immunity.

Professor Shizuo Akira, Director of the Laboratory of Host Defence, WPI Immunology Frontier Research Center, Osaka University

Professor Shizuo Akira was the most cited scientist in immunology between January 1998 and October 2008 for his work in defining innate immunity.1 His work strives to develop a fundamental understanding of immunity, and vaccines at the most basic level using scientific research to unlock the physiological secrets of how the human body elicits an immune response. His review (Akira and Takeda 2004) is a key source on the function of Toll-like receptors (TLRs) in triggering the cascade of innate immunity and setting the stage for adaptive immunity. TLRs play a central role in recognizing the presence of a pathogen (a “danger signal”) in vertebrate systems and discriminating them from host proteins. The first

---

immune response to an invading pathogen is through its recognition by the innate immune system. The initial sensing of infection is mediated by innate pattern recognition receptors (PRRs), which include TLRs, RIG-I-like receptors that detect viral RNAs, nucleotide-binding oligomerization domain receptors (NLRs), and C-type lectin receptors. Akira's work has also clearly shown that activation of the innate immune system is a prerequisite for the induction of acquired immunity involving T- and B-cell mediation and T Helper-cell response.

Professor Akira has used knockout mice to demonstrate that a family of Toll-like receptors recognizes a variety of pathogen-associated molecular patterns (PAMPs). PAMPs such as lipopolysaccharide, lipoprotein and nucleic acids derived from bacteria, viruses and protozoa elicit innate immune responses through the PRRs. The intracellular signaling cascades triggered by these PRRs lead to transcriptional expression of mediators of inflammatory response that coordinate the elimination of pathogens and infected cells (Kumagai and Akira 2010). Though Akira’s group has greatly advanced understanding of innate immune response, the system is complex and new receptors and ligands are discovered routinely; some form new bases for vaccine discovery.

The Laboratory of Host Defence utilizes engineering principles of monitoring outputs as a function of input parameters to probe the components and interactions of immune response. Vaccines and adjuvants are the inputs to the in vivo immune response system; a “black box” of extraordinary complexity. The levels of immunogenicity and adverse reactions that develop provide the measurable outputs of this system and suggest the structure and dynamics of the system. Understandings that arise inform the design of new (and better) vaccines and adjuvants that provide greater immunity with minimal adverse reactions. These studies also provide a more transparent understanding of how vaccines function in vivo.

A deeper understanding may also support prediction of individual biomarkers or surrogate markers for vaccine efficacy and safety in human populations. As the granularity of understanding improves it may be possible to predict vaccine potency across individuals, allowing a more effective approach to personalized vaccines. Professor Akira’s study of single gene deletion in test mice map the functional genes of immune response and is already unravelling the complexities of innate immunity and its communication with adaptive immunity.

Professor Akira predicts that the next frontier in immunology will be at the crosstalk interface of innate immunity and adaptive immunity.

Professor David C. Jackson, Department of Microbiology and Immunology, Faculty of Medicine, Dentistry & Health Sciences, University of Melbourne

Professor Jackson’s accomplishments stand on the shoulders of pioneers like Akira and his colleagues. Advances in understanding the involvement of Toll-like receptor (TLR) ligands in presenting antigenic markers of pathogenic organisms to the innate immune system, and the role of cytokines in recruiting adaptive immune response, present an opportunity to literally design the molecular architecture of a vaccine candidate.

Rational design of vaccines becomes possible as we understand how the immune system coordinates a response to recognized antigens. The cells of the innate immune system, principally the dendritic cell (DC), are among the first cells to encounter an antigen as it enters the body. Plasma membrane receptors facilitate the targeting and transport of vaccines to DCs. Toll-like receptor 2 (TLR-2) on the surface of immature DCs, when triggered by an antigen, leads to uptake of the antigen and any components bound to it (ligands). Engagement of TLR-2 leads to DC activation and maturation initiated by signal transduction
pathways. Activation of the DC in this way leads to its migration, bearing its antigen cargo, to the draining lymph node where it presents the processed antigen to T cells, triggering their activation. Jackson has used this knowledge of the function and specificity of various DC surface receptors to design novel vaccines.

Professor Jackson was recently awarded the David Syme Prize for creating synthetic, self-adjuvanting vaccines that target DCs through the endocytic toll like receptor TLR-2. His studies have shown that this new class of vaccines is effective against viruses, bacteria, and tumors in test animals. These lipopeptide constructs cause DCs to mature through a TLR-2 targeting and loading mechanism, launching a cascade (Figure 3.1) that results in both long-lived antibody response and cytotoxic T Lymphocytes (CTL) memory. The antibody responses are T helper cell dependent.

![Figure 3.1. Use of simple synthetic lipid structures for targeting different vaccine cargos to dendritic cells (from Jackson 2009).](image)

The synthetic vaccine scaffold contains a synthetic version of the TLR-2 ligand, S-[2,3-bis(palmitoyloxy)-propyl]-cysteine (Pam2Cys), and a DC activating danger signal (e.g., lipopolysaccharide) targeting TLR-2. Jackson's totally synthetic epitope-based vaccine, which incorporates a CD4+ helper T cell epitope and a pathogen target epitope (Figure 3.2), is capable of eliciting either an antibody or a CD8+ T cell response, with the TLR-2 Pam2Cys ligand covalently attached between the two epitopes. The DC targeting and activation properties are generic to the structure of the synthetic vaccine and provide a self-adjuvanting character to vaccines. His studies with a Group A Streptococcus (GAS) conserved M protein antigen demonstrated the presence of opsonizing antibody in mice, after intranasal vaccination, that protected against bacterial challenge (Batzloff et al. 2006).

![Figure 3.2. The simplest immunogen consists of a helper T cell (Th) epitope and a pathogen target epitope (from Jackson 2009).](image)
Encouraging and persuasive results using this strategy have been obtained with a variety of vaccine candidates in several animal models ranging from immunocontraceptive vaccines that elicit high titers of anti-gonadotrophin releasing hormone antibodies (Chua et al. 2007), to those that induce protective anti-influenza CD8+ T cell responses (Pejoski et al. 2010).

Dr. Jackson’s results have demonstrated an innovative influenza vaccine modality, utilizing conserved viral epitopes, that might bypass the necessity of having prior availability of emergent pandemic or seasonal strains to achieve vaccine protection. This potential is also reflected in the broad range of anti-HPV (HPV-15, -5, -18, and -45) cross-reacting antibodies elicited by a single L2 lipopeptide vaccine (Alphs et al. 2008). Jackson’s accomplishments clearly show the ability to design vaccines based on understanding of the intimate molecular-level details of immune response.

Others are also developing the potential for broad immunologic cross-reactivity. Adrian Hill and Sarah Gilbert told us of their plans to investigate the highly conserved nucleoprotein (NP) and matrix proteins (M1) of influenza type A during our visit to their laboratories at Oxford University in 2007. They recently published an article that identifies a recombinant vaccine in modified vaccinia virus Ankora (MVA) that successfully boosted cross-reactive immune responses to all influenza A subtypes (Berthoud et al. 2011).

**Professor Christopher Parish, Cancer and Vascular Biology Group, Immunology Program, The John Curtin School of Medical Research (JCSMR), Australian National University**

Professor Parish’s laboratory developed the first demonstration, in the early 1970’s, that cell-mediated immunity and antibody formation are mutually antagonistic responses, a finding that illuminated the “recognition” and “verification” signal, Th1/Th2, paradigm in immunology. The Cancer and Vascular Biology group focuses on the molecular basis of cell adhesion, cell migration, and cell invasion, with a particular emphasis on the immune system, tumour metastasis and angiogenesis.

In collaboration with Dr. Paul Foster’s group, Division of Molecular Biosciences, JCSMR, a new approach to cancer immunotherapy has been developed. Traditional attempts at cancer immunotherapy have involved the generation of CD8+ cytotoxic T lymphocytes (CTLs) against tumor-specific antigens. However, the genetic instability of typical cancers often ensures that resistance arises through variation in the tumor-specific antigens. Parish reasons that a successful vaccine strategy must lead to a response that is difficult for the cancer cell to avoid. That is, one that uses more than a single cancer cell epitope and that elicits devastating response.

Dr. Parish’s innovative strategy for cancer vaccine development utilizes liposome-based vaccine constructs that target multiple tumor antigens (pan-epitopes) to DCs *in vivo*. Liposomes have been used for decades to deliver cancer-cell toxic drugs, such as doxorubicin, but normal phagocyte function quickly clears liposomes, reducing their effectiveness. Parish developed a new chemical linker that can covalently bind to a liposome, act as a linker or ligand to attach other components, ultimately hiding the surface of the liposome from circulating phagocytic leucocytes. The linker, 3-nitrolotriacetic acid di-tetradecylamine (3-NTA-DTDA) chelates nickel (Ni2+) and binds to histidine residues in proteins or to an engineered 6-histidine “his tag”. The “his tag” affinity allows virtually any protein to be engrafted to the liposome and therefore can be used to target the liposome to virtually any cell in the body. Parish’s team has focused on antibody fragments (e.g., surface receptors
DEC-205, DC-SIGN, and CD11c) that target dendritic cells (DCs) to deliver a variety of cancer epitopes and cytokines to the immune system (Figure 3.3).

![Dendritic Cell Targeted Cancer Vaccine](image)

**Figure 3.3.** Dendritic cell targeted cancer vaccine (courtesy of C. Parish).

Though the derivatized synthetic liposomes trigger the immune cascades through dendritic cells, they carry a limited number of cancer-related epitopes. Parish’s solution to this problem has been to fuse the 3-NTA-DTDA derivatized liposome with membrane vesicles derived from tumor cells (of test animals, but potentially, from human subjects in autologous therapy). These new liposome vaccines carry the his tag-linked receptor ligands for DCs, cytokines (e.g., interferon gamma) that activate DCs, and literally hundreds of epitopic markers specific to the cancer cell. In their most recent work, they use the DC-specific ligand DC-SIGN to achieve a 300-fold binding bias to DCs over phagocytic leucocytes.

A complex and unique human melanoma vaccine formulation (Lipovaxin) which includes fully human domain targeting antibodies has been developed for use in Phase 1 clinical trials, which commenced December 16, 2009 (see Figure B.5 in the Australian National University (ANU) site report). The revolutionary pan-epitope Lipovaxin platform has profound implications for therapeutic access to historically intractable vaccine targets beyond neoplasias, including malaria, tuberculosis, and HIV. Lipovaxin required over five years of laboratory development and testing prior to the launch of the Phase 1 clinical trials (safety precursor to autologous therapy). The synthesis and assembly of the Lipovaxin construct (which contains a number of new chemical entities) is a milestone in vaccinology and, as with Dr. Jackson’s work, represents a uniquely promising Australian approach to immunoprotection targeting dendritic cells.

Dr. Parish occupies a very unusual position in Australian translational vaccine science. He is a well-established entrepreneur with access to start-up funding and his position at the JCSMR facilitates access to human clinical trial resources. Dr. Parish posited that a key success factor in Lipovax development was identifying an individual who understood all of the steps required to translate laboratory results into clinical trial material and the ability to integrate
the diverse activities of other members of the team. He has started four independent companies, including Lipotek, to further develop concepts initiated in his laboratories and holds 25 patents on his inventions. Lipotek has formed development agreements with Domantis and GlaxoSmithKline. Recent work has targeted other cell types (Poon, Hewlett, and Parish 2010) and cancer models (Altin and Parish 2009).

**REDUCING BUSINESS RISK**

**Public/Private Partnerships That Accelerate Vaccine Design and Development**

Innovations that arise in academic, government, or small company laboratories face daunting hurdles on the path to product license for clinical application. Innovators often find it too expensive to advance their concepts to pre-clinical and clinical testing (angst reflected by Liljestrom and Hill during our 2007 study of vaccine manufacture in Europe; Bielitzki et al. 2007). They may need to establish relationships with larger pharmaceutical or biotechnology companies to design processes for manufacture, scale-up the processes, manufacture clinical supplies, manufacture full-scale supplies, and design, manage and defend clinical safety and efficacy studies. The individual inventor needs the development skill, experience, expertise, capital infrastructure, and financial “deep pockets” of established industry. Industry needs deep scientific understanding of disease, innovative new products, novel analytics, and minimized risk of failure. Clearly economics drives many of the decisions from the invention of a vaccine candidate, across the “Valley of Death” (Butler 2008, Coller and Califf 2009), to a licensed vaccine product. Professor Peter Liljestrom (Karolinska Institute), during our discussions in 2007 (Drew 2007), stated that legal issues (e.g., intellectual property rights) and economics (e.g., safety and efficacy trials, scale-up), not microbiology, virology, or the science of vaccines, are “the greatest obstacles to the development and introduction of new vaccines into the marketplace”. He concluded that until these systemic issues are fixed, very few new vaccines that have their roots in academic research centers would reach the market. In other words, the rate of progress, from vaccine concept to licensed product, may be controlled by transit across the “Valley of Death”—the landscape of the public/private partnership.

Our studies in Australia and Japan identified two very successful examples of public/private partnerships that share intellectual and physical resources, manage economic risk, and reduce business uncertainty.

**Research Institute for Microbial Diseases, Osaka University and Biken, the Kanonji Institute**

Osaka University’s world-rank research laboratories hold a very special relationship with a world-class manufacturer of vaccines. The Kanonji Institute (Biken) was established by Osaka University at Kanonji City, Kagawa, Japan for manufacture of vaccines. The Kanonji Institute is the operating structure of Biken, formed as part of its Foundation for Microbial Diseases, created by government edict to separate basic and applied research. The headquarters office and clinical examination division of Biken are located on the premises of the Research Institute for Microbial Diseases, Osaka University, Osaka, while some aspects of research, and all of production are performed at the Kanonji Institute, in Kagawa and other satellite sites. The Japanese authority, the USFDA, the Korean FDA, the Chinese SFDA and other international regulatory authorities have licensed more than 20 vaccines manufactured at the facilities of the Biken Kanonji Institute. Vaccines manufactured at Biken are distributed and sold worldwide, including attenuated and recombinant inactivated virus vaccines, live virus vaccines, and bacterial vaccines for human and animal (fish) use.
Osaka University established the manufacturing Foundation for Microbial Diseases in 1934, developing vaccines for typhoid, cholera, pertussis, smallpox and other diseases. In 1946, the Kanonji Institute was established to develop manufacturing processes, execute process scale-up and manufacture vaccines to meet the Japanese healthcare demand. Over the intervening years, Biken has developed and manufactured a wide range of vaccines originating from the Osaka University laboratories as well as those invented by other academic or industrial partners around the world.

Biken has been highly successful because of the close cooperation and synergy between the Foundation for Microbial Disease (Biken) and the Research Institute for Microbial Diseases of Osaka University. The goal of improving human lives through prevention and treatment of microbial diseases is embedded in their shared philosophy and their individual decision making processes. The Institute provides basic, academic research needed for vaccine development using private and public funding. The Foundation performs the applied research and translation of the basic research into products and then manufactures them for the domestic and international marketplace. Funding for Biken's Foundation comes from both charitable contributions, revenue from the marketing and sale of their vaccine products, and savings from preferred tax status. Both organizations support each other synergistically. The Foundation transfers operating funds to the Institute, has established a fellowship program for students at Osaka University and funds the Takahashi Memorial Award with the Japanese Society of Vaccinology to honor special achievements in Vaccinology. The Institute provides a pool of capable, well-educated individuals for entry-level positions at the Foundation. These individuals have the opportunity to advance and become experts in the vaccine industry. The Institute also gives back to the Foundation. The recent new facilities at Biken were made possible, in part, by donation of royalty revenue received by Osaka University (Professor Takahashi). More than 50% of the Foundation's Board are Emeritus Professors at the University.

The public/private partnership relationship between Biken and Osaka University captures the best attributes of both organizations; world class manufacturing strategy and tactics, and world class basic and applied research and development.

Challenges for Biken and Osaka lie in the changing global vaccine landscape. Large multinational companies, which currently supply most of Europe and the United States and export some vaccines to Japan, exercise a broad spectrum of resources to translate basic research into products around the world. Biken and Osaka also compete in the global vaccine market, but their primary focus is on the healthcare needs of Japan. The Japanese regulatory environment is not well harmonized with other countries and vaccine regimens developed by Biken and Osaka University are largely unique to Japan. This creates a hurdle for Biken to enter the international marketplace.

Government funded clinical centers are not available (although there was some recent government funding of influenza clinical studies for pandemic vaccines), thus requiring more resources for companies who want to clinically test a new (Japanese) vaccine for the first time in man. Both the government and the vaccine industry have recognized this situation as

---

2 The Research Foundation for Microbial Diseases of Osaka University, Internet website
http://www.biken.or.jp/english/about/background.html
sub-optimal for Japanese exports and are working on solutions that include development of expanded guidelines, harmonization with other nations and more government support for vaccine programs. One example is the proposed government cell culture facility for pandemic influenza vaccines for which $1 billion has been set aside (see the site report for the Japanese Ministry of Health, Labor, and Welfare in Appendix B of this volume.)

The Royal Melbourne Institute of Technology (RMIT) and Bioproperties Pty. Ltd.

The Royal Melbourne Institute of Technology (RMIT) and Bioproperties Pty. Ltd. share an unusually effective public/private partnership. RMIT was founded in 1887 and has more than 70,000 students at three campuses in Victoria, and two campuses in Vietnam. They operate online, distance education programs and on-site courses at partner institutions throughout the world. Offsite study locations include Singapore, Hong Kong, Kuala Lumpur, Shanghai, and Wuhan. Academic programs range from apprenticeship training to doctoral programs across the university spectrum of disciplines. In 2006 RMIT established research institutes for Design Research, Global Cities, Health Innovation, and Platform Technology that represent areas of research excellence and opportunities for support of industry.

RMIT has established an operating plan beyond academic programs that encourages cooperative research and translational development of inventions and discoveries with selected industry partners. The university leases laboratory and office facilities as incubator space for new and maturing small industry. In the case of Bioproperties Pty Ltd, they have provided access to enabling intellectual property that includes sophisticated basic research and analytical capability in molecular biology, microbiology, and virology; generating a royalty fee on manufactured goods. RMIT has benefited from Bioproperties’ product-focused collaborative research funding that has resulted in graduation of well trained students and post doctoral fellows. Employees of Bioproperties Pty. Ltd. participate in the academic environment as part of the faculty, facilitating the translation of new insights in vaccine design to products in the commercial arena.

Bioproperties Pty Ltd was established as a privately-held company in September 1989 and has become famous in Australia and internationally for the speed with which it can develop and market live vaccines for animal health. Their technology thrusts include live, temperature sensitive mycoplasma vaccines, aroA (aromatic amino acid auxotrophy) gene deletion for live bacterial vaccines and gene deletion to limit virulence for viral vaccines. Bioproperties also has the capacity, in emergencies, to produce autogenous vaccines for outbreaks limited to specific farms (please see the Bioproperties site report for more details) with vaccines for this specific use prepared in the RMIT laboratories. From its inception the company has utilized a collaborative model with key Australian research universities and institutions to undertake platform research and development for its vaccines. Bioproperties maintains its own research laboratories and staff based within several universities, including RMIT. The collaborative relationship at RMIT includes the joint operation and funding of a GMP certified scale-up laboratory. RMIT and Bioproperties also jointly apply for research grants of mutual interest, for which Bioproperties completes funding of successful outcomes. Where intellectual property (IP) rights accrue from RMIT inventions, the university receives a royalty return.

The development of live, attenuated vaccines for animal health leads the world in low-dose, high-immune response, low-cost vaccines. As in our 2007 assessment of rapid vaccine manufacture in Europe, our observations in Asia suggest that translation of insights from animal vaccine development to the design and development of safe and effective human vaccines could yield significant benefit.
Bioproperties’ business model relies on collaborative research and development with RMIT and others to leverage end product development through significantly enhanced basic and applied research, combined with their own experienced development and manufacturing capability. The RMIT/Bioproperties relationship allows the company to accept more risk in development of novel live vaccines without the burden of huge capital outlays. It provides a vehicle for unique advanced learning by the university’s best students through work – study opportunities with Bioproperties and supports rapid development of novel vaccines by supporting the right people, at the right time, in an environment that nurtures both creativity and accomplishment. This cooperative relationship also provides Bioproperties with a pool of talented and motivated potential employees.

**The Role of Platform Technologies in Accelerating Vaccine Design and Development**

The foundation science, method development, and vectors for molecular design of vaccines have advanced dramatically since our first study in 2007. Vaccine design and drug discovery, scale-up and testing, and manufacturing are moving inexorably toward platform technologies that speed progress, reduce risk, control capital and other resource expenditure, and minimize the overall monetary investment to bring new, safe and effective products to clinical practice and the marketplace. Figure 3.2 from Leighton and Bielitzki 2007 (p. 35) presents an integrated view of the pathway from vaccine concept to market introduction and distribution. Technology platforms are the bricks and mortar of most of these efforts; they reduce both risk and uncertainty and accelerate decision and investment (Figure 3.4). Optimization of the technical pathway to new vaccines must be rooted in the optimization of each of these technology platforms, as the least efficient steps will control the overall rate of development.

![Figure 3.4. The role of technology platforms on the critical path to safe, effective vaccine.](image)

**TECHNOLOGY PLATFORMS**

- Technology platform steps are linked, but may be overlapped (discovery, analytics, scale-up, product testing, regulatory review, etc.)
- Risks and uncertainties change across the path
- The least efficient step will control the overall progress toward field application of a new vaccine

At this point in time, the conventional minimum timeframe required for technology steps leading from discovery through manufacturing is ~3.5 to 5 years\(^3\). That is, if all technology platforms on the path to a licensed vaccine were to operate at their current maximum efficiency, history tells us that technical manufacture of a vaccine could require approximately five years to complete. However, *in vitro* technology platforms in the arenas of

---

\(^3\) Joseph DiMasi, Tufts Center for the Study of Drug Development, Director of Economic Analyses, Biotechnology Database, Tufts University, Boston.
3. Technology Platform Advances for Rapid Vaccine Manufacturing

pre-clinical and clinical assessment of vaccine safety and efficacy are only marginally developed. Across all of our discussions, it is clear that we do not have reliable laboratory technologies for the prediction of animal and human safety and efficacy. Further, the United States FDA licenses vaccine products, but not vaccine technology platforms. (See p. 17 in Ritchey 2007 for a discussion of the European EMEA “core dossier” concept of pre-approval of facilities and processes for pandemic influenza as a counterpoint to United States regulatory control.) Technology platforms can increase the speed of process and analytical development, and they can support predictable levels of process-related safety. However, technology platforms cannot generally define (1) predictable levels of biochemical or biophysical properties of vaccines, (2) vaccine pharmacology, (3) product-related safety issues, or (4) product-related efficacy issues. Significant reduction of the timeline from discovery to market will require investment in technology platforms that can shorten, augment or eliminate animal and human studies.

REFERENCES


CHAPTER 4

VACCINE ECONOMICS, DISTRIBUTION, AND SUPPLY CHAIN MANAGEMENT

Sheldon H. Jacobson

Abstract

This chapter reviews the economics of vaccine manufacturing, distribution, and supply chain management. A survey of these issues is discussed, ranging from vaccines for routine pediatric immunization, pediatric combination vaccines (including their economic and decision-making impact), the economics of pediatric vaccine shortages and stockpiling, vaccine production and demand for seasonal influenza vaccines, and preparations in the event of a pandemic influenza outbreak. A comparison between United States, European, Australian, and Asian practices is also discussed. The chapter ends with a list of challenges for the future and areas that require research attention and breakthroughs to support planning for a pandemic outbreak.

BACKGROUND: IMMUNIZATION AND VACCINES

The World Health Organization (WHO) states that immunization against infectious diseases has had an enormous impact on world health (Plotkin and Orenstein 2004). Immunization spares millions of children each year from contracting potentially debilitating (and sometimes fatal) infectious diseases. For example, one estimate is that pediatric immunization prevents three million worldwide deaths in children each year (Diekema 2005). In 1966, there were approximately twenty million cases of smallpox worldwide, while by 1980, vaccination prompted the WHO to declare that smallpox was no longer an infectious disease threat (Mackay and Rosen 2001). Today many healthcare professionals still regard the eradication of smallpox as one of the greatest accomplishments of public health (Cohen 2000, Mackay and Rosen 2001). In the United States, there have been no cases of indigenous poliomyelitis, and a 99% decrease in the number of cases of diphtheria, measles, mumps, and rubella since vaccines became available. Furthermore, pediatric immunization prevents an enormous cost burden (both tangible and intangible) for individual children, families, and society-at-large (Cohen 2000). For example, the 2005 National Immunization Survey, administered by the United States Centers for Disease Control and Prevention (CDC), estimates a savings of $27 in direct and indirect costs for every dollar spent on vaccinating against diphtheria, tetanus, and pertussis (Cochi 2005). Similar favorable cost-to-benefit ratios make pediatric immunization an excellent investment in support of a nation’s public health well-being and infrastructure.

There remains much work in the area of vaccine development and distribution, even with the enormous progress that has been made over the past fifty years. In 1998, over 20% of the deaths worldwide (13M+ of the 54M deaths) were due to infectious disease (Cohen 2000), with an estimated 1M of these deaths attributable to measles (a disease with an available vaccine at a relatively modest cost; Cohen 2000, Plotkin and Orenstein 2004). Moreover, the emergence of new infectious diseases such as human immunodeficiency virus (HIV) and
Lyme disease, the resurgence of diseases such as tuberculosis, and the recent threat of bioterrorism (e.g., anthrax, smallpox) and pandemic influenza highlight the need for continued vigilance in the effort to combat infectious diseases and to move forward with the creation of new vaccines to protect the lives of people worldwide (Binder et al. 1999, Plotkin and Orenstein 2004).

ROUTINE PEDIATRIC IMMUNIZATION

Each year, based on recommendations from the United States Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP), the CDC publishes a Recommended Childhood Immunization Schedule that outlines vaccination requirements for children through adolescence (CDC 2010a). Similar schedules exist for other countries around the world; see http://www.euvac.net/graphics/euvac/vaccination/vaccination.html for a list and description of childhood immunization schedules for over thirty European Union (EU) countries. Japan’s schedule has a list of both required and optional vaccine. For example, the polio and measles vaccines are required, while hepatitis B and the Haemophilus influenzae type b vaccine are optional, where required means that the cost of the vaccine is paid for by the government, while optimal means that it is not. Japan’s schedule is also not as closely aligned with the United States and most EU schedules. Clearly, all these schedules have several common elements, though a variety of political, economic, and social issues have resulted in slight differences in how immunization is implemented. The first United States immunization schedule was presented in 1983, while the harmonized schedule (i.e., all the stakeholder organizations (ACIP/CDC, American Academy of Pediatrics, and the AAFP) agreed to the same immunization schedule recommendations) was made available in 1995. The United States Recommended Childhood Immunization Schedule (see for example CDC 2010a) outlines the vaccines required to protect a child against several infectious diseases that pose a risk to children living in the United States (note that the ACIP has also put forward an adult immunization schedule; see CDC 2010b).

Each pediatric vaccine dose is typically delivered by injection during a scheduled wellness visit at a healthcare clinic. For example, an infant is scheduled to receive vaccine doses for hepatitis B, diphtheria, tetanus, pertussis, Haemophilus influenzae type b, polio, and pneumococcus at their two-month wellness visit. Using currently licensed vaccines, a child may receive as many as five injections during this particular visit. Under extreme conditions, a fifteen-month old child may receive as many as eight injections in a single clinic visit. The resulting crowding and complexity of the Recommended Childhood Immunization Schedule is only likely to grow worse as new infectious diseases emerge and/or new vaccines are developed. These complexities increase the likelihood that a parent/guardian will reject or delay some vaccinations, resulting in noncompliance with the Recommended Childhood Immunization Schedule and the associated risks. For a discussion on vaccine injection overcrowding, schedule complexity, and the cost of vaccinating a child, see Weniger (1996).

The cost of vaccinating a child also contributes to the underimmunization of children, through the opportunity cost of time for a parent/guardian to make clinic visits as well as the monetary cost of vaccination (Plotkin and Orenstein 2004). These costs often contribute to either missed clinic visits or missed vaccine doses. For example, the 1990-1992 measles epidemic in the United States involved 28,000 cases of measles, most of which were due to inadequate vaccination of these patients when they were under two years of age (Mackay and Rosen 2001). Clearly, noncompliance with the Recommended Childhood Immunization Schedule puts children at risk of contracting numerous infectious diseases.
The extensive healthcare delivery system in the United States, through private and public clinics and facilities, has facilitated the delivery of pediatric vaccines to the over four million children born in this country each year. Immunization registries have also made it easier for healthcare providers and parents to track a child’s up-to-date immunization record, and hence, determine when vaccines have been missed or delayed. A stated goal of the CDC is to achieve and sustain a 95% immunization coverage rate for all children by the time they enter school, for the first six diseases listed in the Recommended Childhood Immunization Schedule (CDC 2010a). Details of pediatric immunization guidelines are regularly disseminated throughout the medical community (e.g., see Kroger et al. 2006 or http://www.cdc.gov/vaccines), and have become a foundation for the United States’ public health infrastructure.

The strong and well developed public health infrastructure in EU countries has been the mainstay of their pediatric immunization programs. For example, in the United Kingdom, the Health Protection Agency provides guidance on vaccines and immunization policies and procedure, though the United Kingdom Department of Health implements such policies. This creates a natural “checks and balance” framework that provides multiple levels of control and guidance for the system.

**PEDIATRIC COMBINATION VACCINES AND PRICING**

Given that combination (multivalent) vaccines reduce the number of required injections and may be more economical, pediatricians, public health policy-makers and administrators, and parents/guardians will likely choose combination vaccines over multiple single antigen (monovalent) vaccines. However, using combination vaccines may inject a child with antigens they have already received in the recommended quantity and timing sequence. For example, injecting a child with a DTaP-HBV-IPV (diphtheria, tetanus, pertussis, hepatitis B, and polio) combination vaccine at age 4 months would provide extraimmunization for hepatitis B, since (according to the Recommended Childhood Immunization Schedule, assuming both doses of hepatitis B were administered) no dose of vaccine is required at that age. Such extraimmunization poses biological risks and amplifies philosophical concerns with immunization in general. Biologically, extraimmunization of some antigens increases the risk of adverse side effects, as is the case with diphtheria and tetanus vaccines (CDC 1999). Philosophically, many people challenge the safety and effectiveness of vaccinating children and particularly object to the use of combination vaccines, since they believe injecting a child with multiple antigens simultaneously overwhelms the infant immune system; extraimmunization due to combination vaccines only increases these fears (Edwards and Decker 2001, Chen et al. 2001). This philosophical barrier to vaccination is an increasing concern for pediatricians and public health administrators. For example, a recent national survey reported that 54% of pediatricians had encountered parents over a 12-month period that refused to vaccinate their child, citing safety concerns as the top reason for this refusal (Flanagan-Klygis et al. 2005). In another survey, 70% of pediatricians had encountered a parent in the 12-month period preceding the survey that refused at least one immunization for their child (Diekema 2005). In addition to these biological and philosophical concerns, the economic toll of extraimmunization is significant. For example, the annual societal cost burden of providing one extra dose of a vaccine for each child born in the United States is over $28 million, which assumes a birth rate of 11,100 births per day (see Jacobson et al. 2006b) and a vaccine cost of $7, both of which are conservative estimates.

Given such obstacles and challenges, the practical advantage of having combination vaccines available (and hence, the opportunity to administer fewer injections) has resulted in vaccine
manufacturers becoming more adept at creating new combinations vaccines, which can make for fierce competition between such products, particularly when a single vaccine formulary must be stocked with only one of several such products. For example, Pediarix®, a combination vaccine manufactured by GlaxoSmithKline that immunizes against diphtheria, tetanus, pertussis, polio, and hepatitis B, gained United States FDA approval in December 2002. In addition, Pentacel®, a combination vaccine manufactured by Sanofi Pasteur that immunizes against diphtheria, tetanus, pertussis, polio, and *Haemophilus influenzae* type b, gained FDA approval in 2008. On the surface, having several combination vaccines to choose from would appear to be a good thing for pediatricians, healthcare administrators, and the public health community. However, the fact that these two vaccines are partially overlapping makes them ill-suited to be stocked within a single pediatric vaccine formulary. Therefore, pediatricians, healthcare administrators, and the public health community, in general, must choose which of these products to stock in their particular pediatric vaccine formularies. The dual issue faced by vaccine manufacturers is how to price their vaccines (particularly their combination vaccine, since it will form the backbone of any pediatric vaccine formulary) so as to maximize their overall revenue. Given that the pediatric vaccine market in the United States is a more than $2 billion industry, each 1% shift in market share translates into more than $20 million of revenue. Therefore, it is in the best interest of each company to appropriately price their combination vaccines (or equivalently, appropriately set the price premium inherent in a combination vaccine, where this price premium is the difference between the price of a combination vaccine and the sum of the prices of the individual vaccines that comprise the combination vaccine). However, since any change in price of one combination vaccine can be responded to by a change in price in a partially overlapping (and hence, competing) combination vaccine, a natural question to ask is whether there exist equilibrium prices for combination vaccines. As more combination vaccines become available, market forces will operate to move towards and reach an equilibrium market share for all these products, as well as price premiums that support such equilibriums.

Combination vaccines have been more aggressively incorporated into immunization schedules within the EU. For example, in the United Kingdom, the diphtheria, tetanus, pertussis, polio, and *Haemophilus influenzae* type b vaccine is the vaccine of choice for the months 2, 3, and 4 immunizations. This vaccine only gained FDA approval for use in the United States in 2008. In Austria, the diphtheria, tetanus, pertussis, polio, hepatitis B, and *Haemophilus influenzae* type b vaccine is the vaccine of choice for the months 3, 4, and 5 immunizations. As of this writing, this vaccine has yet to gain FDA approval within the United States, hence is unavailable to meet the nation’s immunization needs. Clearly, longer regulatory approval times in the United States make it more difficult for vaccine manufacturers to launch products, which have been deemed safe for use in many EU countries, creating a fragile vaccine manufacturer and supplier infrastructure and its associated suboptimal immunization environment.

**PEDIATRIC VACCINE SHORTAGES AND STOCKPILING**

Over the past decade, vaccine production interruptions in the United States have led to widespread vaccine supply shortages, resulting in children not being fully immunized according to the Recommended Childhood Immunization Schedule. Numerous factors have contributed to this vaccine supply shortage crisis (Sloan et al. 2004). First, over the past decade, there has been a downward trend in the number of pediatric vaccine manufacturers (NVAC 2003), which means that any single vaccine production interruption is more likely to lead to widespread vaccine supply shortages. In 2010, only four pediatric vaccine
manufacturers (GlaxoSmithKline, Merck, Sanofi Pasteur, and Wyeth/Lederle) provided all the vaccines needed to meet the routine immunization requirements for the (over) four million children born in the United States each year (note that three others manufacturers, Chiron, CSL, and Medimmune, produce influenza vaccines). Second, since the United States federal government purchases over one-half of all pediatric vaccines that are delivered, they have negotiated contract prices that are significantly lower than those paid in the private sector. The resulting limited profit margins make it economically unattractive for new vaccine manufacturers to enter the pediatric vaccine market or for existing manufacturers to increase production capacity, through either new investments or reallocation of production capacity. This has also made it difficult to appropriately price pediatric combination vaccines, which often require high research investments, yet whose prices are closely tied to their monovalent vaccine components that are already priced and available in the market (Jacobson et al. 2003a, 2003b, 2005). Third, the FDA has become increasingly more stringent when certifying vaccine manufacturing facilities (FDA 2004). Therefore, if a production facility is cited for production violations and is temporarily shut down by the FDA, it must go through a rigorous recertification process that can delay and limit production even further. Fourth, when new vaccines gain FDA approval, vaccine manufacturers may not be able to accurately predict the rate at which pediatricians and other healthcare providers will welcome the use of such products. The very nature of the resulting uncertain (stochastic) demand function makes it highly challenging to determine reasonable vaccine production runs without creating either excessive shortages or inventory surpluses in the process. Lastly, if the ACIP modifies the Recommended Childhood Immunization Schedule, which results in additional doses of a particular vaccine, or changes the timing of a particular vaccine, this may create unpredictable demand surges to which vaccine manufacturers may be unable to respond in a timely manner. All these issues must be considered when designing and managing the vaccine manufacturing production process.

The National Vaccine Advisory Committee (NVAC) formed the working group, “Strengthening the Vaccine Supply of Routinely Recommended Vaccines” (NVAC 2003), which held a workshop (in 2002) with industry representatives, regulatory authorities, public health officials, purchasers, providers, consumers, legislators and academic investigators to discuss and identify solutions to the pediatric vaccine supply shortage problem. The outcome of this deliberation led to several recommendations, including providing financial incentives for vaccine manufacturers, instituting policy and regulation changes, and growing the rotating pediatric vaccine stockpiles (USGAO 2002). Sloan et al. (2004) present the structure for a pediatric vaccine subsidy system that could serve as a catalyst to attract more pharmaceutical companies into the vaccine production industry, and hence, create a more stable vaccine supply environment. The United States Government Accountability Office (GAO) and the CDC believe that a national pediatric vaccine stockpile is the best avenue to protect against vaccine production interruptions and the ensuing supply shortages (USGAO 2002). It is worth noting that the first national pediatric vaccine stockpiles were created in 1983 to address short term vaccine supply interruptions. The CDC has gone on record that these stockpiles have eliminated or reduced the impact of vaccine supply shortages on at least eight different occasions since 1983.

Given the challenges that exist in creating and maintaining pediatric vaccine stockpiles, it is imperative that most, if not all, economic and production barriers be minimized, and hopefully, completely eliminated. As recently as 2005, an economic disincentive existed for vaccine manufacturers to create and maintain pediatric vaccine stockpiles, whereby accounting rules and procedures did not permit vaccine manufacturers to list such vaccine
stockpiles as revenue from sales. After much deliberation and negotiation, on December 5, 2005, the Securities and Exchange Commission (SEC) stated that vaccine manufacturers could recognize revenue on vaccines placed into government stockpiles instead of waiting to count such payments until when the vaccines are physically taken out of the stockpile (Security and Exchange 2005). National policy changes as such provide a more business friendly and welcoming environment for vaccine manufacturers to work with government agencies to provide the necessary public health protection afforded by pediatric vaccine stockpiles.

The goal of the national vaccine stockpile program is to maintain a six-month rotating inventory for all routinely recommended pediatric vaccines (i.e., inactivated polio (IPV), measles-mumps-rubella (MMR), *Haemophilus influenzae* type b (Hib), hepatitis B (HBV), hepatitis A (HAV), varicella (VAR), diphtheria-tetanus-acellular pertussis (DTaP), pneumococcal conjugate (PNU7), and a pentavalent combination vaccine (DTaP-HBV-IPV). To increase the existing vaccine stockpile levels to the recommended levels (Manning 2004), the United States federal budget allocated more than $170 million for fiscal year 2003 to provide partial funding to support the necessary expansion of the national vaccine stockpile program. Jacobson et al. (2006a, b) analyze the proposed vaccine stockpile levels using a stochastic inventory model. They use this model to examine the adequacy of the proposed six month rotating pediatric vaccine stockpile levels, as well as provide insights into what the appropriate pediatric vaccine stockpile levels should be to achieve prespecified vaccination coverage rates. Since the average pediatric vaccine production interruption has lasted more than one year, they determine appropriate pediatric vaccine stockpile levels sufficient to absorb the effect of such vaccine production interruptions. The level of funding needed to create such pediatric vaccine stockpile levels is also reported and discussed.

Each EU country sets its own pediatric vaccine stockpile policy and maintains its own vaccine stockpiles. Given the advisory role of the European Centres for Disease Prevention and Control (ECDC), they can facilitate communication between the various countries, through each country acts independently and autonomously. This parallels each state in the United States receiving guidance from the CDC, but ultimately each setting its own immunization agenda, within the accepted national immunization schedule guidelines. On the other hand, the United States maintains a single stockpile for the entire country, which it releases as needed and appropriate. Therefore, the EU is ultimately more decentralized than the United States in how it is prepared to deal with vaccine shortages.

**INFLUENZA VACCINE PRODUCTION AND DEMAND**

Routine pediatric vaccines account for a large proportion of vaccine manufacturing. Such vaccines can be considered mature or well developed, with no (or little) changes needed to the vaccine production process. Therefore, vaccine production interruptions can be mitigated through vaccine stockpiling and inventory management. On the other hand, the seasonal (annual) influenza vaccine uses a conventional manufacturing process that requires the identification of three virus strains that are likely to be the influenza virus in the ensuing influenza period (which changes each year, due to antigen shift/drift). Vaccine manufacturers then use eggs to grow the vaccine components (Gerdil 2002). Given the limited number of vaccine manufacturers that provide the influenza vaccine in the United States (Sanofi Pasteur, Chiron, and GlaxoSmithKline), the stability of the influenza vaccine supply chain rests at the production source. This became most apparent during the 2004-2005 influenza season, when production problems and compliance issues created a massive vaccine shortage during this period. The resulting supply shortage prompted academic researchers to gain some
understanding of what brought on this crisis, and how it may be avoided in the future. Deo and Corbett (2009) show how the interaction between yield uncertainty in the influenza vaccine production process and corporate strategy contribute to the small number of vaccine manufacturers and the resulting reduction in production output. Chick et al. (2008) show that influenza production risks lead to inadequate vaccine supply. Their analysis focuses on the middle of the vaccine supply chain, namely, designing business contracts that allow vaccine manufacturers to remain profitable and government entities to balance cost with public health needs. Hehme et al. (2008) discuss critical factors in securing a safe and reliable influenza vaccine supply, both for seasonal and pandemic influenza, which utilize the same production facilities. New advances in manufacturing processes coupled with on-going increases in production capacity will make it possible to rapidly produce large number of vaccines. Pre-pandemic vaccines for stockpiling and pre-emptive use are also becoming a reality, which will offer a new defense in the event of an influenza pandemic. More generally, Muzumdar and Cline (2009) discuss critical issues in vaccine supply and demand in the United States. They note that overly strict regulatory policies significantly increase vaccine development costs and time to reach market, creating unnecessary negative incentives to vaccine manufacturers. They suggest several approaches that would mitigate some of the obstacles to stabilizing the vaccine supply, including government subsidies for basic vaccine research, enhanced vaccine manufacturer liability protection, and opportunities for fast-track approval for new vaccines. Recently introduced policies such as market commitments prior to launch and Medicare Part D vaccine coverage have been implemented and may also aid in resolving some of these problems.

The 2004-2005 seasonal influenza vaccine shortage also provides some lessons that can be applied during an influenza pandemic. Ransom et al. (2007) highlight how local health departments responded to this shortage. They observed that local health departments were critical in adjusting to this shortage, by reaching out to the entire health community, using preparation plans to mitigate the impact of the shortage, and reallocating and redistributing their limited supply of influenza vaccine to targeted populations. Although policy recommendations typically come at the national level, local implementation and adjustment to the unique features of each community are critical to ensure that vaccine supply and distribution is efficient and effective.

The CDC recommends seasonal influenza vaccination for particular at-risk and targeted populations. Over the past several years, this group has grown to include, for example, young children. Universal influenza vaccination has been discussed as a comprehensive plan for the United States (Schwartz et al. 2006). Such a policy would create a new set of challenges, including vaccine supply maintenance, expanded vaccine delivery logistical issues, and higher utilization of the public health infrastructure. Addressing such issue will provide much needed preparation during a widespread influenza pandemic vaccination campaign.

Recent studies also suggest that some protection from influenza illness can be acquired through the use of the pneumococcal conjugate vaccine (PCV7), which is part of the Recommended Childhood Immunization Schedule. Researchers have observed that the PCV7 may serve to reduce the morbidity associated with influenza, as well as other viral respiratory illnesses (Kalvaitis 2007). Researchers have also conjectured that people who have received seasonal influenza vaccines may also have some partial protection against a pandemic influenza. Such research makes a strong case for routine immunization in general, as well as suggests possible interdependencies between different vaccines. Further research is needed to quantify and further validate and explore such hypotheses.
VACCINE DISTRIBUTION, PANDEMIC INFLUENZA RESPONSE AND PRODUCTION ISSUES

The United States healthcare delivery system provides the infrastructure to deliver routine pediatric vaccines to the (over) four million children born in the United States each year. This includes a comprehensive system of well-baby office and clinic visits during a child's first two years of life. Support for such services is available not only through the private payer health insurance system, but also through government programs like the Vaccine for Children Program (see information available at the CDC web site, http://www.cdc.gov/vaccines, which has a comprehensive collection of information and web links to all matters related to immunization and vaccination). Similar web sites exist for EU countries (e.g., the Health Protection Agency in the United Kingdom: http://www.hpa.org.uk/).

For non-routine immunization, such as during a pandemic influenza outbreak, the public health infrastructure must serve as the first line of defense to efficiently and effectively collect, distribute, and deliver vaccines (and other medical supplies, like syringes, antivirals, facemasks, and latex gloves) to either targeted subgroups of the population (e.g., healthcare workers, critical infrastructure workers) or in the worst case, the entire population. The United States federal government has worked to provide guidelines to follow in the event of pandemic influenza outbreak. However, specific procedures are (appropriately) being planned at the local levels (states, counties, cities, towns). Clearly, there is no "one size fits all" procedure that can be effectively applied across the wide spectrum of communities, ranging from those in large cities to those in small towns. Attempts at implementing a single uniform approach is destined to create a "Viral Katrina" in urban centers, where public health clinics are certain to be overwhelmed and vulnerable to collapse in the event of mass vaccination and treatment needs. On the other hand, short term quarantining in very small rural communities may be feasible. Clearly, given the potential for misinformation being disseminated and limited avenues for transmitting accurate communications (and the possibility for widespread public panic), it is vital to have systems in place and well-defined procedures available that can analyze and create plans of attack for numerous likely (or even unexpected) scenarios.

Academic researchers have begun to meet this challenge by creating computer-based, real-time tools and systems to assist with this process. Aaby et al. (2006a, b) report the results of a simulation study to design and operate a public health clinic charged to stock and deliver/dispense vaccines and medication during a disease outbreak. Their simulation tool allows one to play “what-if” games with different disease outbreak scenarios, and hence, allows public health administrators to proactively have plans in place for a variety of such scenarios. Miller et al. (2006) use a simulation model to show how a public health community can design and effectively respond to a bioterrorism attack (like smallpox). In such environments and situations, mass vaccination may provide the best defense in preventing widespread fatalities (Kaplan et al. 2002). Zhang et al. (2006) describe FluSurge, a computer software tool that estimates the number of hospital admissions and deaths that may arise during a pandemic influenza outbreak, under a variety of scenarios. Based on a case study for the Atlanta metropolitan area, they suggest that the city’s hospital system will be severely taxed during such a crisis, largely due to the near capacity utilization of hospital resources during normal operations. Hanfling (2006) provides a cost plan for supplies and personnel during an emergency response. Medlock and Galvani (2009) describe a model for distributing pandemic influenza vaccines, based on five different measures associated with mortality, morbidity, and economics. They conclude that the highest priority groups for vaccination should be children and their parents, based on their high transmission rates into the broader community. Such conclusions are in contradiction to CDC recommendations for both seasonal
and pandemic influenza (CDC 2009). Tanner et al. (2008) use stochastic programming to identify optimal vaccination policies for controlling infectious disease epidemics. They consider a variety of scenarios, including finding the optimal vaccination policy when there is a limited vaccine supply and a cost-benefit scenario.

Alternative means of distribution may also be appropriate during a pandemic influenza mass vaccination campaign. Westrick et al. (2009) survey the role of pharmacies in the distribution and administration of several common vaccines. They observe from their data that just 10% of several common adult vaccines were administered in pharmacies, suggesting the apparent limited utilization of pharmacies in the vaccine distribution and administration supply chain. This also suggests that there is significant potential to better utilize pharmacies in the event of a pandemic outbreak. Coady et al. (2007) describe project VIVA (Venue-Intensive Vaccination for Adults), designed to vaccinate difficult to reach populations within urban settings. They focus on taking the vaccination process to such individuals, rather than waiting for such individuals to come for vaccination. They also note that such a program could be replicated in cities during a pandemic outbreak. Iwane et al. (2007) assess how vaccine rates in the United States for high risk adult population could be improved for seasonal influenza. They observe that assessment tools for vaccine utilization based within physician practices may be highly effective to improving vaccination rates. Such observations suggest that localized immunization strategies may be more effective than national strategies in improving immunization rates for high risk populations, provided adequate levels of vaccines are available (possibly through vaccine stockpiles) to meet such demand. High-risk populations with limited mobility also present their own unique vaccination challenges. Lam and Chung (2008) discuss the results of a pharmacist-conducted on-site influenza vaccination in an assisted-living facility. By taking the vaccination programs into such facilities, vaccination rates were significantly increased.

In 2003, avian influenza (H5N1) appeared to be the most lethal threat to become a worldwide pandemic (Neumann et al. 2009). The outbreak, that first appeared in southeast Asia, rapidly spread to other parts of Asia, as well as Europe and Africa. The origin of this virus was traced to South China. With the world anxiously waiting for this virus to become the next influenza pandemic, the novel influenza H1N1 appeared in March 2009 in Mexico, and rapidly became what is now recognized as a worldwide influenza pandemic (the World Health Organization officially designated it as such in the fall of 2009). This situation highlights the unpredictable nature of influenza viruses, and the need to have well established policies and infrastructures in place to respond to such outbreaks. Indeed, the H1N1 pandemic influenza has brought to light the enormous challenges faced by the entire world in managing vaccination campaign, treating the ill, and limiting spread of the disease. Bartlett and Borio (2008) discuss plans proposed in the United States in managing a pandemic influenza outbreak. These plans, conceived prior to the 2009 H1N1 pan influenza outbreak, identify several factors that challenge such plans, including limitations to handle demand surges for health care services, limitations on rapidly producing and distributing a vaccine, limited understanding of the impact of nonpharmacological and social interventions. They note that international cooperation and collaboration will be critical in such environments. Swain and Ransom (2006) observe the challenges presented by the influenza vaccine supply and distribution system, and propose that universal influenza policies be implemented to alleviate such challenges for the public health community. Hessel (2009) summarizes the key supply chain issues associated with the manufacture, distribution, delivery, and administration of vaccines in response to an influenza pandemic. Given the enormous strain that such an event will place on all aspects of the vaccine supply chain, the authors identify several key issues that need to
be considered. As vaccine manufacturers become adept in stretching limited antigen supplies into the greatest number of vaccines, distribution issues become even more critical. Hessel (2009) also notes that it may be possible to develop pre-pandemic vaccine stockpiles based on cross-clade reactivity with H5N1 viruses, which would further accentuate the importance of inventory management and distribution. Timely and effective distribution strategies will require a well-defined national strategy and local public health infrastructure, all designed to minimize the time between vaccine production and vaccine delivery. Moreover, logistical issues in physically moving such vaccines (and the associated ancillary medical supplies) will require a well-defined transportation infrastructure and strategy.

During the early phase of an influenza pandemic, when only a limited amount of antigens (pandemic or pre-pandemic) are available, it is critical that the resulting vaccines be used strategically. Indeed, prioritizing who will get a pandemic influenza vaccine when there is a limited supply can be quite challenging and controversial. Proposed policies often target at-risk populations. Prior to the availability of the H1N1 pan influenza vaccine, the United States CDC outlined their recommended protocol in distributing the vaccine for the novel influenza A (H1N1pan) virus (CDC 2009a). Supply of the vaccine, which first became available on October 5, 2009, was expected to ramp-up until all targeted populations were vaccinated (estimated to be approximately 159 million people). The initial targeted populations were pregnant women, persons who live with or provide care for infants (under the age of six months), health-care and emergency medical services personnel, children and young adults (aged between six months and 24 years), and persons between the age of 25 and 64 years with underlying medical conditions that place them at risk for influenza-related medical complications. The CDC noted that as of the beginning of 2010, approximately 61 million people (which equates to slightly over 20% of the United States population) had received an H1N1pan vaccine, which included almost 28% of this initial target group. They also estimated that almost 30% of United States children (6 months to 18 years) had received the vaccine (CD 2010c). By comparison, approximately 40% of Canadians received an H1N1pan vaccine. This high immunization level may be attributed to their SARS outbreak in Toronto just a few years earlier, and hence, making the population more receptive to vaccination in such environments. On the other extreme, Australia saw only a 10% H1N1pan vaccination rate, which they attributed to poor communication on the importance of the vaccine and possible fears within the population of being immunized with a new vaccine.

Miller et al. (2008) observe that other factors, such as the signature pandemic pattern in which mortality risk is shifted to particular age groups, likely reduced vaccine response in seniors, and differences in remaining years of life with age should also be considered for initial vaccination. They use such information to project the age-specific years of life lost (YLL), which moves the focus of pandemic vaccination strategies onto younger populations and illustrates the need for real-time surveillance of mortality patterns in future pandemics. Wynia (2006) discusses ethical issues associated with distributing a limited amount of vaccines during a public health crisis, such as a pandemic outbreak. By focusing on what they refer to as the three R’s: rationing, restrictions, and responsibilities, Wynia (2006) argues that ethical principles must be considered in making and revising such difficult decisions during a public health crisis. Moreover, international cooperation will be critical in such events. Zimmerman (2007) argues that the mortality pattern for an influenza pandemic may provide a basis for allocating vaccines during such an event. Moreover, the two competing ethical principles that must be considered for vaccine rationing are utilitarianism (i.e., practical value) and egalitarianism (i.e., fairness). Zimmerman (2007) also notes that vaccination for health care workers satisfies both these criteria. For other populations,
multiple issues should be considered before such decisions can be made that satisfy ethical values. Riley et al. (2007) use a mathematical model to compare the impact of administering a limited number of full strength pre-pandemic vaccines versus widespread administration of a weakened vaccine, on the infection attack rates. They observed that both vaccine efficacy and population-level implications of pre-pandemic vaccine are both critical when setting appropriate vaccine stockpile levels and vaccine dosing. A key finding was that the most effective approach to reducing the infection attack rate was using lower vaccine dose across a wider population.

In 2006, the United States and the European Union (EU) were in the early planning stage to stockpile H5N1 pre-pandemic vaccines. For example, the United States planned to stockpile 20M doses of a H5N1 vaccine. Several EU countries also placed preorders for pandemic influenza vaccines, once it became available. The events of 2009 refocused attention on the H1N1 pandemic influenza vaccine, though the same planning issues need to be addressed. For example, given that several EU countries have export limitations on vaccines manufactured within their borders, then in the event of a pandemic influenza outbreak, when a vaccine becomes available, its distribution may be limited by specific EU country export policies. This issue could lead to widespread panic in countries that do not have vaccine manufacturing plants within their borders, as well as the propagation of counterfeit vaccines on the internet being offered to such (desperate) populations. Note that such policies also provide an incentive for countries to attract vaccine manufacturing facilities to within their borders. Given that a significant proportion of vaccine manufacturing capacity currently lies outside the United States, the United States federal government has invested in attracting vaccine manufacturing facilities, with the accompanying vaccine manufacturing capacity, within its borders. For example, the United States Department of Health and Human Services has partnered with Novartis to build a large-scale cell-culture influenza vaccine manufacturing facility in North Carolina. Once fully operational, this facility will be positioned to produce 150 million doses of a pandemic influenza vaccine within six months of the onset of a pandemic (Novartis 2009).

A growing number of international organizations are making efforts to formulate plans in the event of a pandemic outbreak. Kieny et al. (2006) describes the results of a World Health Organization (WHO) meeting held May 2-3, 2006 in Geneva, Switzerland, that discussed the framework for a global response action plan in the event of a worldwide pandemic influenza outbreak, including the rapid production of vaccines and the surge-capacity before and during the outbreak. On December 14, 2006, the United States Department of Health and Human Services issued a public request (through the Federal Register) soliciting ideas and comments on which subgroups of the population should have priority in being immunized with prepandemic and pandemic influenza vaccines (HHS 2006). The resulting prioritization policy would have an enormous impact on vaccine distribution during a pandemic influenza outbreak, given the limited amount of vaccines that are likely to be available during the initial phase of such a crisis. Clearly, significant planning and coordination is needed between both the public health community and the private health sector to ensure that a country (or more accurately, the entire world) is adequately protected and treated before, during, and after a pandemic influenza outbreak, to ensure that each nation’s social and economic infrastructures are preserved during such a period.

The population density in Europe (in particular, several densely populated urban areas), coupled with the challenges in coordinating efforts across several countries, makes it highly vulnerable to pandemic influenza outbreak. The social and economic consequences of a pandemic influenza outbreak are difficult to accurately predict. For example, Page et al.
(2006) consider a case study on managing tourism in Scotland in the event of a pandemic influenza outbreak. The ECDC serves as an advisor to all the EU countries in coordinating efforts in addressing immunization and public health issues. Each EU country maintains full autonomy in managing their immunization programs, including setting their routine pediatric immunization schedules, ordering vaccines and maintaining vaccine stockpiles, and negotiating prices and costs for such products. A February 2007 interview with ECDC leadership reported concerns that EU countries are not moving sufficiently fast in preparing for a pandemic influenza outbreak, and that the EU needs at least two years to be adequately prepared to respond to such an outbreak.

As the threat of pandemic influenza outbreaks grow, vaccine manufacturers are making important advances in creating new vaccines for such emerging viral threats. Given that such threats may surface both quickly and (to some degree) unexpectedly, the need for efficient and effective vaccine distribution systems is critical. In the best case scenario, a pandemic influenza vaccine can be created in six months, which was the case for the H1N1 pandemic influenza vaccine in 2009, though 18-24 months may be required in a more challenging environment using conventional (egg-based) methods. Several issues must be considered to determine the optimal process of moving large amounts of vaccines from a vaccine manufacturing facility into the hands of healthcare personnel who are responsible for their delivery. First, the balance between depth and breadth of the vaccine supply chain must be addressed. In particular, is it better to have several manufacturing and/or distribution centers, each servicing a small population area, or a small number of manufacturing and/or distribution centers, each feeding vaccine supplies into a secondary and/or tertiary set of distribution centers? Second, how many doses of a vaccine should be produced and be made available? Factors to be considered include whether adjuvants will be used (see the section, “Questions and Challenges: The Future” for further commentary on this issue), vaccine production yield and production process variability, start-up and set-up costs, as well as time when initializing a production run for a vaccine. Another issue to consider is whether the vaccine will be cell-based or DNA-based, with each having unique production, safety, efficacy, and delivery challenges that will need to be addressed. In addition, determining the optimal and minimal dosage requirements for a vaccine to achieve a specified efficacy, as well as the impact of the herd effect on determining what fraction of a population to immunize, are two factors that require further study and consideration. Third, the need for and size of a vaccine stockpile are two issues that require research attention and investigation. In particular, weighing the risk of a pandemic influenza outbreak versus the size, the shelf-life of prepandemic vaccines and antivirals (including cold-chain storage issues), and the cost of building and maintaining a vaccine supply and stockpile requires attention. All these issues, which are being discussed both in the United States and in the EU, will become even more urgent and complex as new pandemic influenza vaccines are being developed.

The 2009 influenza season in Australia was dominated by the H1N1 pandemic. In anticipating this situation, sufficient vaccine doses were available for the entire population, though only 10% were actually administered. Such a low uptake was a result of personal choice rather than any systematic or supply limitations. In addition, Australia aggressively tested individuals who showed flu or flu-like symptoms providing the appearance that the rate of infection was higher than in other countries. Given that mortality rates across the different age cohorts paralleled those observed in the United States, this is not likely the case, which suggests that surveillance and detection approaches and rates should be compared across different countries with care.
Vaccination has historically received considerable policy and public health attention. For the 2009 H1N1 pandemic influenza, Japan worked diligently to monitor the incidence of cases. Over 75% of the cases were in children and young adults (i.e., under the age of 19 years). They also, like many countries, shifted their seasonal influenza vaccine capacity into producing the H1N1p vaccine. In particular, with a normal production of 28M doses of seasonal influenza vaccine each year, only 22.5M doses of the seasonal influenza vaccine were produced, and 15M doses of the H1N1p vaccine were produced, with all additional doses imported. The priority system used to determine the order in which the population would be vaccinated was similar to that used in the United States and other countries. A comprehensive strategy for containing the spread of H1N1p was installed, including vaccination, social distancing, surveillance, medical staff preparedness, and anti-flu medication, among others. One area that could be improved was communication of developments to the general population, so as to not incite unnecessary fear and encourage the misinformation. It was estimated that only 10% of the population were infected by H1N1p, with 16,500 hospitalizations and 185 deaths, which compared favorably to other countries. The key statistic was that of the 185 deaths, 74% were under 30 years of age, with 71% having some underlying chronic condition. Overall, Japan was well prepared in dealing with the 2009 H1N1 pandemic influenza, which bodes well for future pandemics.

The government-directed manufacture, distribution, and administration of H1N1p vaccines in China facilitated a rapid and cohesive effort to immunize their population. The Chinese equivalent of the CDC, through their provincial and local centers, undertook a massive logistics project resulting in an enormously successful and rapid distribution and delivery plan. The success of their top-down administration of the supply chain suggests that, in the event of national crises of this type, such an approach merits further attention and investigation, in contrast to market driven operations, which may be too slow to respond to a rapidly changing public health emergency.

Given that infectious diseases cross borders, and can strike people in any country at any time, there are numerous common practices being following in EU countries, Australia, and the United States. The decentralized structure of the EU and each country’s public health system will facilitate a rapid response in the event of a pandemic outbreak. Interestingly, the ECDC has been effective in bridging communication between the EU countries, so that autonomy does not appear to correlate with disorganization and conflict. Australia has a similarly strong public health network that they deployed in distributing the H1N1 pandemic influenza vaccine. The United States has been promoting a decentralized pandemic response strategy, while providing national guidelines, though at present, it is not clear how successful this has been. This approach is consistent with EU procedures, and hence, will facilitate a worldwide response in the event of a global pandemic outbreak.

QUESTIONS AND CHALLENGES: THE FUTURE

The vaccine supply chain, which in the broadest sense, includes the development, testing, approval, manufacturing, distribution, and delivery phases, is long, thin, and fragile, and hence, is only as strong as its weakest link. In the event of a pandemic influenza outbreak, assuming that a vaccine can be rapidly manufactured and made available in large quantities (which may still require several months, based on expert opinion), several challenges remain in moving the vaccines from the manufacturer into the hands of the healthcare professionals and public health clinics responsible for delivering the product.

Public health agencies around the world have been discussing and preparing for an impending influenza pandemic for many years. Hirota (1996) summarizes the discussion and
recommendations made at two conferences (one in 1993 in Germany and the other in the United States in 2005) and contrast this with the perspective on influenza in Japan. In the 1990’s, Hirota (1996) notes that influenza was not considered a serious public health threat in Japan. As a result, little medical or public health attention or resources were targeted to combat its effect or spread. However, in the 1980’s, Japan had a high vaccination rate for school children (Fedson et al. 1997). The shutting down of such school children programs were the prime factor in the low vaccination rates observed in the 1990’s. However, by 2003, Japan’s vaccination rates were only slightly lower than those reported in the United States (Fedson 2005).

Orenstein and Schaffner (2008) provide an overview of the critical issues that impact influenza vaccine production and distribution in the United States. They note that the ACIP has steadily increased the number of people in the population recommended to receive the season influenza vaccine. This has increased vaccine production capacity, which in turn has increased vaccine supply. Given that the same production facilities can be used to manufacture a pandemic influenza vaccine, this production capacity increase is both of practical and strategic value.

A key challenge is determining who should receive the vaccine, given that its availability and distribution will likely be limited by a ramp-up period. Clearly, this issue is highly sensitive and fraught with controversy. A plan is needed to quickly distribute the vaccines in a manner that allows priority populations to be immunized. The ability to rapidly adapt the existing public health infrastructure to achieve this will require further study and investigation. Moreover, the conflict between reaching people to deliver vaccines (and medicines) versus the need to keep people from closely congregating to limit disease transmission presents unique challenges to the public health communities. Research is needed to introduce novel, more flexible paradigms for the delivery of public health services that can accommodate both existing and pandemic influenza outbreak distribution requirements and needs.

The 1918 “Spanish flu” influenza pandemic outbreak resulted in entire communities quarantining themselves. This resulted in restrictions in how people moved around and through their communities, limiting the transmission of the disease. The value of this approach is to focus on disease prevention over disease treatment, which would be far more cost-effective, both in terms of morbidity and mortality. However, given the global world which exists, with rapid worldwide travel, the potential for widespread transmission of the virus is great, making quarantining a significant challenge. Using information gleaned from the 1918 influenza pandemic, Davey et al. (2008) discuss strategies for reducing morbidity and mortality in the event of an influenza pandemic outbreak. They consider several pandemic scenarios and identify effective strategies involving networked-based (e.g., social distancing, school closings) and case-based (e.g., the use of antivirals) measures. They observed that using age-group or randomly targeted pre-pandemic vaccines (that may only be 50% effective, given the limitations of antigen matching using a stockpiled vaccine)) with 7% population coverage was mostly ineffective in reducing morbidity and mortality. They also note that the most effective strategies involved rapid response, high compliance rates for recommendations, regionally-focused mitigation strategies, and rigorous rescinding criteria, which all served to facilitate community resilience during an outbreak. Of particular note is that well formulated preparation plans and public education are critical for enduring community compliance during a pandemic outbreak. Note that technologies like the internet provide an important avenue for maintaining social and economic networks during such quarantine periods, which in turn may impose an enormous strain on such communication systems. Novel approaches to quickly disseminate and update accurate information during
such periods will be critical to maintain social order and keep people updated on travel restrictions, water and food safety warnings, and other primary life sustenance requirements. Research is needed to provide the necessary support for the technology infrastructures to ensure that they remain reliable in the event of such overwhelming information demand surges.

Bringing a new vaccine to market often takes as much as one to two decades, with costs upwards of $1 billion. The creation and production of a malaria vaccine is one such current example, where the hope is that such a vaccine will be available by 2025 (IDN 2007). Vaccine manufacturers are willing to make such investments if the profit potential is sufficient to overcome the risks in not succeeding. As new manufacturing processes are developed and refined, the time frame for this process is likely to shrink, with an associated reduction in development costs. However, the costs will remain significant, and the risks will continue to exist (if not increase due to this collapsed time frame). A key challenge is creating new and appropriate incentives for such investments. Flexible manufacturing facilities, which allow for a smoother, seamless production transition across two or more vaccines offers significant potential to mitigate risk. Distributed production, whereby modularized production plants are created and located around international population centers where the vaccines are needed, works to combine the manufacturing and distribution network. Challenges as such can provide a new paradigm for vaccine manufacturing and distribution that overcomes the traditional economic model currently employed by vaccine manufacturers.

During a pandemic influenza outbreak, if a vaccine can be rapidly developed, the ramp-up period from when production begins to when a sufficient amount of vaccine is available to protect the targeted populations may be prohibitively long. One approach to extending a vaccine supply is through the use of adjuvants, which can enhance and boost the immune response to the vaccine’s antigen. A recent study using adjuvant MF59 with an experimental H9N2 vaccine suggests that it may increase the number of doses available for immunization (Pigliacelli 2007). At present, adjuvant MF59 is licensed for human use in Europe, but not in the United States. The use of such adjuvants may be an important vehicle to immunize a wider group of people during the early immunization phase of a pandemic influenza outbreak, when a limited vaccine supply is available. Note that the United States FDA has begun to recognize the reality of this situation, and has begun to give more serious attention to their use, as is already the case in Europe.

Clearly, the challenges of vaccine distribution are most critical when the demand and need for a vaccine far outstrips its supply. For example, when an HIV/AIDS vaccine is eventually developed and become available, it will initially only be available in limited quantities and priced far beyond the reach of the most at-risk populations (Johnson et al. 2007). This suggests the need for alternative strategies in allocating such scarce resources. For example, with a pandemic influenza vaccine, should health-care workers, who interact with sick patients have higher priority than children, who are aggressive spreaders, or adult with underlying health issues that make them more at risk for a poor outcome if they contract the disease? Research is needed to consider different scenarios and populations to understand the impact of different vaccine allocation strategies.

As new vaccines become available, the types of delivery devices and ancillary medical supplies needed to safely and effectively deliver such vaccines will become a challenge. For example, traditional syringe delivery devices may be inadequate for DNA vaccines. The volume of ancillary medical devices needed to deliver pandemic influenza vaccines or antiviral medication may be an unexpected bottleneck in the system. Determining ways to
handle and dispose of the resulting biohazard waste materials presents a unique set of transient challenges. It may be possible to stockpile such supplies before a pandemic influenza outbreak. Alternatively, research is needed to design novel vaccine delivery systems that are safe, inexpensive, user-friendly, recyclable, and storable for long periods of time.

As the vaccine supply chain is unrolled and set into motion during a pandemic influenza outbreak, numerous economic and social issues will need to be considered to protect this supply chain’s effective and safe operation. At the national level, the Trust for America’s Health issued a report detailing the impact of a pandemic influenza outbreak on the United States economy (Trust for America’s Health 2007). They project a $683 billion economic loss during such an outbreak, which represents over 5% of the goods and services produced in the United States. States that rely most heavily on tourism, like Nevada and Hawaii, would feel the greatest impact of such an economic downturn, which would most likely move the United States, as well as the entire world, into an economic recession.

Counterfeit pandemic influenza vaccines will be advertised on the internet, increasing the volume of spam email being sent. Unwary and desperate people will pay large amounts of money for such worthless products. Vaccine and antiviral shortages, particularly during the early phase of an outbreak, will create social panic and concern, which could lead to violence and economic destruction in urban areas. Law enforcement may also be strained during such periods, due to manpower shortages and fears of contracting the virus. As was observed in New Orleans after Hurricane Katrina, a “Viral Katrina” effect may surface across several cities in the nation, depending on how information is disseminated, and how people choose to receive, use, and act upon such information.

In conclusion, the economics of vaccine manufacturing provides both enormous constraints and incentives for maintaining the existing vaccine supply chain infrastructure, as well as creating new manufacturing supply chain vectors. As biotechnology advances make it possible for vaccine manufacturers to rapidly produce and manufacture new vaccines, the economic drivers of cost and profit must be considered to push such potential into practice, particularly in the event of a pandemic influenza outbreak. Moreover, innovative ways to distribute vaccines into the hands of healthcare providers is critical to realize the full benefit of such advances.

**RESEARCH OPPORTUNITIES**

The challenges posed in the manufacturing, distribution and delivery of routine and pandemic vaccines provides wealth of research opportunities across the vaccine supply chain. The following are five particular research issues that deserve immediate attention, and whose solution would provide significant benefit to our nation’s battle with infectious diseases.

**I. Vaccine Prioritization Strategies**

During the initial phase of a pandemic, when there is an insufficient amount of vaccines to meet the needs of the nation, vaccination priorities must be set. Research is needed to better understand this phenomenon, and provide models and analysis methodologies that can be used to rapidly assess the impact of different vaccine prioritization strategies on a variety of health and social metrics. Moreover, models to better understand how to allocate vaccines within priority group would also be of value in determining optimal vaccine administration strategies.
II. Vaccine Distribution Strategies
Distribution of vaccines for a pandemic, particularly during the initial immunization period (once a vaccine first becomes available), is fraught with numerous challenges. In addition to the sheer logistics of such an undertaking, models that can be used to rapidly determine where such vaccines should be directed, and how they should be distributed and administered, would provide invaluable insights to help public health officials maximize the benefit of various strategies.

III. Vaccine and Ancillary Medical Supply Stockpiling
Stockpiling vaccines and ancillary medical supplies provides protection in the event of vaccine shortages, demand surges, and unexpected disease outbreaks. Models that provide insights into the risks and benefits of stockpile strategies would provide public health officials with important tools to cost-effectively build and maintain such entities in preparation for and during public health crises.

IV. Vaccine Manufacturing Capacity
Given that there exists a limited amount of vaccine manufacturing capacity, vaccine manufacturers must decide how to best allocate this capacity across a spectrum of products. In particular, for influenza vaccine production, a tradeoff between seasonal and pandemic influenza vaccines must be determined well before one knows how many of each will be needed. Models that provide insights into this decision making process, from both the public health and the vaccine manufacturers perspectives, will provide important tools for public health officials to negotiate contracts that provide appropriate economic incentives while optimizing the public health value of vaccine manufacturing capacity.

V. Impact of Non-Pharmaceutical Interventions and Strategies
Social distancing and quarantining were employed with varying success during the 1918 pandemic influenza. Much has changed since then, and as result, it is unclear how effective such techniques would be in today’s society. Models that provide a better understanding of the impact of such strategies, as well as guidelines of when they should be used and not used, would provide public health officials with important insights into their value as well as how they should be implemented.

ACKNOWLEDGMENTS
The author wishes to thank the members of the WTEC Panel on Rapid Vaccine Manufacturing, Dr. Joseph Bielitzki (Lead), Dr. Stephen W. Drew, Dr. Cyril Gay, Dr. Terrance J. Leighton, and Dr. Mary B. Ritchey, for numerous stimulating discussions and inputs that have provided valuable insights that have gone into the preparation of this chapter. The author also wishes to thank Mr. Hassan Ali, Dr. Grant Lewiston, and Ms. Remi Kumagai for their outstanding support during the panel discussions and interactions, as well as the sponsors of the project: National Science Foundation, the U.S. Department of Health and Human Services, and the U.S. Department of Agriculture.

REFERENCES


Weniger, B.G. 1996. Economic analysis to meet the challenges of new combination vaccines, Presented at Vaccine Economics: Planning a Research Agenda for the Challenge of New and Improved Vaccines, Atlanta, GA.


APPENDIX A. DELEGATION BIOGRAPHIES

PANEL

Joseph T. Bielitzki, MS, DVM (Panel Chair)

BS in Biological Sciences, University of Illinois at Chicago
BVS, MS, DVM, University of Illinois at Urbana-Champaign

Joe Bielitzki has a diverse background in science. His early experience was in the enteric infectious agents affecting nonhuman primates. He worked for 18 years in the National Primate Center System at both the University of Washington and the Yerkes Center of Emory University, supporting research across a wide range of biomedicine. In 1996, he became the Chief Veterinary Officer for NASA, where his efforts focused on coordinating the agency-wide animal care and use program, compliance issues, hardware design, and training. Joe served on the working group for safety issues surrounding sample-return missions from Martian environments. In 2000, he served as a government advisor on a task force for a Defense Science Board looking at defense against biological warfare. In 2001, Joe accepted a position as a program manager at the Defense Sciences Office at DARPA. At DARPA, he managed an extensive research portfolio in the life sciences, including Long Term Storage of Blood Products, Peak Soldier Performance, Rapid Vaccine Assessment, Surviving Blood Loss, Restorative Injury Repair, Biofilms for Defense, Pathogen Countermeasures, and Accelerated Anthrax Therapeutics. During this period, Joe interacted with a variety of Federal agencies in the area of biological warfare defense. After DARPA, he relocated to Orlando, where he served as Chair of the Institutional Review Board for the University of Central Florida and a consultant in science and technology. He also consults in the area of science and technology development for academia, industry, and government. Microbiology, pathogen evolution, and protective mechanisms of immunity are primary areas of interest for him. He is recognized for his expertise in the ethical issues surrounding the use of animals in research.

Stephen W. Drew, PhD

BS and MS in Food Science, the University of Illinois
PhD in Biochemical Engineering, Massachusetts Institute of Technology (MIT)

Since retiring from Merck, Dr. Drew founded two companies that support the biotechnology and pharmaceutical industries: Drew Solutions LLC, a direct consulting firm, and Science Partners LLC, an advocacy company for medicines and technologies. Prior to his retirement, he held the positions at Merck & Co., Inc., of Vice President of Vaccine Science and Technology, of Vaccine Operations, and of Technical Operations & Engineering. He joined Merck in 1980 to create the Department of Biochemical Engineering. At Merck, he contributed to the process development and manufacture of several conventional and recombinant microbial products ranging from antibiotics to vaccines. Dr. Drew has expertise in the following areas: manufacturing processes for human and animal vaccines; recombinant biologics; chemical, biological, and engineering technology for bulk manufacture of pharmaceuticals and biologics; capital project engineering; process engineering; and fermentation, cell culture, isolation, and purification processes for sterile products. He was elected to the National Academy of Engineering in 1993; has held offices in the American Institute of Chemical Engineers, the American Chemical Society, the American Society for Microbiology, and the Society for Industrial Microbiology; and is a Founding Fellow of the American Institute for Medical and Biological Engineering. He has served as Chairman of the advisory committee to the Engineering Directorate of the National Science Foundation. He is a member of two standing committees of the National Research Council (NRC) and has participated in many NRC studies.
Sheldon H. Jacobson, PhD
BSc and MSc (both in Mathematics), McGill University
MS and PhD (both in Operations Research and Industrial Engineering), Cornell University.
Sheldon H. Jacobson is a Professor and Director of the Simulation and Optimization Laboratory at the University of Illinois at Urbana-Champaign. Since 1996, he has been applying operation research methodologies to address healthcare problems associated with pediatric immunization and vaccination economics, pediatric vaccine pricing, and pediatric vaccine stockpile economics. He has received numerous awards for his research, including a Best Paper Award in IIE Transactions Focused Issue on Operations Engineering, a John Simon Guggenheim Memorial Foundation Fellowship, and the IIE Award for Technical Innovation. His healthcare research has been published in a wide spectrum of operations research and medical journals, including Health Care Management Science, Journal of the Operational Research Society, Pediatric Infectious Disease Journal, and Vaccine, among others. He has briefed the Advisory Committee on Immunization Practice (ACIP), the committee that provides guidance to the Secretary of the Department of Health and Human Services on issues related to immunization policy in the United States. He has also worked to transition his research into a publicly available website, http://www.vaccinewebsite.com, which has been widely used by both government and private sector organizations. He has received research funding from several government agencies and industrial partners, including the National Science Foundation and the Air Force Office of Scientific Research.

Terrance J. Leighton, PhD
BS, Microbiology, Oregon State University, 1966
PhD, Microbiology, University of British Columbia, Vancouver, B.C., 1970
Postdoctoral Fellow, Biochemistry, University of California, Davis, 1972

Since 2002, Dr. Leighton has held the position of Senior Staff Scientist, Children’s Hospital Oakland Research Institute (CHORI), where he has worked on technologies related to biological threat agents. These include sporidal decontamination, DNA and immuno-based threat agent detection, urban surveillance, and microbial forensics. Objectives of his recent work include single particle ultrastructural and chemical threat agent signatures, large area sporidal sterilization of building environments and recovery of microbial forensic evidence, broad-band PCR (polymerase chain reaction) pandemic and seasonal influenza biosurveillance in tropical environments, and broad-band PCR (TIGER, Triangulation Identification for the Genetic Evaluation of Risks) and next generation DNA sequencing bio-threat detection and characterization. While at CHORI, Dr. Leighton has pursued various special assignments, including Capitol Hill anthrax decontamination (2001-2002), U.S. Postal Service anthrax decontamination (2002-2004), and emergency response planning for the Environmental Protection Agency and St. John’s Medical Center, Oxnard, California. Prior to joining CHORI, Dr. Leighton held professorships in biochemistry/molecular biology and microbiology at the University of California, Berkeley, and prior to that was senior staff scientist in the Earth Sciences Division, Lawrence Berkeley National Laboratory.
Mary B. Ritchey, PhD
BA in Biology, Emmanuel College
PhD in Microbiology, Cornell University
Postdoctoral studies on influenza viruses, Mount Sinai School of Medicine

Dr. Ritchey, of Ritchey Associates, Inc., is currently engaged in consulting for the pharmaceutical industry with a focus in the vaccines area. Prior to taking on consulting assignments, Dr. Ritchey spent 29 years in the pharmaceutical industry working on the development, manufacturing, and quality aspects of vaccines and other sterile pharmaceutical products. She joined Lederle Laboratories in 1977, where her initial assignments involved developing processes for manufacturing influenza and poliovirus vaccines. During her tenure at Lederle and then at Wyeth Pharmaceuticals, she held positions of increasing responsibility in the areas of R&D, manufacturing, quality, and technical services. In 1992 she became Vice President of Operations for the Vaccines group and held additional vice president positions until her retirement in 2006. During her years at Lederle and Wyeth, she was involved in numerous product areas: vaccines for viral influenza and polio, including live attenuated and inactivated; diphtheria, tetanus, and pertussis, including acellular pertussis; *Haemophilus influenzae*, meningitis, and pneumonia, including polysaccharides and conjugates.
OTHER DELEGATION MEMBERS

Michael DeHaemer, PhD

BS in Physics, University of Notre Dame
MS in Operations Research, U.S. Naval Postgraduate School
MS in Industrial Engineering, MBA, Rensselaer Polytechnic Institute
Ph.D. in Management Information Systems, Rensselaer Polytechnic Institute

As Executive Vice President of WTEC, Mike DeHaemer’s focus is on the WTEC mission: assessment operations with the goal of providing valuable and timely information for Federal research agencies about engineering and scientific research activities abroad to stimulate more effective research and new research initiatives. Mike returned to WTEC and Baltimore in 2003, after a previous association from 1992 until 1996, when WTEC was located at Loyola College and he was a member of the Sellinger School faculty. He was the Director of WTEC and JTEC for 1995-1996. Overall he has managed 25 international assessment studies. During 1996 to 2002 Mike was Managing Director of ASM International, a 30,000 member society for materials science and engineering. He also served as the Executive Director of the Heat Treating Society, an organization promoting the engineering and science of thermal processing of materials. His first career was in the U.S. Navy and nuclear powered submarines. Captain DeHaemer, USN, commanded the USS Simon Bolivar (SSBN 641), a fleet ballistic missile submarine, for six deterrent patrols, and a major ship overhaul and conversion to the Trident Missile System. Following retirement from the Navy, Dr. DeHaemer joined the faculty at Loyola University in Maryland. He served as Department Chair for Information Systems and Decision Sciences, taught strategic use of information technology, published concerning human factors in computing, and founded and directed the Lattanze Center for Human-Computer Interface Research.

Cyril Gerard Gay, DVM, PhD

BSc in Chemistry and DVM, Auburn University
PhD in Microbiology, The George Washington University

Dr. Gay has worked in the veterinary vaccine and animal health fields for the last 20 years, holding several positions of increasing responsibility in the Federal government and the pharmaceutical industry. As Chief, Biotechnology Section, Center for Veterinary Biologics (CVB), United States Department of Agriculture (USDA), Dr. Gay developed the procedures for licensing molecular vaccines that led to the first license for a live recombinant vectored vaccine worldwide. Dr. Gay has led several cross-functional teams in industry that developed veterinary vaccines. As Director, Global Product Development, Pfizer, Inc., he developed strategic and tactical plans that interfaced R&D, clinical development, manufacturing, marketing, and product life-cycle management. Dr. Gay is currently the National Program Leader, Animal Health, Agricultural Research Service (ARS), USDA. He provides program direction and national coordination for the department’s intramural Animal Health National Research Program, comprised of 124 scientists located in 11 research locations throughout the United States, including the National Animal Disease Center (Ames, IA); the Avian Diseases and Oncology Laboratory (East Lansing, MI); the Meat Animal Research Center (Clay Center, NE); the Southeast Poultry Research Laboratory (Athens, GA); the Plum Island Animal Disease Center (Orient Point, NY); the Animal and Natural Resources Institute (Beltsville, MD); the Arthropod-Borne Diseases Research Center (Laramie, WY); and the Poultry Research Unit (Mississippi State, MS). Vaccine discovery is a core component of the Animal Health National Research Program.
Fred Heineken, PhD

BS in chemical engineering, Northwestern University
PhD in chemical engineering, University of Minnesota

Following graduate school, Dr. Heineken worked for Monsanto for five years where he did enzyme product development work. He then joined the University of Colorado where he did research in respiration physiology and taught chemical engineering. After four years at the University of Colorado, Dr. Heineken joined COBE Laboratories where he worked on hemodialysis research and product development. After nine years at COBE, he joined the National Science Foundation (NSF) as a program director doing funding of biotechnology and biochemical engineering in the Engineering Directorate. After 24 years of service, he recently retired from NSF. While at NSF, Dr. Heineken received an NSF Award for Meritorious Service. Within the American Chemical Society, he was recently selected to be a Fellow of the Society.

Narayan Iyer, PhD

PhD in molecular biology, Indian Institute of Science, Bangalore
Postdoctoral research, UT Southwestern Medical Center and Johns Hopkins School of Medicine

Dr. Narayan Iyer is a Project Officer in the Chemical, Radiation, and Nuclear Section of the Division of CBRN Countermeasures in the Office of the Biomedical Advanced Research and Development Authority (BARDA) within the Department of Health and Human Services Office of the Assistant Secretary for Preparedness and Response. As a Project Officer and Contracting Officer’s Technical Representative (COTR), he is responsible for providing oversight on the execution of development contracts for medical countermeasures for Acute Radiation Syndrome. His other area of focus is development of medical countermeasures for thermal burn injuries in mass-casualty situations. Prior to this, he was the Acting Chief, for the Anthrax Vaccines Section, at CBRN. He was responsible for key activities in strategy and procurement of anthrax vaccine countermeasures to the Strategic National Stockpile as well as initiating development programs. He also participates in many Working Groups and interagency activities that support advanced product development.

Dr. Iyer has been in the biotech and vaccine industry for over 10 years. He managed both early and advanced product development of two product lines—anthrax vaccine as part of the Biodefense portfolio and vaccine against travelers’ diarrhea at Iomai Corporation (now Intercell USA). As a senior manager in Technical Operations, he has worked in bioprocess development for drug substance and product manufacturing as well as applications of quality by design (QbD) to late-stage processes, ensuring compliance for licensure requirements. He has received awards and citations for his contributions to advanced product development. Prior to that, at Corning Inc, he managed product development of oligonucleotide-based microarrays for monitoring regulation of gene expression.
APPENDIX B. SITE REPORTS

Site reports are arranged in alphabetical order by organization name.
All India Institute of Medical Sciences (AIIMS)

**Site Address:**
All India Institute of Medical Sciences (AIIMS)  
Meeting at Taj Palace Hotel, New Delhi, India

**Date Visited:**
October 17, 2010

**WTEC Attendees:**
J. Bielitzki, M. DeHaemer, F. Heineken, M. Ritchey (report author)

**Host(s):**
Dr. D.N. Rao  
Department of Biochemistry  
All India Institute of Medical Sciences  
Ansari Nagar, New Delhi 110 029, India  
Tel: +011-26593545  
Fax: +91-11-26588641, +91-11-26588663  
dnrao311@rediffmail.com, dnrao@aiims.ac.in

The All India Institute for Medical Sciences was established by an Act of Parliament in 1956 with the objective of providing medical education at the undergraduate and post-graduate levels to demonstrate a high standard of medical education in India. AIIMS has comprehensive facilities for teaching, research, and patient care. Teaching and research are conducted in 42 disciplines and AIIMS awards its own degrees.

Dr. Rao provided us with an overview of his research areas and some general information about research in the vaccine and immunology area. His interests include a novel delivery system for HIV and malaria antigens, plague vaccine, vaccine adjuvants, immunodiagnostic reagents and the role of T regulatory cells in leprosy. He has numerous publications in these areas and a number of international collaborations.

The delivery system that he is working on involves the use of biodegradable nanoparticles made with polylactic acid. Vaccine antigens are attached to these particles for use in immunization. The feasibility of using nanoparticles that degrade very slowly offers the possibility of developing a vaccine that requires only one immunization rather than requiring booster doses. The antigens can be produced using platforms such as baculovirus in insect cells.

Key targets for vaccines include malaria and HIV. These are complex organisms and will require multiple antigens or conserved antigens that are capable of stimulating immunity. Dengue is also an important pathogen in the region and there are 4 serotypes that must be covered.

Dr. Rao is also studying *Yersinia pestis*, the bacterium that causes plague. There are two potentially protective antigens that can be used to develop a serological assay. A live, attenuated vaccine is being studied.

Adjuvants are key to developing an immune response and studies are under way to select for enhanced targeting of dendritic cells.

Dr. Rao and others at AIIMS are also working on diagnostic assays. A highly specific ELISA assay for detecting HIV antibodies has been developed that costs less than imported tests and is more sensitive. A diagnostic kit for Hepatitis C has been developed in addition to a method for screening blood donors. A PCR method for diagnosis of TB has been developed which only takes 24-48 hours to perform.
With respect to pandemic H1N1 influenza, India did not have a vaccination program last year. Tamiflu was provided to those who tested positive by serology and PCR. Vaccines became available this year. Research is ongoing to look for influenza antigens that provide broader protection.

AIIMS has extensive capabilities for in vitro and in vivo evaluation of vaccine candidates. Formal toxicology needs to be done by the Institute of Toxicology or other certified organization. Outside sources are needed for primate models. Collaboration with South America is being pursued to use green monkeys for malaria testing.

Once a vaccine candidate is identified and characterized, AIIMS researchers must partner with an outside company to transfer technology for further development. Low interest government grants are available to help companies perform early development work on a candidate vaccine.

Regarding research funding, there is money available from government grants for work on diseases that have significant impact in India. (Grants for more basic investigation are not as plentiful.) These dollars are made available through departments under the Ministry of Science and Technology. The Department of Defense also has grant money available for work on bioterrorism threats, such as anthrax. There are also sources of funding from outside of India and collaboration with companies, universities and government agencies in the United States and Europe is common.

India’s universities produce qualified graduate students, but it is difficult to get good post-doctoral students. Many choose to gain their post-doctoral experience outside of India.

Vaccines provided by the government are procured through a bid system by the central government. Distribution is via the states and primary care health centers. The routine vaccines are free of charge.

AIIMS has many research programs that are designed to facilitate the more rapid development of vaccines important for the region.

REFERENCES

http://www.aiims.edu


Appendix B. Site Reports

Australian National University (ANU)

Site Address: Australian National University (ANU)
John Curtin School of Medical Research (JCSMR)
Cancer and Vascular Biology Group
Department of Immunology
GPO Box 334
Canberra City, ACT 2601, Australia

Date Visited: February 22, 2010

WTEC Attendees: T. Leighton (report author), S. Drew, S. Jacobson, M. Ritchey

Host(s): Christopher R. Parish, Leader, Cancer and Vascular Biology Group
Tel: + 61 2 6125 2604; Fax: +61 2 6125 2595
E-mail: christopher.parish@anu.edu.au

BACKGROUND

Professor Chris Parish is currently Leader of the Cancer and Vascular Biology Group, Department of Immunology, John Curtin School of Medical Research (JCSMR), ANU. His laboratory has made seminal discoveries in immunobiology including the first demonstration that cell-mediated immunity and antibody formation were mutually antagonistic responses, a finding that illuminated the Th1/Th2 paradigm in immunology. One of his current research interests is to exploit immune deviation for the production of novel anti-cancer vaccines. Professor Parish has also elucidated the role that complex carbohydrates play in cell adhesion and cell migration. These studies have formed the theoretical basis for the development of several carbohydrate-based drugs, such as PI-88 (Muparfostat), that inhibit inflammation, tumor metastasis and angiogenesis. In addition, Professor Parish’s laboratory has developed a number of important immunological technologies, such as fluorescent dyes (e.g., CarboxyFluorescein Succinimidyl Ester - CFSE) for monitoring lymphocyte migration and proliferation. His research findings have launched several Australian biotechnology companies, including Progen Pharmaceuticals, Biotron and Lipotek. In 2005 Prof. Parish was awarded the Clive and Vera Ramaciotti Medal for Excellence in Biomedical Research in recognition of his scientific achievements. Professor Parish has also been awarded the Gottschalk Medal and has published over 280 papers and filed 27 patent applications.

The Cancer and Vascular Biology group focuses on the molecular basis of cell adhesion, cell migration and cell invasion, with a particular emphasis on the immune system, tumor metastasis and angiogenesis. Of particular interest has been the role of anionic carbohydrates, such as heparan sulfate, in these processes. The group applies basic research findings to the development of new drugs which inhibit inflammation, cancer spread and angiogenesis.

DEVELOPMENT OF A NOVEL TUMOR VACCINE

In collaboration with Dr. Paul Foster's group, Division of Molecular Biosciences, JCSMR, a new approach to cancer immunotherapy has been developed. The majority of attempts at cancer immunotherapy involve the generation of CD8+ cytotoxic T lymphocytes (CTLs) against
tumor-specific antigens. Dr. Parish and coworkers have demonstrated that tumor-specific CD4+ T cells, which exhibit a cytokine secretion profile characteristic of Th2 cells, are capable of clearing established lung and visceral metastases of a B16 melanoma that is resistant to CTL lysis. Clearance of these lung metastases by Th2 cells was found to be dependent on degranulating eosinophils, with the eosinophil chemokine eotaxin playing an essential role, as shown in a slide from Dr. Parish, rewritten below:

**Features of Tumor Elimination by CD4+ Th2 cells**

- Tumor antigen (OVA) specific
- Totally eotaxin (eosinophil chemokine) dependent
- Tumor elimination does not depend on recipient lymphocytes
- Degranulating eosinophils appear to eliminate tumors, although other anti-tumor processes may also be involved

**Mode of Action of Th2 Immunity Against Tumors**

Dr. Parish and coworkers elucidation of the mode of action of Th2 tumor immunity is summarized as follows:

- Eosinophils recruited into tumors (eotaxin dependent)
- Eosinophils adhere to tumor cells and are induced to degranulate
- Induction of alternatively activated macrophages: produce arginase-1 that depletes arginine in tumor microenvironment

In contrast, tumor-specific CD4+ Th1 cells, which recruited macrophages into the tumor, had no effect on tumor growth. This work provides the basis for a new approach to cancer vaccination that is effective against CTL-resistant tumors and is, potentially, less susceptible to immune evasion. This approach has been applied to the development of a novel immunotherapeutic cancer vaccine, with the problems associated with the development of such immunotherapeutic vaccines listed below:

**Is Cancer Immunotherapy Feasible?**

- Problem of identifying appropriate tumor antigen(s)
- Problem of suitable adjuvants for human use
- Need to induce an anti-tumor immune response resistant to immune evasion
- Will auto-immunity be a problem?
- Clinical trial design critical; is initial testing in Stage IV cancer patients a viable option?

**Dendritic Cell-Based Vaccines**

Dr. Parish, in collaboration with Dr Joe Altin (School of Biology, ANU), has developed an innovative strategy for cancer vaccine development utilizing liposome-based vaccine constructs that target multiple tumor antigens (pan-epitopes) to dendritic cells (DCs) *in vivo*. This approach overcomes many of the problems associated with pulsing DCs *ex vivo* with tumor antigens and reinfusing the DCs back into patients, the problems associated with this *ex vivo* approach being listed below:

- Usually involves isolating DCs from peripheral blood of patients, pulsing them with tumor antigens and reinfusing them into patients
Appendix B. Site Reports

- Dealing with a limited subset of DCs
- Costly; complicated and time-consuming in vitro manipulations required
- Unclear whether reinfused DCs home to the right tissues?

Drs. Parish and Altin asked the question, “Is it possible to directly target DCs in vivo?” The technology developed by the Parish/Altin laboratories involves the use of liposomes, the general properties of which are outlined in Figure B.1.

**Figure B.1.** General properties of liposomes used by Parish/Altin as a vaccine technology.

A novel “glue” 3-NTA-DTDA (left side of Figure B.2) has been developed to allow the engraftment on the surface of liposomes polyhistidine-tagged (usually 6 His-tagged) proteins that target DCs and, thus, the assembly of DC-targeted liposomes (right side of Figure B.2).

**Figure B.2.** *(Left)* 3-Nitrilotriacetic acid di-tetradecylamine (3-NTA-DTDA) chelates metal ions (Ni2+) and binds multiple histidine residues in proteins (i.e., 6 His tags); *(Right)* Dendritic cell targeted liposome with engrafted His-tagged scFv or dAb specific for DC surface antigens and encapsulated tumor antigen and/or cytokines (Courtesy of Australian National University).
The DC targeting molecules used have been single chain Fv (scFv) or domain antibodies (dAb) specific for mouse (CD11c, DEC-205) or human (DC-SIGN) DCs, respectively. Multiple tumor antigens displayed on tumor cell membrane vesicles are loaded onto this DC-targeting scaffold as shown in Figure B.3, as well as cytokines or purified tumor antigens (right side of Figure B.2).

![Diagram of DC targeting molecules](image)

Figure B.3. Dendritic cell targeted cancer vaccine: contains membrane vesicles derived from tumor cells (courtesy of Australian National University).

B16-OVA melanoma tumor cell vesicles were used to evaluate the role of DC stimuli (IFN-γ and LPS danger signals) on anti-tumor immunopotency (Figure B.4). A very broad range of tumor antigen-specific responses is elicited by these vaccine constructs, which is danger signal dependent, and results in almost total elimination of melanoma lung metastases.
Figure B.4. Potent tumor protection is induced by DC targeted tumor antigens (B16-OVA Tumor). TMV = Tumor membrane vesicles from B16-OVA melanoma, L2 is a 6 His tagged peptide with no affinity for DCs, CD11c and DEC-205 refers to scFv specific for these antigens on mouse DCs and engrafted on the liposome-TMV vaccine construct (courtesy of Australian National University).

A complex and unique human melanoma vaccine formulation (Lipovaxin), which includes a fully humanized domain antibody (dAb)-specific for DC-SIGN on human DCs, has been developed for use in Phase 1 clinical trials, which commenced on December 16, 2009 (Figure B.5). The components of Lipovaxin MM are (1) tumor membrane vesicles from the human melanoma cell line (multiple tumor antigens); (2) incorporation of 3NTA-DTDA ("molecular glue"); (3) encapsulated human IFN gamma (DC activator); and (4) targeting DCs with His-tagged dAb (prepared by Domantis-GSK) specific for DC-SIGN.
Figure B.5. Schematic representation of Lipovaxin. The vaccine construct is prepared by fusing 3NTA-DTDA liposomes with tumor membrane vesicles from the human melanoma cell line MM200, incorporation of IFNγ as a DC activator, addition of nickel and engrafting, via Ni-3NTA, a dAb specific for human DC-SIGN on DCs (Courtesy of Australian National University).

CONCLUSION AND VACCINOLOGY IMPLICATIONS

The revolutionary pan-epitope Lipovaxin platform has profound implications for therapeutic access to historically intractable vaccine targets beyond neoplasias, including malaria, tuberculosis, and HIV. Lipovaxin required over five years of laboratory development and testing prior to the launch of the Phase 1 clinical trials. The synthesis and assembly of the Lipovaxin construct (which contains a number of new chemical entities) is a milestone in vaccinology and as with Dr. Jackson's work represent a uniquely promising Australian approach to immunoprotection targeting dendritic cells.

Dr. Parish occupies a very unusual position in Australian translational vaccine science. He is a well established entrepreneur with access to start-up funding and his position at the JCSMR facilitates access to human clinical trial resources. Dr. Parish posited that a key success factor in Lipovaxin development was having an individual (very hard to find) who understood all of the steps required to translate laboratory results into clinical trial material and the ability to integrate the diverse activities of other members of the team.
Bharat Biotech

Site Address: Bharat Biotech
Genome Valley, Shameerpet
Hyderabad – 500 078 Andhara Pradesh, India

Date Visited: October 21, 2010

WTEC Attendees: J. Bielitzki, M. Ritchey, M. DeHaemer, F. Heineken (report author)

Host(s): Dr. V. Krishna Mohan, President
Vamsi Sadan Plot #256/266
Kamalapuri Colony, Phase II
Hyderabad 500 073, India
Tel: +91 40 2348 0567
kmohan@bharatbiotech.com
Dr. Sai D. Prasad, VP – Business Development (Presenter)
Genome Valley, Shameerpet
Hyderabad 500 078 AP, India
Tel: +91 40 2348 0567 (343)
prasadsd@bharatbiotech.com
Dr. G.V.J.A. Harshavardhan, Director, Rotavirus Development Project
Genome Valley, Shameerpet
Hyderabad 500 078 AP, India
Tel: +91 40 2348 0567

Bharat Biotech International Limited (BBIL) is a company founded by Dr. Krishna M. Ella in 1996 to address the problem of Hepatitis-B in the Asian countries. The company started with $3.5 million to get the Hepatitis-B project started. Since 1996, the company has grown without venture capital funds and has invested its revenues in R&D and fixed assets. No dividends have been issued. The company focuses on pioneering and innovative research that leads to medical products for the developing world, including India. All company technologies have been generated internally.

The vision of BBIL is to be a leader in region-specific neglected diseases and to be a leader in the emerging markets. The Business Philosophy of the company is not to compete with other countries or other companies, but to combat infectious diseases. Growth for the company is to be found in India and the emerging (developing) countries in Asia, Africa and Central and South America), not in the developed countries. There is a strong emphasis on being as cost effective as possible in order to provide vaccines at a reasonable cost to India and the developing countries. The company has a portfolio of 17 vaccines, 9 of which are currently marketed and 8 of which are currently in the pipeline. A vaccine for H1N1pan has just been launched, and is made in cell culture using a dog cell line (MBCK). The company has also launched the world’s first cesium chloride-free Hepatitis-B vaccine. The enabling technologies involved separation techniques that did not use an ultracentrifuge.

In accordance with its vision, the company has focused its recent R&D efforts on two diseases that the company considers to be neglected in the Developing World, Typhoid and Rabies. A new generation typhoid vaccine (TYPBAR) has been launched as well as a new rabies vaccine (INDIRAB).
A public/private partnership (the first of its kind) for a rotavirus vaccine development program is currently underway. It involves BBIL, AIIMS New Delhi, IISc Bangalore, Stanford University, NIH, and the Center for Disease Control (CDC) in Atlanta. This is being funded by the Bill and Melinda Gates Foundation. Other new vaccine development programs include various vaccines for malaria, a dengue vaccine, a staph vaccine and a chikungunya vaccine. Other non vaccine products (e.g., recombinant epidermal growth factor (r-EGF) for foot ulcers) are also being developed. BBIL has 47 global patents and 8 product patents and has received a number of National Innovation Awards. Recent visitors have included the president of India, the president of South Africa, the United States Secretary of HHS, the United States Commissioner of the FDA, Senator John Kerry, and the director of the CDC in Atlanta.

REFERENCES

http://www.bharatbiotech.com
Appendix B. Site Reports

Biological E Ltd.

Site Address: Biological E. Limited
18/1&3, Azamabad
HYDERABAD-500 020
A.P. INDIA
www.biologicale.com

Date Visited: October 21, 2010

WTEC Attendees: J. Bielitzki, M. DeHaemer (report author), F. Heineken, M. Ritchey

Host(s):

Dr. Rayasam (Ray) Prasad, Chief Operating Officer
Tel: +91-08418-304211; Fax +91-08418-304159
prasad.ray@biologicale.co.in

Dr. M. Sai Ram, General Manager – Process R&D
Tel: +91-40-30284819; Mobile 97011 10032
sairam@biologicale.co.in

Dr. Rakesh K Sinha, General Manager – R&D Biotechnology
Tel: +91-40-30214147 Fax: +91-040-27615309
rakeshsinha@biologicale.co.in

Dr. Martin Reers, Head – Technical Operations
Tel: +91-40-30128222; Fax: +91-40-30128222
martin.reers@biologicale.co.in

Dr. Goetz Reiner, Head – Primary Manufacturing
Tel: +91-40-30213999; Fax: +91-40-30214070
goetz.reiner@biologicale.co.in

BACKGROUND

Biological E Limited (BE) is a private biotechnology and pharmaceutical company with headquarters in Azamabad, Hyderabad, Andhra Pradesh. Estimated annual revenues are about $50 million. The company was formed in the 1950s and in the 1960s became the first Indian private company to enter the vaccine field. Vaccine development and mass production is one of the core areas of the company’s business model. BE is the leading supplier of vaccines to the India central government, state governments, the army, and public sector institutions, supplying 60% of pediatric vaccines, more than 135 million doses sold. In 2010 BE is expected to supply more than 250 million doses of vaccine to the government of India.

BE manufactures vaccines at three sites: Gaganpahad, Shameerpet (India’s Genome Valley), and Azamabad, the headquarters site. Production at each site is as follows:

Gaganpahad – tetanus, anti-tetanus serum, anti-snake-venom serum

Azamabad – bulk facility, Japanese encephalitis

Shameerpet – bulk antigens (diphtheria, pertussis, hepatitis B); bulk conjugates and intermediates (Haemophilus influenzae B kartik); and finished products (DPT, TT, DT; hepatitis B, HIB (Lyo), tetravalent (DTP, hep B, liquid), IPV).

BE has a number of international partnerships, including Netherlands Vaccine Institute, Intercell, U.S. National Institutes of Health, and an unnamed U.S. vaccine company.
Through major investments in vaccine R&D for international certifications of quality, global recruiting for technical leadership and marketing expansion, BE seeks to become a more global player.

TECHNOLOGIES

BE commissioned a new large scale manufacturing facility at the Shameerpet site in 2006. The objective of the manufacturing addition is to enhance capacity with the highest level for certification of GMP, providing opportunities for more vaccine products to meet international standards. Vaccine products in the R&D pipeline include DTwP-IPV, acellular pertussis, live tetravalent dengue vaccine, live tetravalent rotavirus vaccine, and meningococcal ACWY conjugate.

DISCUSSION OF ISSUES RELATED TO VACCINE MANUFACTURING

The Biological E representatives highlighted a number of challenges for the success of manufacturing vaccines. Chief among them was the drive to produce vaccines at low cost and remain profitable. Making vaccines requires great investment with risks that are not well defined. Some observations made by the various participants include:

- Quality control systems are important and may be the time controlling critical feature in setting up the manufacturing chain for vaccines.
- For more rapid vaccine manufacturing needs are:
  - More rapid microbiology
  - More automation
  - More trained personnel, rapidly brought up to speed
- Advances in testing are desirable:
  - Eliminating animal testing for potency
  - Using certifiable equivalent testing
  - Eliminating tests for regulatory requirements that are not really relevant
  - Advancing in situ testing
  - Incorporating microfluidics in characterization systems
  - Aligning pharmacopeial requirements to regulatory requirements
- Create a more efficient system of regulations by government to allow faster scale-up and more rapidly bringing manufacturing on line:
  - Eliminate repetition of certification in various phases of qualification
  - Provide better information to manufacturers, linking related SOPs
- More collaboration with regulatory agencies is required to educate them on new technologies, methods, and the potential fast track for approval of these new technology products. Sometimes regulators don’t have an end point for their questions.
- Since vaccines are not drugs, toxicity testing requirements should be eliminated or modified.
- Bridge funding is needed between researches and manufacturing technology.
- Standards need to more rapidly incorporate new knowledge
• More international harmonization of qualification standards is needed.

WRITTEN RESPONSE TO PANEL QUESTIONNAIRE

In their written response to a questionnaire provided to Biological E prior to the panel’s visit, the following were identified:

• Key future technologies for development and testing
  – Recombinant technology
  – Use of novel immune modulators
  – More automation of upstream systems
  – More in vitro testing

• Areas for funding research
  – R&D for new technology for development of new process
  – Preclinical studies to understand immunogenicity
  – Studies for safety of vaccine long term and short term
  – Shorten critical phase between basic research and clinical tests (translational medicine)

REFERENCES

Export Bureau Biological E Ltd India Company Report,

Biological E Ltd registers yet another milestone achievement, Reachouthyderabad.com,
Bioproperties Pty. Ltd. & Royal Melbourne Institute of Technology

**Site Address:**
Bioproperties Pty. Ltd.
36 Charter Street
Ringwood, Victoria 3134, Australia

Royal Melbourne Institute of Technology
GPO Box 2476
Melbourne, Victoria 3000, Australia
http://www.rmit.edu.au/

**Date Visited:**
February 22, 2010: Bundoora Campus, Victoria, and Royal Melbourne Institute of Technology (RMIT)
February 23, 2010: Glenorie Vaccine Manufacturing Facility, Sydney

**WTEC Attendees:**
S. Drew (report author), S. Jacobson, T. Leighton, M. Ritchey, R. Kumagai

**Host(s):**

*Bioproperties Pty Ltd.*
Dr. David Tinworth, Director
Tel: +61 (0) 3 9879 0039
Fax: +61 (0) 3 9879 0713
david.tinworth@bioproperties.com.au

Dr. Youssef Abs El-Osta, Senior Bacterial R&D Scientist
Tel: +61 (0) 3 9925 6612
youssef.abs.el-osta@bioproperties.com.au

*Royal Melbourne Inst. Tech.*
Professor Peter J. Coloe, Pro Vice-Chancellor, College of Science, Engineering and Health
Tel: +61 3 9925 9518
Fax: +61 3 9925 9650
pcoloe@rmit.edu.au

Dr. Rima Youil, R&D Manager, Adjunct Professor, RMIT
Tel: +61 (0) 3 9925 6609
rima.youil@bioproperties.com.au

**BACKGROUND**

The mission of Bioproperties Pty Ltd is to be a leading source of novel live vaccines for global application in intensively farmed food animals. David Tinworth and James Judd established the company in September 1989. The current directors of Bioproperties are David Tinworth and Anthony Roberts. The company is privately owned by the directors and founders. From its inception the company has utilized a collaborative model with key Australian research universities and institutions to undertake the platform R&D for its vaccines. Bioproperties maintains research labs and staff based within several universities, including RMIT. The collaborative relationship at RMIT includes the joint running and funding of a GMP certified scale-up laboratory. Bioproperties senior staff provide the university supervision of post-grad students involved in funded product focused research and industry focused teaching. RMIT and Bioproperties also jointly apply for research grants in our mutual areas of interest.
for which Bioproperties funds successful outcomes. Where intellectual property (IP) rights accrue from RMIT inventions, the university receives a royalty return.

**BIOPROPERTIES’ PRODUCTS**

The company’s first product, Vaxsafe® MG, a live attenuated (temperature sensitive) *Mycoplasma gallisepticum* vaccine strain for commercial broiler breeders was launched globally in 1990. Legacy research and development prior to formation of the company drove the rapid approval. Bioproperties maintains its growing impact through Australian manufacture of live vaccines for the food animal industry (currently chickens, swine and cattle; with expanding interest in fish) and direct sales to the food animal industry. International distribution channels have been established through the major pharmaceutical marketers. Bioproperties’ strength lies in its ability to identify and respond promptly to emerging market opportunities through design, development and rapid scale-up of bacterial, viral and protozoal vaccines manufactured in their GMP facilities at RMIT (small scale and developmental vaccines) and Glenorie, New South Wales (full-scale production; see the following report on that site). Their business model relies on collaborative R&D with RMIT and others to leverage end product development. Approximately 50% of their sales volume arises from international demand (Japan is their largest international venue) and Dr. Tinworth anticipates that this segment may represent as much as 95% of Bioproperties’ growth in the next 5 years. The company invests heavily in research and development (currently 12% of gross company turnover) to drive innovation and new market development. Vaccine products for the poultry industry can command roughly 2 cents per animal while cattle vaccines command up to $2 per animal. Current vaccine development is highlighted in Figure B.6.

![Figure B.6. Vaccine development outline for Bioproperties Pty Ltd.](image)
**Technology Thrusts**

Bioproperties' technology thrusts include live temperature sensitive mycoplasma vaccines, $aroA$ (aromatic amino acid auxotrophy) gene deletion for live bacterial vaccines and gene delete viral vaccines.

**Special Circumstance Capability**

In addition to its marketed product line, Bioproperties also has the capacity in emergencies to produce autogenous vaccines for outbreaks limited to specific farms. The Department of Primary Industries, a governmental organization involved in disease monitoring and control, can isolate organisms from diseased animals, and develop a vaccine seed and dosage regimen for the remaining healthy animals. Under a permit specific to the outbreak that needs to be controlled, Bioproperties takes this seed and prepares enough vaccine for the animal farm or enterprise to administer to their population to prevent further spread of disease. These vaccines, limited in volume, are prepared in the RMIT Development facilities.

**FACILITIES**

The company currently has approximately 50 full time equivalent staff, 44 of whom are located at the Glenorie manufacturing site. Physical plant facilities and capabilities include the following:

**Research and Development at the RMIT Campus Incubator Facilities**

- RMIT Viral and Bacterial scale-up (3 L stirred vessels up to 40 L [30 L operating volume]).
- Freeze drying of up to 1500 vial per batch.
- Strain development, diagnostics, and QC.

For live vaccines, unit dose is usually defined in terms of viable cell count or infective viral titer. The laboratories at Bioproperties' RMIT facility have sophisticated analytical capability (e.g., DNA sequencing and synthesis, PCR and melting point PCR, small scale analytics for fermentation and cell culture) and rapid access to the broad capabilities of RMIT.

**GMP Manufacturing at Glenorie, NSW, Australia**

- Five GMP production suites
- Bacterial, viral, protozoan vaccine production
- Large scale GMP filling and Freeze Drying facilities
- QC Laboratory

The Vaccine Manufacturing Facility at Glenorie is Australian APVMA and EU certified (for several exported vaccines) as a Class 1 sterile biologicals manufacturing facility with capabilities for large scale cGMP production of live viral, bacterial and protozoal vaccine products.

There are also areas (Quarantine Approved Site) within the Glenorie complex that have approval from the Animal Quarantine Inspection Service (AQIS) to handle biological materials of concern. These are generally animal-derived raw materials or processing materials that could potentially be contaminated with transmissible agents for other diseases. These materials must be quarantined and not used in manufacturing until cleared. AQIS inspects to ensure compliance with handling procedures.
Other areas with the complex are qualified to handle genetically modified organisms. Within Australia, the Office of the Gene Technology Regulator (OGTR) within the Department of Health and Aging develops and ensures compliance with rules that govern the use and containment of any genetically modified organism.

The company’s five licensed cGMP vaccine production suites include one dedicated viral, two bacterial, and two protozoal trains. Manufacturing capabilities include:

- Large-scale egg handling and cell culture roller bottle incubation
- 17 L to 450 L fermentation capacity for aerobic (e.g., Salmonella) and microaerophilic (e.g., mycoplasma) organisms including a 120 L unit designed for highly aerobic fermentation
- Downstream processing (centrifugation, microfiltration, membrane processing, freeze drying) oriented toward live vaccine production

High-capacity cGMP formulation and filling capabilities include vial and ampoule sterile filling lines, freeze drying, capping and labeling. The facility also has a laboratory animal complex to support primary oocyst production (SPF birds) for live protozoal development and manufacture.

The production suites and supporting laboratories at Glenorie have instrumented production vessels with data logging capability. Suites have segregated air handling capability and can be operated simultaneously for microbial, protozoal, and viral vaccine production; overlapping campaigns appear to be the norm for current operations. Individual production suites are operated on a campaign basis with only one product in the suite at a time with validated cleanout between products. Facility utilization is currently at ~80% of overall capacity. A major expansion is planned to accommodate newly developed bacterial vaccines and increased protozoal production capacity within the next year. A new QC laboratory is also being built and adding sophisticated new technologies such as Quantitative PCR with High Resolution Meltpoint Analysis to its capabilities that will assist in process control and identity testing.

The current operation at Glenorie has all of the components required to produce vaccines from start to finish, including packaging for shipment. Incoming materials are strictly controlled, including the egg farms that are the sources of embryonated SPF eggs used to produce some of their vaccines. Typical production cycles for the current group of products include 1 to 2 weeks for production and an additional 6 weeks for testing.

Australian SPF Services Pty Ltd is a subsidiary of Bioproperties and maintains a separate quarantine site in Woodend, Victoria for the large scale production of SPF eggs and birds for use for all Australian vaccine production (including egg based live vaccines produced for Australia overseas) with the excess being exported to other areas of Asia.

**REGULATIONS**

Vaccine production for animals is regulated by the Australian Pesticides and Veterinary Medicines Authority (APVMA). Lot release and certification is performed by the company without additional certification by the national authority for use in Australia. (They currently export some vaccines to Japan where additional lot testing and permission to market each lot is required to be performed by the national authority.) Inspections are performed by independent contractors, paid for by the company undergoing the inspection. The inspectors are certified and can only inspect a given company three times. Inspections are generally
Appendix B. Site Reports

done every 12 to 18 months. Regulations in principle are generally consistent with those for human vaccines, but APVMA regulations are generally written as principles to be adhered to rather than more detailed rules as given under the Therapeutic Goods Administration (TGA) for human vaccines.

In the case of export to the EU, however, inspection of manufacturing facilities and documentation are performed under contract to the TGA, which has regulatory authority for human vaccines. Harmonization with the guidelines and regulations of the European Agency for the Evaluation of Medicinal Products (EMEA) allow acceptance of TGA findings in European registration of animal vaccines without requiring a separate inspection by the EMEA. Bioproperties has been inspected by the TGA and is approved to export mycoplasma vaccine products to the EU. It is anticipated that the TGA will undertake a further inspection in the next 2 years to add protozoal vaccines to Bioproperties EU certification.

Rapid response to pandemics is also a concern for animal populations. An industry and government collaboration has resulted in a plan for an avian flu epidemic that has a defined regulatory pathway for licensing vaccines and Bioproperties is an integral Australian production resource in emergency plans.

PRODUCT PIPELINE

As a small company, Bioproperties is able to exercise individual decision trees for rapid progress against its objectives. Whereas it once out-licensed technology, its operating philosophy is to develop and manufacture novel vaccines in the special category of live organisms and sell directly to worldwide customers.

ROYAL MELBOURNE INSTITUTE OF TECHNOLOGY (RMIT)

The unusually effective relationship of Bioproperties Pty Ltd with the Royal Melbourne Institute of Technology and The University of Melbourne supports and strengthens rapid evaluation of alternatives and decision making. The Royal Melbourne Institute of Technology was founded in 1887 as the “Working Men’s College” and is now one of Australia’s leading educational institutions. The mission of RMIT is given as follows:

RMIT is a global university of technology with its heart in the city of Melbourne. We create and disseminate knowledge to meet the needs of industry and community and foster in students the skills and passion to contribute to and engage with the world.

The institute has more than 70,000 students at campuses in Melbourne, regional Victoria, in Vietnam, online, by distance education and at partner institutions throughout the world. There are more than 1000 academic staff members. There are 3 Victoria campuses that are located in central Melbourne, Brunswick and Bundoora. There are 2 campuses in Vietnam. Offsite study locations include Singapore, Hong Kong, Kuala Lumpur, Shanghai, and Wuhan. There are 921 higher education and vocational programs ranging from apprenticeship training to doctoral programs. There are also multi-disciplinary programs, such as nanotechnology that are designed to prepare students for jobs that require training in more than one area. In 2006 RMIT established Research Institutes for Design Research, Global Cities, Health Innovation, and Platform Technology that represent areas of research excellence and scale. They form the university-wide component in the hierarchy of research clusters and centers at RMIT.
We toured a number of laboratories at the Melbourne campus that had state of the art rooms and facilities for examining viral, bacterial and plant systems at the molecular level. Ongoing work was as diverse developing a strain of strawberries to retain flavor longer to investigating small peptide regions of the hemagglutinin of influenza viruses.

The relationship that Bioproperties has with RMIT is an excellent example of the RMIT mission in action. RMIT has established an operating plan beyond academic programs that encourages cooperative research and translational development of inventions and discoveries with selected industry partners. The university is prepared to lease laboratory and office facilities as incubator space for new and maturing small industry. In the case of Bioproperties Pty Ltd, they have provided access to enabling intellectual property, generating a royalty fee on manufactured goods, and have been the beneficiary of significant product focused collaborative research funding resulting in a graduation of well trained post docs and significant government sponsored industry collaborative grants. In addition, employees of Bioproperties participate in the academic environment as part of the faculty, making the translation of good vaccine ideas into eventual products rewarding on both an intellectual and practical level for everyone involved. It seems clear that their success in this area of translational research and development is due in significant part to the energy and vision of Professor Peter J. Coloe, Pro Vice-Chancellor of RMIT.

RMIT makes its facilities available for lease by a range of small industries, including Orica, a company producing enzymes for land remediation, located adjacent to the Bioproperties’ laboratories. Area segregation and the use of key-card electronic lock-access allow reliable control over materials and personnel flow. The RMIT/Bioproperties relationship allows the company to accept more risk in development of novel live vaccines without the burden of huge capital outlays. It provides a vehicle for unique advanced learning, of the university’s best students through work–study opportunities with Bioproperties and supports rapid development of novel vaccines by supporting the right people, at the right time, in an environment that nurtures both creativity and accomplishment. This cooperative relationship also provides Bioproperties with a pool of talented and motivated potential employees.

**REFERENCES**


BACKGROUND

With reported global sales of $1.5 billion at United States price parity from all health care product lines in 2009, Cadila Pharmaceuticals Ltd. is one of the largest privately held
pharmaceutical companies in India. Headquartered at Ahmedabad, in the State of Gujarat, the company was founded in the 1950s with the focus of producing high quality pharmaceuticals at prices affordable in India and the developing world.

Cadila currently markets products in more than 90 countries. Its manufacturing facilities have certified GMPs to meet requirements of western countries as well as India. Immunologicals are one of many lines of products, which cover most areas expected for a larger pharmaceutical company. The company has manufacturing facilities at Dholka, Ankleshwar, Kadi and Hirapur in Gujarat; Samba in Jammu and Kashmir; and Addis Ababa in Ethiopia.

Currently about 20 products, including conventional and recombinant vaccines, anti-cancer biotherapeutics, diagnostics using recombinant antigens, and natural thrombolytics with high market potential are in the Cadila Pharmaceuticals biotechnology basket. Examples are Immuvac, a potent, unique immunomodulator, and Stpase, a natural thrombolytic agent. Immuvac, a heat killed mycobacterium, has been shown to be effective therapeutically for tuberculosis and leprosy and is being tested for effectiveness in prophylaxis for HIV.

TECHNOLOGIES AND RESEARCH

The state-of-the-art research and development (R&D) facility at Cadila Pharmaceuticals is staffed by more than 350 scientists. The Cadila scientists are also closely collaborating with more than 30 other Indian R&D centers. Cadila Pharmaceuticals has focused on novel approaches for cancer management and cancer vaccines, and Cadila is the first Indian company to get multiple investigational new drug applications (INDs) cleared by USFDA.

CPL Biologicals is a newly formed company evolved from a joint venture by Cadila Pharmaceuticals Ltd and Novavax, Inc. CPL Biologicals will be developing and manufacturing vaccines, biological therapeutics, and diagnostics in India using technology contributed from Novavax and Cadila Pharmaceuticals. In addition, CPL Biologicals will establish manufacturing facilities in India to develop, produce, and sell products such as seasonal influenza vaccine and potentially other novel vaccines against dengue fever and chikungunya fever based on Novavax’s virus-like-particle (VLP) vaccine technology (Figure B.7).

Clinical trial applications using imported VLP vaccine have been approved by the Drug Controller General of India for seasonal trivalent influenza VLP vaccine and for H1N1 pandemic influenza VLP vaccine. Animal testing and Phase I and II human trials have shown that recombinant VLP vaccines are well tolerated and immunogenic.

Cadila is implementing this new technology utilizing recombinant baculovirus for the production of VLPs that contain antigens for vaccines. The use of baculovirus increases the yield of antigen and provides a mechanism for rapidly engineering the structure of the epitope of interest. Baculovirus could have been used in dealing with the H1N1 pandemic for production, but the required regulatory compliance issues slowed its use. At present vaccines for rabies are being produced using this system in the Wave Bioreactor, which is a component in the disposable manufacturing production line.
Appendix B. Site Reports

Figure B.7. Development of recombinant influenza VLP vaccines (courtesy of Cadila Pharmaceuticals Limited).

The disposable manufacturing line has many single use components, which makes manufacturing product turnover time shorter and less expensive. The term wave bioreactor comes from the fact that components are combined in a large disposable poly bag, which is agitated with a rocking motion causing observed wave action. Figure B.8 shows components of the disposable system, now being used for rabies vaccine production.

The new facility that was constructed for VLP manufacturing is an example of how disposable manufacturing technologies can accelerate the process of bringing new vaccines to market. This facility was available for validation and commissioning 12 months after facility design was initiated.

A new filling facility, with state of the art equipment has also been completed to support the development and manufacturing of Cadila’s vaccine products.
Cadila has an active adjuvant program that includes proprietary adjuvants to enhance the immunogenicity of both conventional vaccine antigens and novel antigens. Extensive animal testing has demonstrated improvements for rabies and hepatitis B vaccines. The adjuvants are also under test for potential use in cancer vaccines.

Cadila has a 100,000 sq. ft. dedicated R&D facility focused on:

- **Formulation development**
  - Novel dosage form development
  - Novel drug delivery systems
- **Biotechnology**
  - Vaccines
  - Diagnostics
  - Biotherapeutics
- **Chemical research**
  - Anti-hypertensive, anti-histaminic, anti-diabetic
  - Anti-ulcerants, anti-depressant, anti-TB
- **Clinical research**
  - Clinical pharmacology,
  - Pharmaco-kinetics
  - Bio-equivalence
  - Toxicity studies (Toxicity studies conducted by Cadila CRO for RSV were approved by USFDA leading to permission for Novavax to proceed to clinical studies.)
The Clinical Pharmacology Unit, which has 90 beds, has successfully completed more than 190 studies. Early stage exploratory vaccine trials are among them. In addition, sizeable research talent is associated with the Quality Control and Analytical Research Laboratory.

Novel drug delivery research is being conducted in areas of
- Sustained release
- Pelletization
- Osmotically releasing oral systems
- Microparticulates
- Transdermal
- Chewing gum

**DISCUSSION OF ISSUES RELATED TO VACCINE MANUFACTURING**

Our hosts at Cadila Pharmaceuticals expected improved results for novel adjuvants and novel antigens. Research has been showing promising results in cancer (pancreas and melanoma) vaccines, rabies vaccine, TB vaccine, and others.

Reducing regulatory problems with respect to gaining approval for clinical trials would reduce the timeline for response to pandemics. Some risk vs. efficacy considerations might be used by regulators. Education of regulators in innovative processes and differences from conventional methods would produce quicker understanding and confidence in more rapid approvals.

**REFERENCES**

Welcome to Cadila Pharmaceuticals Ltd., Gujarat, India, company brochure produced for WTEC Panel, October 20, 2010.

http://www.cadilapharma.com
Department of Biotechnology

Site Address: Department of Biotechnology  
Ministry of Science and Technology  
Government of India  
Block-2, CGO Complex  
Lodhi Road, New Delhi 110 003, India

Date Visited: October 18, 2010

WTEC Attendees: J. Bielitzki, M. DeHaemer, F. Heineken, M. Ritchey (author)

Host(s): Dr. T.S. Rao, Advisor  
Department of Biotechnology  
Ministry of Science and Technology, Government of India  
Block-2, CGO Complex  
Lodhi Road, New Delhi 110 003, India  
Telefax: 011-24364065  
Fax: 011-24362884  
tsrao@dbt.nic.in

The Department of Biotechnology was established in 1986 under the Ministry of Science and Technology of the Government of India. This organization promotes the growth and application of biotechnology in agriculture, health care, animal science, the environment and industry. Its mandate includes: promote the large scale use of biotechnology, support R&D and manufacturing in biology, promote university and industry interaction, establish infrastructure and facilities to support R&D and production, evolve biosafety guidelines for manufacture and application of cell-based vaccines, serve as a focal point for specific international collaborations, and collect and disseminate information relating to biotechnology.

The organization uses both internal staff and outside experts to accomplish its objectives. There are 23 established committees including groups for: infectious disease biology, medical biotechnology, immunology, diagnostics and vaccines, and bioinformatics.

Dr. Rao described some of the programs that promote vaccine development, as follows:

- Money is available to both researchers and companies to investigate concepts for vaccines and begin initial development work. To advance an idea from the bench, researchers must partner with a company in order to manufacture clinical testing supplies and then further development, if successful. Money provided to companies is in the form of “soft loans”, wherein companies have 10 years to pay it back with minimal interest. Recently, some of this funding was used to support development of H1N1pan vaccines for use in India.

- Scientific advice is made available through meetings with staff and experts and open office hours.

- Partnership with outside agencies, including the USFDA is used to help define standards and provide guidance, especially with respect to regulation of vaccines made using new technologies.
Vaccine regulation and licensing includes both state and central government agencies. An additional agency is involved when genetically modified organism is used. A central government laboratory is responsible for testing and release of each vaccine lot, in addition to the manufacturer’s own testing and release. This laboratory is in the process of adding enhancements to ensure that it can handle testing on new vaccines and is partnering with other laboratories, including the United States to accomplish this. Efforts to reduce animal testing via alternate methods are ongoing. Standardization of toxicology testing is also a goal.

Some goals for enhancing vaccine programs for India include:

- Focus on issues that will specifically improve the rates of vaccination via reducing the required number of clinic visits. This can be accomplished by making more multi-valent vaccines available that incorporate serotypes important in the region and by using vaccines that are formulated in a way that limits the number of doses required for protection.
- Develop and implement technologies that reduce costs, e.g., automated injection devices, disposables
- Develop thermostable formulations, thus reducing the cold-chain demands
- Develop formulations that do not require an addition of diluent in the field
- Focus on diseases important to the area and develop them quickly
- Resolve intellectual property (IP) issues that inhibit vaccine development, for example in the adjuvant area, and promote technology sharing
- Acquire a better understanding of how to select antigens and develop vaccines that produce a broader immunity
- Acquire a better understanding of how differences in the flora of the GI tract of different populations affect the ability to immunize using oral formulations

The Department of Biotechnology is actively engaged in supporting vaccine development within India.

REFERENCES

www.dbtindia.nic.in
Green Cross Veterinary Products Co., Ltd.

Site Address: Green Cross Veterinary Products Co., Ltd.
227-5 Kugal-Dong Giheung-ku, Youngin-Si
Kyunggi-do, 446-569, Korea
http://www.gcvp.co.kr/english/e_ceo.htm

Date Visited: March 5, 2010

WTEC Attendees: J. Bielitzki, C. Gay (report author), N. Iyer, R. Kumagai

Host(s): Jong-Man Kim, DVM, PhD, Director of Research Institute
Tel: +82 31 283 3422-4, Ext. 400
kimjm6688@hanmail.net
Bo-Kyu Kang, DVM, PhD, Principal Researcher
Tel: 82 31 283 5141, Ext. 403
suyun@gcvp.co.kr
Dae-Sub Song, DVM, PhD, Senior Researcher
Tel: +82 31 283 5114
hfsong121@hotmail.com
Hyoungho Min, Strategic Planning Board
Tel: +82 31 283 3422, Ext. 407
mhj1219@naver.com
Young-Eun Kim
Tel: +82 31 283 3422-4, Ext. 504
kissme-0412@hanmail.net

GENERAL INFORMATION

There are five veterinary vaccine manufacturers in Korea. The Green Cross Veterinary Products (GCVP) company considers itself one of the leading animal health companies in Korea. Green Cross was first established as a veterinary and human biologics subsidiary, but was reorganized in 1973 as an independent entity of Green Cross Veterinary Products separated from the company, Green Cross Co., as an independent corporation.

GCVP is a comprehensive animal health company involved in the research and development, manufacture, and marketing of veterinary vaccines, drugs (antimicrobials, coccidiostats, antiparasitics), disinfectants, and insecticides. Feed additives and taste masking technologies are also in their product line. Products cover the full spectrum of food and companion animals from fish and poultry through dogs. GCVP currently manufactures vaccines for pigs, cattle, dogs, poultry, and fish.

GCVP is committed to the manufacture of products that meet high quality standards and comply with Korean Veterinary GMP regulations. GCVP develops and improves innovative products to control infectious diseases of livestock and poultry in collaboration with
university and government institutes. GCVP has obtained ISO 9001 and ISO 2000 certification.

Multinational drug companies currently hold 70 percent of the Korean veterinary product market. GCVP management considers access to international markets (China) the company's biggest challenge. GCVP has successfully exported products to Asian countries and has an excellent track record of developing good relationships with foreign partners. Denkavit in The Netherlands is collaborating on milk replacers, and BioMar in France is working with GCVP on technologies to enhance fish farming and feeding.

**VACCINE RESEARCH**

The GCVP maintains a scientific staff that is primarily focused on the development of veterinary vaccines and their registration with the Korean regulatory authorities. New vaccines technologies are generally obtained from universities and government laboratories.

The National Veterinary Research and Quarantine Service (NVRQS) in Anyang, South Korea, is responsible for the large majority of vaccine discovery research for biological agents that threaten Korean animal agriculture and is a key partner for GCVP. The NVRQS administers the following government functions:

- The primary government animal health research institute
- Regulatory body for the registration of veterinary drugs and vaccines;
- Sanitary inspection of animal products
- The national reference laboratory for the diagnosis of many exotic diseases, including foot-and-mouth disease, classical swine fever, high pathogenic avian influenza (HPAI), and bovine spongiform encephalopathy (BSE).

Many of the livestock and poultry vaccines manufactured in Korea were developed by the NVRQS and transferred to the GCVP and the other Korean animal health companies. GCVP shared with the WTEC panel members information on their vaccine development program for canine influenza virus (CIV) A/H3N2.

- H3N2 is a new emerging influenza virus in Korea and was determined to be a reassortant strain of several avian influenza viruses.
- CIV H3N8 of equine origin was first reported in 2003.
- CIV H3N2 of avian origin was reported in 2007.
- Dogs and humans share the same SA 2,3 gal influenza virus receptor
- CIV strains are very homogeneous with very little genetic drift within a species.
- CIV transmission was determined as follows: (1) influenza virus contaminated and uncooked poultry meat fed to meat dogs; (2) transmission within a dog population through nasal discharge; and (3) experimental infection of CIV to pigs and specific pathogen free (SPF) chickens displayed no clinical sign and serological responses.
- GCVP is currently testing the efficacy of an inactivated H3N2 vaccine adjuvanted with rehydraGel obtained from General Chemical, Berkeley Heights, NJ.

GCVP has broad research and development capabilities and is able to collaborate with many research institutes. GCVP currently has a few international collaborations but would like to expand its research collaborations. As with many other animal health research institutions,
GCVP specializes in the development of animal infectious models to test new drugs and vaccines. GCVP is currently collaborating with the International Vaccine Institute (IVI) and testing universal influenza vaccine using dogs and ferrets.

GCVP has a product line focused on vaccines for swine, cattle, fish, poultry, and dogs. These include an oral vaccine for Porcine Epidemic Diarrhea (PED), porcine circovirus-2 vaccine, swine influenza virus inactivated vaccine for pigs, an influenza vaccine for dogs, and Streptococcus iniae inactivated vaccine, E. tarda/S. iniae/S. parauberis combined vaccine for fish. They have conducted research on interspecies transmission of influenza strains looking at those specific to dogs, swine, chickens and ferrets. These include evaluation of A/H3N2 an avian strain seen in the Korean dog population. Vaccine production utilizes small batch production systems with little automation. Production systems include roller bottles, chicken eggs and other culture/fermentation processes.

**SPECIFIC ANSWERS TO WTEC QUESTIONS**

**Broad Issues**

The South Korean system has a relatively shorter period for the approval of new commercial vaccines. Autogenous vaccines have flexible guidelines leading to rapid production and approval for *E. coli, Acentiobacillus pleuropneumoniae*, and *Pasteurella* spp.

For veterinary vaccines for new pathogens it takes a minimum of 3 years to move from pathogen identification through approval. Mean times vary from 3 to 5 years.

Following pathogen identification, the most time consuming steps involve optimization of the replication system and characterization and optimization of the antigen.

Entering the international marketplace requires cooperation with and an understanding of the agencies’ requirements for approval.

GCVP main strength rests in its R&D manpower, and with its ability to interact with academia and other elements of industry to acquire new science and technology.

**Science and Technology**

For small production lots, improved cell culture lines for roller bottle systems and automation of the fermenter system for microbial culture has greatly increased efficiency in production.

New needs include enhanced cell lines and suspension culture systems and improved culture systems for anaerobic bacteria. Methodology is needed for improved isolation and quantification of antigen and protein.

The cold chain distribution system is effective for most veterinary products and within South Korea the need for veterinary vaccines at ambient temperatures is not an issue.
Hilleman Laboratories & General Vaccine Review

Site Address: Hilleman Laboratories & General Vaccine Review
Taj Palace Hotel, New Delhi, India

Date Visited: October 18, 2010

WTEC Attendees: J. Bielitzki, M. DeHaemer, F. Heineken, M. Ritchey (report author)

Host(s): Altaf A. Lal, PhD
CEO, Hilleman Laboratories
7th Floor, Vatika Tower-B, Sector-54, Gurgaon
Haryana-122001, India
Tel: +91-124-4647300
altaflal@hillemanlabs.org

Nirmal Kumar Ganguly, MD
Director General ICMR (former)

HILLEMAN LABORATORIES

Dr. Lal has recently been named CEO of the Hilleman Laboratories, a joint venture between The Wellcome Trust and Merck & Co., Inc. He spent the last 20 years working for the National Center for Infectious Diseases at the U.S. Centers for Disease Control and Prevention (CDC) and was the Chief of the Molecular Vaccine Section in the Division of Parasitic Research. His work focused on a molecular understanding of the malaria parasite and evaluation of candidate vaccine antigens, including the use of adjuvants and the interaction of HIV/AIDS with the malaria parasite. His awards and honors include one from the Ministry of Health and Family Welfare for the establishment of the Public Health Foundation of India. Currently he serves as the Health Attaché and Department of Health and Human Services Regional Representative for South Asia at the Embassy of the United States of America, New Delhi, India.

Dr. Ganguly, a patriarch of the vaccine industry, is the former head of the Indian Council on Medical Research. Previous positions include President of India’s National Academy of Medical Sciences, Professor and Head of the Department of Experimental Medicine and Biotechnology, Postgraduate Institute of Medical Education and Research. He has published hundreds of articles and book chapters dealing with ethical issues in biomedical research, microbiology, parasitology and diarrheal diseases. He is the recipient of numerous national awards and honors, including the Shakuntala Amir Chand Award from the Indian Council of Medical Research.

The MSD Wellcome Trust Hilleman Laboratories is the first of its kind research and development joint venture with a not-for-profit mission to focus on developing affordable optimized vaccines to help prevent diseases that affect low-income countries. The institute was established by its founders to operate with a not-for-profit business model. Initial funding will come from the Welcome Trust and Merck, with other third party grants also anticipated in the future. The institute plans to partner with other organizations to develop some of its technologies. The partners will have the option of retaining commercial rights to
products developed by Hilleman Laboratories as long as affordable and broad access to low-income countries is secured.

When fully functional, Hilleman Laboratories with an initial staff of 60 will first focus on optimization of existing vaccines. Programs will be taken through Phase II clinical studies, thereby reducing the risk of failure for companies that receive the technology for further development. The last objective is to develop a training program to assist others working to develop vaccines. A Strategic Advisory Group (SAG) for the Hilleman Laboratories has been established to provide guidance on matters of vaccine development, delivery, regulation, finance, policy, and advocacy. Dr. David Heymann, Chairman of the U.K.’s Health Protection Agency chairs the SAG.

The first project of the Hilleman Laboratories will be a study of how new technologies might be used to develop a rotavirus vaccine designed specifically with developing country needs in mind. Formulations based on dissolving thin strips or granules will be examined for their potential to improve product stability, ease of use, transportation, and affordability. The therapeutic focus of the project has been selected because of the tremendous global impact of rotavirus diarrhea on childhood mortality. If the initial study is successful, options to further develop the technology for rotavirus and other oral vaccines of importance to developing countries health will be explored.

INDIAN VACCINE INDUSTRY OVERVIEW

A general overview of the vaccine industry in India was also provided. There are several companies that manufacture vaccines that are recommended by the WHO for routine immunization of children. Some of the vaccines or technologies are imported, while others are being developed in house with the technology based on what is available to the public. Some of these companies are also beginning to develop their own innovative technologies. One biotechnology startup company is working on an E. coli expression system that allows for proper protein refolding. H1N1pan vaccines were produced this past year for the first time. Both cell culture and egg-based methods and live attenuated and inactivated vaccines were produced.

Because of the limited potential for profit in India, companies rely on high volumes and exports to make vaccines affordable. Obtaining WHO certification allows export to areas of the world that receive funding for vaccine purchases through WHO or PAHO. When Chinese companies obtain WHO certification, they will also likely begin competing in these markets.

The regulatory environment is also changing. Currently, both the central government and individual states are involved in vaccine regulation. The government is working toward defining and implementing regulations and policies that will enable a more efficient and faster uptake of new vaccines and technologies.

Vaccine programs that are needed for India include adoption of combination vaccines that are used in other parts of the world to cover immunization for diphtheria, tetanus, pertussis (including the use of an acellular pertussis vaccine), Haemophilus b disease and hepatitis B. Currently live, oral polio vaccine is used, but it is desirable to add an inactivated polio vaccine to the program in combination with other childhood vaccines. Diseases more common in this part of the world need to be addressed, such as cholera, malaria, JE, yellow fever, leishmania and Dengue, among others. Overall vaccination rates also need to be improved.

The support for vaccine development in India and the developing world that will be provided by Hilleman laboratories and guidance provided experienced individuals such as members of
SAG and Dr. Ganguly will enhance the speed at which new vaccines relevant to the region can be developed.

REFERENCES

http://www.hillemanlaboratories.in/
Indian Immunologicals Ltd. (subsidiary of the National Dairy Development Board)

Site Address: Rakshapuram, Gachibowli Post
               Hyderabad – 500 032, India
               www.indimmune.com

Date Visited: October 21, 2010

WTEC Attendees: J. Bielitzki (report author), M. DeHaemer (report author), F. Heineken, M. Ritchey

Host(s): Dr. V. A. Srinivasan, Research Director
          Rakshapuram, Gachibowli Post
          Hyderabad – 500 032, India
          Tel: +91-40-23005; Fax: +91-40-23005958
          srini@indimmune.com
          Dr. L. Rajendra, Manager R&D
          Rakshapuram, Gachibowli Post
          Hyderabad – 500 032, India
          Tel: +91-40-23005957; Fax: +91-40-23005958
          rlingala@indimmune.com

BACKGROUND

Indian Immunologicals Ltd. (IIL) is wholly owned a subsidiary of the National Dairy Development Board with a mission slogan of "Immunity made Affordable." IIL was set up in 1982 with the objective of making foot and mouth disease (FMD) vaccine available to farmers at an affordable price. The technology for FMD vaccine manufacture was obtained from M/s. Wellcome Foundation Limited, United Kingdom. With annual sales of $63 million for the financial year 2010-11, IIL is the manufacturer of India's largest selling brand of FMD vaccine. IIL today is the largest veterinary biological company in India with a large range of vaccines for the cattle, sheep, and canine segments. Combined with its presence in the formulations segment, IIL holds the third position in the Indian animal health market.

IIL is a major player in the human vaccine market in India, especially in the pediatric vaccine and the rabies vaccine segments. In the human vaccine market, IIL holds the fourth position.

The FMD manufacturing facility at Hyderabad in India is one of the largest vaccine producing plants in the world. IIL’s plants have WHO-GMP, and ISO 9001 certifications. A newly expanded Hyderabad plant has the capacity for 240 million trivalent doses of FMD vaccine annually (Figure B.9).

With a large repository of various FMD virus strains maintained in the laboratory, IIL is able to provide FMD vaccines of the customer’s choice for other countries to meet epidemiological requirements. IIL is one of the principal suppliers of FMD vaccine to FAO.

IIL operates a manufacturing facility in Ooty to manufacture the vero cell culture rabies vaccine for use in human beings. This plant was set up in 1998 at the specific request of the government of India in order to phase out use of the older and unsafe sheep brain vaccine (also termed nerve tissue vaccine, or NTV) with the modern tissue culture vaccine.
The IIL veterinary vaccine plant, part of the 213 acre Hyderabad site, is one of the largest plants in the world with state-of-the-art technology, WHO-GMP and ISO-9002 certified (courtesy of Indian Immunologicals Ltd.).

IIL is one of the largest manufacturers of human health vaccines in India with an annual capacity of more than 300 million doses, which includes a capacity of 7 million doses of the human rabies vaccine.

IIL’s animal vaccines are exported to more than 40 countries in the Arabian Gulf, Asia, Africa, and the CIS, as well as Spain and Turkey. Human rabies vaccine-Abhayrab is also widely exported.

IIL successfully introduced a new concept, franchised vaccination clinics, also known as Abhay Clinics. The popularity of the clinics has prompted the company to expand its manufacturing of human vaccines by constructing new facilities in Hyderabad for hepatitis B, measles, DPT, TT, and DT and to also serve UNICEF needs. The facilities are organized as dedicated units for production of each of the antigens. There is also a research unit with small scale operations to support development of new and improved vaccines.

TECHNOLOGIES AND RESEARCH

From a one-product company, IIL has grown to a multi-product company because of its in-house R&D and process development. A separate R&D center was established in 2003 with 60 research scientists from various disciplines to work on conventional and novel technologies to develop vaccines, diagnostics, monoclonal antibodies, and biologicals. The focus is on infectious diseases of animals and human beings with the goal of improved affordability.

IIL introduced in India during 1989, a rabies vaccine that was the first vaccine for animals that was manufactured using tissue culture. In 1999 the company introduced a human, purified rabies vaccine prepared using vero cells. The company is also using virus like particles (VLPs), conjugates and live attenuated vector technologies for its pipeline programs.
As well as with Indian research institutes, IIL has numerous collaborations for vaccine development research with commercial, academic, and government institutes in the United States, Germany, South Korea, United Kingdom, Taiwan, and Switzerland.

Current research areas and products in the R&D pipeline are:

- **For Human Vaccines**
  - Hepatitis A
  - Hib
  - Combination DPT + Hep B
  - Human Papillomavirus
  - Hep A + Hep B
  - DPTH + Hib
  - Chikungunya vaccine
  - Japanese Encephalitis Vaccine

- **For Animal Vaccines**
  - Pox virus vector expressing PPRV antigens (Sheep/goat)
  - Canine Parvo Vaccine, Canine Distemper Vaccine, Canine Adeno Virus Vaccine and Leptospirosis Vaccine (Dogs)
  - Coccidiosis (Poultry)
  - Rabies DNA vaccine (Dogs and domestic animals)
  - Combined IBR + Brucella (Cattle and buffalo)
  - Tick vaccine (Cattle)
  - rET vaccine (Sheep & goats)
  - Brucella LPS + OMP (Cattle and buffalo)
  - FMD VLPs (Cloven hoofed animals)
  - Oral live attenuated Rabies Vaccine

**DISCUSSION OF ISSUES RELATED TO VACCINE MANUFACTURING**

As with other companies that focus on human patients, Indian Immunologicals hosts saw the government regulatory approval process as one of the limiting paths for more rapid vaccine manufacturing.

Although IIL had many connections and collaborations with foreign and domestic commercial and government research entities, interest from and collaboration with academe was at a lower level. Better connection with academic research might improve and accelerate the development of vaccines and vaccine manufacturing.

**REFERENCES**

Company presentation to WTEC delegation, October 21, 2010.
Appendix B. Site Reports

Kanonji Institute, The Research Foundation for Microbial Diseases of Osaka University (BIKEN)

Site Address: Kanonji Institute, The Research Foundation for Microbial Diseases of Osaka University (BIKEN)
2-9-41, Yahata-Cho
Kanonji, Kagawa, 768-0061, Japan
http://www.biken.or.jp/english/index.html
http://www.biken.osaka-u.ac.jp/e/index_e.php

Date Visited: February 25, 2010

WTEC Attendees: M. Ritchey (report author), S. Drew, S. Jacobson, T. Leighton, R. Kumagai

Host(s): Yoshinobu Okuno, MD, DMSc, Member of the Board of Directors, Director of Kanonji Institute, BIKEN
Tel: +(81) 875-25-4182; Fax: 1-(81) 875-23-2517
yokuno@mail.biken.or.jp
Toyokazu Ishikawa, Member of the Board of Directors, Kanonji Institute, BIKEN
Tel: +(81) 875-25-4171; Fax: +(81) 875-25-4843
toishika@mail.biken.or.jp
Akihisa Takamizawa, PhD, Member of the Board of Directors, Kanonji Institute, BIKEN
Tel: +(81) 875-25-4171; Fax: +(81) 875-23-2517
atakami@mail.biken.or.jp
Katsumasa Miyatake, Division Manager, Manufacturing Division, Kanonji Institute, BIKEN
Tel: +(81) 875-25-4733 or 4171; Fax: +(81) 875-23-2517
kmiyatak@mail.biken.or.jp
Isao Fuke DVM, Division Manager, Quality Control Division, Kanonji Institute, BIKEN
Tel: +(81) 875-25-4776; Fax: +(81) 875-23-2517
ifuke@mail.biken.or.jp
Hitoshi Fukuda, Division Manager, Vaccine Information Division, Tokyo Office, BIKEN
2-6-4 Higashinbashi, Minato-ku, Tokyo 105-0021, Japan
Tel: +(81) 3-5402-6540; Fax: +(81) 3-3432-3060 fax
hfukuda@mail.biken.or.jp
Hidechika Isono, Division Manager, Administration Division 2 and Production Management Division, Kanonji Institute, BIKEN
Tel: +(81) 875-25-4733 or 4171; Fax: +(81) 875-23-2517
isonoh@mail.biken.or.jp
Yoshikazu Tada, Senior Manager, Kanonji Institute, BIKEN
ytada@mail.biken.or.jp
Shiwo Nagase, Supervisor, Marketing Planning and Policy Section, Marketing Planning and Policy Division, Kanonji Institute, BIKEN
snagase@mail.biken.or.jp
BACKGROUND

We were shown a video that described the founding and history of this organization and its principal accomplishments to date. The video is entitled “Protecting People’s Lives – From Japan to the World; For the Good Health of Everyone”, produced by the Research Foundation for Microbial Diseases of Osaka University. A copy of the video is on file at WTEC headquarters.

The original proposal for the Foundation was made by Dr. Tenji Taniguchi in 1929 who thought that a research organization for infectious disease was needed in Osaka since the Hanshin region was a gateway to foreign diseases. He made a request to the President of Osaka Medical College to establish a foundation. A compromise plan was proposed that the foundation would conduct the applied studies and vaccine manufacturing while a different institute would conduct basic research. Finally, in 1934, with the initial donation from Mr. Gendo Yamaguchi as a basic fund, the Research Foundation for Microbial Diseases of Osaka University (BIKEN) was established, separately from the institute (present Research Institute for Microbial Diseases, Osaka University), in order to perform “research on the prevention and treatment of microbial disease” and also “production of materials for prevention and treatment.” The Foundation was originally located on the premises of the Research Institute to provide a translational bridge between basic and clinical medicine and has advanced projects in close cooperation with the activities of the Research Institute. The responsibilities and contributions to the well-being of Japan increased over the years after WWII. Vaccines for cholera, variola, and epidemic typhus were supplied. The Kanonji Institute was established for producing the typhus vaccine in 1946. In 1951 the Foundation completed work on the first inactivated influenza vaccine in Japan.

Additional Highlights of BIKEN’s Accomplishments

1961 First Japanese production of inactivated polio vaccine was accomplished
1962 “Taniguchi Memorial Fellowship” for young scientists in medical education was established
1965 Ultracentrifuge-purified Japanese encephalitis vaccine (JEV) was completed and released
1966 First Japanese production of inactivated measles vaccine and a live attenuated vaccine was accomplished
1971 Further attenuated measles vaccine “BIKEN CAM” was accomplished
1972 Manufacture of veterinary vaccines commenced with Marek’s disease vaccine
1974 Influenza split vaccine was released
1976 Japanese encephalitis live vaccine for swine was completed
1981 First live attenuated rubella vaccine in Japan was accomplished
1981 First Japanese production of live attenuated mumps vaccine (Urabe strain) was accomplished
1986 Development of acellular pertussis vaccine was completed and incorporated into DTP vaccine
1988 World’s first live attenuated varicella vaccine was approved
1988 Live porcine parovirus vaccine was completed
1990  First varicella skin antigen was approved
1992  U.S. approval for production of acellular pertussis vaccine concentrate was received
      U.S. approval for lyophilized Japanese encephalitis vaccine was received
1993  Recombinant hepatitis B vaccine (yeast derived) was approved
1998  World’s first inactivated iridovirus vaccine for fish was approved.
2003  World’s first inactivated iridovirus-streptococciosis combined vaccine for fish was approved
2005  Preservative-free influenza split vaccine (Influenza HA vaccine “FLUBIK”) was approved
      Measles, rubella combined vaccine “MEARUBIK” was approved
2006  Preservative-free DTaP/DT/T vaccines (“TRIBIK” etc.) were approved, including D
      toxoid for adult use
2007  Adsorbed influenza vaccine for H5N1 was approved
2009  Freeze-dried, cell culture-derived Japanese encephalitis vaccine (Inactivated) “JEBIK
      V” was approved

CURRENT PROGRAMS AND STATUS

Today the head office and clinical studies division of the Foundation are located on the
premises of the Research Institute for Microbial Diseases, Osaka University while product and
process research and production are performed at the Kanonji Institute in Kanonji, Kagawa.
Currently the Foundation supplies more than 20 types of biological drugs. Sales volume is in
excess of $200 million per year.

Profile of the Research Foundation for Microbial Diseases of Osaka University (BIKEN)

Offices:  - Headquarters, Yamada-oka, Suita, Osaka (at Osaka University)
          - Kanonji Institute, Yahata-cho, Kanonji, Kagawa
          - Tokyo Office, Higashi-Shinbashi, Minato-ku, Tokyo

Staff members:  591 (493 in Kanonji, 80 in Osaka, 4 in Tokyo, 14 in Shodo Island) as of Feb.
                2010

Core products:  -Influenza HA vaccine, “FLUBIK”
                 -Freeze-dried live attenuated measles, rubella combined vaccine,
                   “MEARUBIK”
                 -Freeze-dried live attenuated varicella vaccine
                 -Adsorbed diphtheria-purified pertussis-tetanus combined vaccine,
                   “TRIBIK”
                 -Freeze-dried, cell culture-derived Japanese encephalitis vaccine
                   (Inactivated), “JEBIK V”

BIKEN has worldwide recognition for the Oka varicella vaccine strain which is the only
varicella vaccine in the world recognized by the World Health Organization (WHO) as being
safe and effective. This vaccine strain is also used in the United States, and BIKEN’s varicella
vaccine (Oka strain) is used throughout the world in vaccine programs.
In the WHO expanding program on immunization (EPI), BIKEN’s measles vaccine (the first produced in Japan) was adopted and proven effective. WHO has a goal of eradication of measles by 2012. BIKEN is participating in Japan’s effort to eliminate measles by providing vaccine (the first produced in Japan) for a “catch-up” program wherein 13- and 18-year olds will be immunized over the next several years.

In 2009 BIKEN received approval for a pioneering Vero cell culture-derived lyophilized vaccine for Japanese encephalitis virus. This was the first JEV mass-cultured vaccine in the world. The prior vaccine was produced using harvested, infected mouse brains.

**FUTURE PLANS**

BIKEN’s timeline for development of next-generation vaccines with advanced technology includes the steps completed in the list above, with the near-term goals of realizing a recombinant malaria vaccine (in clinical trials), an inactive DPT-IPV combined vaccine, and a cell-cultured influenza vaccine, with the overall goal of developing products that lead Japan and the world.

**FACILITIES**

Vaccines for both humans and animals are produced at the Kanonji Institute in state-of-the-art facilities. The plant has ISO 14001 certification and has a U.S. FDA establishment license. Two new recent additions to Kanonji include a new facility for influenza vaccine production using egg-based technology (Building Y) and a new facility for production of other viral and bacterial vaccines (Building X).

Building X is a multistory building set up with utilities on the top floor, shipping and receiving on the bottom, with facilities for preparation of vaccine bulk for both viral and bacterial vaccines, including filling and packaging on the floors in between. Capabilities include the following:

- Viral harvesting and processing into final bulk
- Large-scale bioreactors, 1200L for cell cultures using bead technology
- Bacterial cell culture fermentors up to 150 liters
- Cell harvesting, purification and processing into final bulk
- Filling lines for both vials and syringes, isolator technology
- Preservative-free single dose vials and syringes
- Freeze-drying capacity of 130,000 doses per batch using liquid nitrogen technology
- Automated inspection and packaging, manual inspection
- Common area for cleaning and sterilizing equipment
- Common media preparation area
- Equipment for water purification, air handling and other utilities required for preparation of sterile products and containment of live organisms

The areas are set up to be sterilized using formaldehyde or hydrogen peroxide vapor so that they can be used to produce more than one vaccine.

Both animal and human vaccines are made in this building as it meets the requirements for both types of products.
Building Y is used for influenza vaccine production using egg-based technology. It is highly automated, including the candling of eggs and egg harvest. It can process 200,000 eggs per day. Ether treatment is used to split the virus and ultracentrifugation steps are used for purification. The building also has syringe and vial filling areas, where preservatives can be used for multi-dose vials and packaging capabilities. Embryonated eggs are procured from special farms, monitored by BIKEN.

BIKEN also has facilities for raising Specific Pathogen Free animals.

INTERNATIONAL COLLABORATION

BIKEN has a history of collaboration and contribution to other countries around the world that continues today:

- It has responded to the Japanese International Cooperation Agency's (JICA) request for technological guidance by establishing a "Vaccine Quality Control Technology Course". Since 1987, 117 trainees from 33 different countries have taken the course. In 1999 this course was approved as the WHO-certified course.
- It has an active oversees technology transfer and fellowship programs to help other nations learn to manufacture vaccines:
  - JEV vaccine for Thailand, India and Vietnam
  - Varicella and influenza vaccine for China
  - Measles vaccine for Brazil and Indonesia
  - Influenza vaccine to Indonesia
  - Oka varicella strain used throughout the world in vaccine programs

SUCCESS FACTORS AND CHALLENGES

BIKEN, the Foundation has been highly successful because of the close cooperation and synergy between the Foundation and the Research Institute of Osaka University. The goal of improving human lives through prevention and treatment of microbial diseases is embedded in their philosophy and decision making processes.

The Institute provides the basic, academic research needed for vaccine development using government funding. The Foundation performs the applied research and translation of the basic research into products and then manufactures them for the population. Funding comes from both charitable contributions and money they obtain from their own activities in addition to a preferred tax status. Both organizations synergistically support each. The Foundation donates money to the Institute, has established the fellowship program noted above and the Japanese Society of Vaccinology prize. The Institute provides a pool of capable, well-educated individuals for entry-level positions at the Foundation. These individuals have the opportunity to advance and become experts in the vaccine field. The Institute also gives back to the Foundation. The recent new facilities were made possible in part by donation of royalty money received by Osaka University (Professor Takahashi). More than 50% of the Foundation’s Board are emeritus professors at the university.

Challenges lie in the changing global vaccine landscape. Large multinational companies that currently supply most of Europe, the United States, and export some vaccines to Japan have many resources to translate basic research into products.
The Japanese regulatory environment is different in that there are fewer international guidelines and vaccine regimens are unique to Japan. The regulations are not harmonized with other countries. This makes the hurdles to enter the international marketplace more difficult.

Government funded clinical centers are not available (although there was some government funding of influenza clinical studies for pandemic vaccines), thus requiring more resources for companies who want to clinically test a new vaccine for the first time in humans. Both the government and the vaccine industry have recognized this situation as not optimal for Japanese exports and are working on solutions that include development of more guidelines, harmonization with other nations and more government support for vaccine programs. One example is the proposed government cell culture facility for pandemic influenza vaccines for which $1 billion has been set aside (see the site report for MHLW). Rapid response issues are similar for BIKEN as other companies, but technology advances, e.g., cell culture influenza vaccine, and advanced planning with regulators are in progress to shorten time frames.
KAKETSUKEN: The Chemo-Sero-Therapeutic Research Institute

Site Address: KAKETSUKEN: The Chemo-Sero-Therapeutic Research Institute
Kikuchi Research Center
Kyokushi, Kikuchi, Kumamoto
869-1298, Japan
http://www.kaketsuken.or.jp/eng/

Date Visited: February 26, 2010

WTEC Attendees: T. Leighton (report author), M. Ritchey, R. Kumagai

Host(s): Hiroyuki Yokote, General Manager, Clinical Development Department
Tel: 1-81-968-37-4070
yokote@kaketsuken.or.jp

BACKGROUND

KAKETSUKEN (The Chemo-Sero-Therapeutic Research Institute) is headquartered in Kumamoto prefecture and also has offices in Osaka and Tokyo. The origins of KAKETSUKEN began in 1926 with the establishment of the “Institute of Experimental Medicine” by Dr. Yamazaki at Kumamoto Medical College. The Institute was housed in the Department of Microbiology and focused on microbiology, immunology and serology research as well as the production of vaccines, anti-serums and diagnostic antigens. The institute was destroyed during World War II. The Institute was reconstructed after WWII and named KAKETSUKEN (an abbreviation of its Japanese name). Production of animal vaccines began in 1950, a blood center was established in 1953, and several research and production facilities were established during 1960 – 80. In 1988 a recombinant Hepatitis B vaccine was commercially introduced and was the first Japanese recombinant antibody product. A dedicated building was constructed for vaccine production in 1993. The Aso Branch Laboratory has animal facilities and houses a Special Pathogen Free chicken facility.

KAKETSUKEN was ISO14001 certified in 2001. Following the closure of Chiba Therapeutic Research Institute in 2002, KAKETSUKEN obtained the rights to six Chiba products including a smallpox vaccine. In 2002 a dedicated facility for the production of influenza vaccine was constructed. A dedicated filling facility was constructed in 2005. KAKETSUKEN is organized as a Juridical Research Foundation and has 1,650 employees of whom 16% are in R&D and 52% are in production.

PRODUCTS

In FY2008 KAKETSUKEN had sales (13 products) of $139 million in human vaccines and $41 million (50 products) in veterinary vaccines. The company is ranked number two in sales among Japanese vaccine producers. It produces two recombinant vaccine products (HBV and Chimeric Mab for Felines) and a cell-based HAV vaccine (initiated in 1995). The human vaccines (the most extensive in Japan) include flu, Japanese encephalitis vaccine (JEV), DPT, DT, tetanus, HAV, HBV, measles, MR, mumps, rabies, cholera and smallpox. A wide range of animal vaccine products are produced including NDV, bronchitis, Marek’s disease, Bursal disease, laryngotracheitis, egg drop syndrome; porcine vaccines for Pasteurella toxoid, erysipelas, gastroenteritis, E. coli, JEV, and parovirus; bovine vaccines for anthrax, Akabane
Disease, Ibaraki Disease, AK-KB-AN, and *Histophilus somni*; equine vaccines for influenza, JEV and anthrax; and small animal rabies vaccine.

**Smallpox Vaccines**

During recent Japanese history, smallpox incidence peaked in 1946 with 17,000 cases and 3,000 deaths. Reconstitution of the Japanese vaccine infrastructure following WWII diminished smallpox incidence to zero by the mid-1950s. Once smallpox was well controlled, public acceptance of smallpox vaccination became problematic due to adverse reactions including post-vaccinal encephalitis. Studies aimed at reducing smallpox vaccine contraindications began in the late 1960s with three strains—Lister, Equadol-EM63, and Ikeda. The Ikeda (Japanese strain) was shown to produce more severe local reaction than the two other strains. The Lister (European) strain has been used in Japan since 1970. Studies were continued in the 1970s to explore the use of attenuated smallpox strains. The Wyeth CV-1 strain demonstrated a very low level of febrile reactions in children, who are the primary vaccination cohort in Japan. However, the CV-1 strain had limited ability to induce neutralizing antibodies and had substantial neurovirulence. During these studies a set of new strains, (LC16, LC16m0 and LC16m8) were developed at the Chiba Institute and subsequently acquired by KAKETSUKEN. The LC16m0 and LC16m8 had temperature sensitive replication when tested at a non-permissive temperature 40.5°C or above due to a mutation in an immunogenic membrane protein B5R. The LC16 strain series was substantially less virulent in monkey and mouse models. The LC16m8 strain was selected for human clinical trials in 1974 due to its low incidence of fever and high vaccine take rate (Table B.1). Over 20,000 children were inoculated with this strain without any serious vaccination contraindications. Presently, 90,000 Japanese children have received the Chiba vaccine. KAKETSUKEN believes that the LC16m8 strain has lower infectivity transmissibility and potential for autoinoculation. Due to these favorable characteristics a third-generation LC16m8 cell-culture smallpox vaccine has been developed for Japanese military personnel. The vaccine is also effective in immunocompromised monkeys. NIID has studied this vaccine in a monkeypox model and shown it to be protective. A human clinical trial of this third-generation vaccine in 3,000 Japanese military personnel showed it to produce a 94% seroconversion in naive subjects with no severe adverse events. The vaccine also was effective in a booster modality.

**Table B.1. Local cutaneous reaction to LC16m0, LC16m8, and conventional vaccinia vaccines (1968-1974)**

<table>
<thead>
<tr>
<th>Vaccine strain</th>
<th>Year of investigation</th>
<th>No. of persons examined</th>
<th>% Successful vaccination</th>
<th>Mean erythema diameter (mm)</th>
<th>Average induction diameter (mm)</th>
<th>Febrile reaction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ikeda</td>
<td>1968-1970</td>
<td>1506</td>
<td>99.1</td>
<td>22.9</td>
<td>18.2</td>
<td>25.0</td>
</tr>
<tr>
<td>Ecuador</td>
<td>1969-1970</td>
<td>1846</td>
<td>67.5</td>
<td>19.2</td>
<td>17.4</td>
<td>21.3</td>
</tr>
<tr>
<td>Lister</td>
<td>1968-1971</td>
<td>3662</td>
<td>93.7</td>
<td>17.6</td>
<td>15.3</td>
<td>26.6</td>
</tr>
<tr>
<td>CV-1-78 (Japan)</td>
<td>1971-1973</td>
<td>22976</td>
<td>92.4</td>
<td>21.1</td>
<td>16.8</td>
<td>8.5</td>
</tr>
<tr>
<td>LC16m0</td>
<td>1973-1974</td>
<td>829</td>
<td>94.8</td>
<td>19.6</td>
<td>14.5</td>
<td>12.1</td>
</tr>
<tr>
<td>LC16m8</td>
<td>1973-1974</td>
<td>10578</td>
<td>95.1</td>
<td>18.4</td>
<td>6.1</td>
<td>7.7</td>
</tr>
</tbody>
</table>

The most commonly available smallpox vaccine is Dryvax, a calf lymph derived product. Recent clinical experience with Dryvax revealed that myopericarditis, a serious adverse event, occurred with high frequency in primary vaccines. Second-generation vaccines
produced in vero cells unfortunately suffered from subclinical or clinically frank myopericarditis. An MRC-5 cell second-generation vaccine had lower seroconversion rates than Dryvax. The two third-generation vaccines, LC16m8 and MVA (a non-replicating vaccine), have quite different properties. The MVA vaccine has an excellent safety profile but may require multiple doses for optimal protection. The human efficacy of MVA is not known with great certainty. LC16m8 has proven human efficacy, has been well tolerated in pediatric and adult populations and induces a high rate of seroconversion with a single dose. The KAKETSUKEN cell-based smallpox vaccine could offer significant advantages over currently available vaccines.

**CHALLENGES**

The vaccine market in Japan is small when compared to the global vaccine market. Even innovative Japanese vaccine producers have limited export capabilities. In the case of the highly antigenic, very low reactivity LC16m8 smallpox vaccine, KAKETSUKEN is finding it difficult to obtain resources to accelerate late-stage clinical testing for large markets such as the United States. Even for existing vaccine products, a new regulatory package must be developed for each country or region and this is especially difficult for older products that were licensed under more minimal guidelines.

There is an unmet need for small company access to vaccine clinical testing centers for innovative next-generation products. Small companies do not have the resources and cannot compete against multi-national enterprises that typically produce vaccines for the United States and Europe. Some form of export/import assistance with proximate Asian markets may also be useful. Toward this end KAKETSUKEN does participate in the Japanese International Cooperation Agency (JICA) and has scientific exchange programs with the Asian region.
Kitasato University, Kitasato Institute of Life Sciences, Graduate School of Infection Control Sciences

Site Address: Kitasato University, Kitasato Institute of Life Sciences, Graduate School of Infection Control Sciences
Shirokane 5-9-1, Minato-ku
Tokyo 108-8641, Japan
http://www.kitasato-u.ac.jp/lisci/index.html
http://www.kitasato-u.ac.jp/lisci/life/LaboData/Labo01.html

Date Visited: February 26, 2010

WTEC Attendees: S. Jacobson (report author), S. Drew

Host(s): Professor Tetsuo Nakayama, MD, PhD, Laboratory of Viral Infection I and Deputy Director, Kitasato Institute of Life Sciences, Kitasato University
Tel: 81-3-5791-6269
tetsuo-n@lisci.kitasato-u.ac.jp

BACKGROUND
The Kitasato Institute was established by Dr. Kitasato Shibasaburo in 1914 and later became Kitasato University. Dr. Kitasato is famous for his pure culture of Clostridium tetani, discovery of tetanus toxin, the study of tetanus immunology, and the establishment of a new field of therapy called serotherapy. The Kitasato Institute for Life Sciences was established in 2001 at Kitasato University.

ACTIVITIES AND FINDINGS
Professor Nakayama, a pediatrician by training, heads a clinical vaccine research program. Yogi Goto, Vice Director, Research Center for Biologicals, joined our meeting. Our discussion initially focused around Professor Nakayama’s research on measles. Professor Nakayama discussed the challenges presented to Japan by measles. He noted that in 2007, a severe measles outbreak occurred among young adults and college students, which resulted in a five year window where two additional measles vaccines were administered (one at age 13 years, the other at age 18 years).

Professor Nakayama gave a presentation on influenza and influenza vaccination in Japan. He highlighted the key differences in population and influenza vaccine capacity for both the world and Japan. There are four manufacturers of the influenza vaccine in Japan, with the live (nasal spray) vaccine current not being used. He provided some historical perspective on influenza in Japan, showing surge of cases occurring approximately once every four years.

He also discussed the early policy on influenza vaccination in Japan, where only young children were vaccinated. He noted that this policy was discontinued in 1994, since it was deemed to be ineffective in preventing spread of infection to the elderly (those older than 65 years). Since 1997, after a particularly high surge in elderly deaths due to influenza, the elderly became the only population for which the influenza vaccine is required. For the 2009 H1N1 pandemic influenza, Japan worked hard to monitor the incidence of cases. They recorded the age distribution of cases, noting that over 75% of the cases were in children and young adults (i.e., under the age of 19 years). They also, like many countries, shifted their
seasonal influenza vaccine capacity into producing the H1N1pan vaccine. In particular, with a normal production of 28 million doses of seasonal influenza vaccine each year, only 22.5 million doses of the seasonal influenza vaccine were produced, and 15 million doses of the H1N1pan vaccine were produced. An additional 12 million doses of the H1N1pan vaccine were imported. Their clinical trials for the H1N1pan vaccine compared 15 mcg per dose versus 30 mcg per dose vaccines. These trials also suggested that side effects and reactions were different between the Japan produced vaccine and those produced by GSK and Novartis. Both the GSK and Novartis vaccines are adjuvanted while the Japanese vaccine does not use an adjuvant. Professor Nakayama indicated that while the Japanese vaccine was less painful and caused lowered inflammation, it was fully effective in preventing infection.

The priority system used to determine the order in which the population would be vaccinated was similar to that used in the United States and other countries. A comprehensive strategy for containing the spread of H1N1pan was installed, including vaccination, social distancing, surveillance, medical staff preparedness, and anti-flu medication, among others. It was estimated that only 10% of the population were infected by H1N1pan, with 16,500 hospitalizations and 185 deaths, which compared favorably to other countries. The key statistic was that of the 185 deaths, 74% were under 30 years of age, with 71% having some underlying chronic condition. Overall, Professor Nakayama noted that Japan was well prepared in dealing with H1N1pan, and the results bear out this observation.

**SUMMARY AND CONCLUSIONS**

Our meeting with Professor Nakayama provided a clear snapshot of routine immunization and the influenza vaccine in Japan.
Ministry of Agriculture of the People's Republic of China, Veterinary Bureau

Site Address: Ministry of Agriculture of the People's Republic of China Veterinary Bureau
No.11 Nongzhanguan Nanli
Chaoyang District, Beijing, P.R. China 100125
http://english.agri.gov.cn/ga/amoa/organs/

Date Visited: March 2, 2010

WTEC Attendees: C. Gay (report author), R. Kumagai

Host(s): Kang Wei, Division Director, Division of Science, Technology & International Cooperation, Veterinary Bureau
kangw@agri.gov.cn

BACKGROUND

The Chinese Ministry of Agriculture (MOA) is responsible for research and development, including national laboratories and the registration of veterinary drugs and biologics.

REGULATION OF VETERINARY VACCINES

The regulation of veterinary vaccines was described as follows:

- A “Bulletin 442 ” provides the regulations
- All Chinese veterinary vaccines as well as imported products must meet the requirements of Bulletin 442
- The MOA uses expert panels to review license applications for veterinary drugs and biologics.
- Applications follow a three step process:
  1. Send to the General Administration
  2. Evaluation control
  3. Testing of final product for quality
- Chinese MOA requires Good Manufacturing Practices (GMP) for veterinary vaccines, including imported products
- China has 77 veterinary vaccine manufacturers. Most are private companies.
- The MOA provides funds to enable the research, development, and manufacture of new vaccines for emerging diseases considered an emergency and threat.
- In the case of emergencies, the MOA will not provide master seeds for vaccine manufacture but will expedite the regulatory process.
- If a company can’t deliver a new vaccine, the Chinese government can ask a company to transfer its R&D to other vaccine manufacturers.
- The Chinese Government considers animal health to be part of public health
- Greatest challenges are considered to be:
  - emerging diseases such as African Swine Fever
– obtaining information from foreign manufacturers

**CONCLUSION**

Veterinary vaccine manufacture in the People's Republic of China is accomplished through privately held companies. In emergency situations, production of vaccines is directed by the MOA to additional manufacturers to meet demand. The review and approval process is expedited to meet need.
Appendix B. Site Reports

Ministry of Health of the People’s Republic of China

Site Address: Ministry of Health of the People’s Republic of China
Beijing, People’s Republic of China
http://www.moh.gov.cn/

Date Visited: March 1, 2010

WTEC Attendees: N. Iyer (report author), J. Bielitzki, C. Gay, R. Kumagai, J. Zhang

Host(s): Dr. He Wei, MD, Professor
Director General, Department of Medical Sciences, Technology and Education
Ministry of Health, People’s Republic of China,
hewei@moh.gov.cn
Nie Jiangang, MHA
Director, Division of European, American and Oceanic Affairs
Department of International Cooperation
Ministry of Health, People’s Republic of China
niejg@moh.gov.cn
Wu Peixin, Vice Director
Division of Health Technology Assessment and Promotion
Department of Sciences, Technology and Education
Ministry of Health, People’s Republic of China,
wpxin@sina.com

Other Attendees: Jeffrey W. McFarland, MD
CDC Country Director, GDD Director, U.S. CDC Influenza Coordinator
Embassy of the United States of America,
Beijing, P.R. China
jwm5@cdc.gov
Elizabeth F. Yuan, RPh
Health Attaché, U.S. Department of Health and Human Services
Embassy of the United States of America
Beijing, P.R. China
Yuanef@state.gov

DISCUSSION POINTS

• Challenges to move from identified pathogen towards a vaccine:
  – Availability of animal models (due to limitations on information about the disease in the model)
  – Similarity of disease pathogenesis between the human and the animal model
  – Pathogen and antigen identification remains important
  – Typical time spent in pre-clinical studies is 2 years and 3 years in clinical phase
• The People’s Republic of China utilizes an accelerated and focused approval process during critical periods of vaccine need
– Ensure they maintain the same production and clinical standards but reduce the review cycle time
– Rely on WHO and other organizations for supplying international standards
– Quickly develop National Reference Standards and match to the international standards
– Reagents for testing are produced nationally and compared to the WHO reference laboratories to assure quality
– Conduct large clinical studies (10,000 subjects through the Chinese CDC and government-supported infrastructure to evaluate studies from vaccination through end of the study)
– During periods of urgency and emergency trained human resources are expected to meet the emergency in terms of length of work day and work week, reducing the time needed to complete the regulatory cycle.

• Preclinical Models developed extensively – mouse, rat, rabbit, NHP may not be sufficient.
  – Recognize the need for in vitro alternatives to vaccine testing
• Development of validated tests including potency assays
  – Relies on information coming from western countries
• Transition and maturation of technology from discovery to commercialization
  – U.S. system driven from initial government based discovery/research investment that transitions later to market driven funding
  – Chinese system uses priorities established by the government to meet national needs and driven by the science community, which focuses on technology transfer for production
  – U.S. model has been successful but has too much reliance on the market demands for vaccine. The Chinese model relies on the central government for priorities and on the market to push new technologies that meet the national needs for vaccines.
  – Science and technology is only one factor in the development of the products; many other factors in development of the product that are important
  – Opening new markets for Chinese products
• China has recognized the importance of investment in basic research. The big challenge is to address the need for new strategic development. China has invested in three Mega Projects that focus on the prevention and treatment of chronic diseases and new therapeutics:
  – Investment in treatment of diseases (e.g., AIDS)
  – Investment in discovery and development of new therapeutics
  – Investment in adjuvant discovery
• In China the cost of goods ($/dose) is a significant factor considering the size of the population (1.3 billion with 16 million births annually), with required vaccinations for 14 specific infectious diseases in children prior to starting in the educational system. Any reduction in production cost results in significant savings for the government.
• The two key technology drivers:
- High-tech solutions focus on product development
- Discovery based solutions (long-term, basic research) are driven by national priorities and needs (e.g., stem cell research would be prioritized over T-cell research)

CONCLUSION

Vaccine manufacturing in the People’s Republic of China faces many of the same problems as those seen in Europe and the nations in the Western hemisphere. A significant difference is in the centralized system of prioritization and the ability to focus national and privately held resources to meet emergency production demands.
Ministry of Health, Labour and Welfare (Japan), Pharmaceutical and Medical Safety Bureau

Site Address: Ministry of Health, Labour and Welfare (Japan), Pharmaceutical and Medical Safety Bureau
1-2-2 Kasumigaseki, Chiyoda-ku
Tokyo, 100-8916, Japan

Date Visited: February 25, 2010

WTEC Attendees: M. Ritchey (report author), T. Leighton, R. Kumagai

Host(s): Nobumasa Nakashima, Deputy Director
Blood and Blood Products Division
Pharmaceutical and Medical Safety Bureau
[current address: Economic Affairs Division, Health Policy Bureau]
Tel: +81-3-3595-2395; Fax: +81-3-3507-9064
nakashima-nobumasa@mhlw.go.jp

BACKGROUND

“From the cradle to the grave” is the phrase that is used to describe the scope of activities covered by the Japanese Ministry of Health, Labour and Welfare (MHLW). Services provided for various life stages include medical services, public health, the working environment, employment security, human resources development, child care, long-term care, welfare, and pensions. In 2001 the Central Ministries were reorganized to integrate the Ministry of Health and Welfare and the Ministry of Labour in order to support people's lives systematically.

There are 22 bureaus and related organizations within the Ministry of Health, Labour and Welfare. The Health Services Bureau and the Pharmaceutical and Medical Safety Bureau are involved in activities related to vaccination. The Health Services Bureau promotes local health-care through health centers and works toward controlling infectious diseases and lifestyle diseases. Within this bureau there is a Specific Diseases Control Division and a Tuberculosis and Infectious Diseases Control Division. The Pharmaceutical and Food Safety Bureau is involved in reviewing and licensing drugs and devices and collecting and providing information on products to ensure safety and effectiveness. Within this bureau there is an Evaluation and Licensing Division and a Safety Division.

GENERAL FUNCTIONS RELATED TO VACCINES

Our host gave us a general description of how this Ministry supports vaccines by both regulations and support for the industry. The organizations within this ministry that support vaccines are responsible for licensing vaccines for use in the Japanese population and for ensuring that there is an adequate supply of vaccines. Reference was made to the National Institute of Infectious Diseases (NIID) which has extensive research and disease surveillance efforts and WHO collaborative activities that provide information that is necessary for making policy decisions regarding vaccines (see the separate site report on NIID).
PHARMACEUTICALS AND MEDICAL DEVICES AGENCY

An independent organization, the Pharmaceuticals and Medical Devices Agency (PMDA) has the responsibility for reviewing license applications for compliance with the Pharmaceutical Affairs laws, reviewing post-marketing surveillance data, implementing safety measures, and providing compensation to individuals who suffer from adverse drug reactions and infections from biological products. This agency was established in 2004 as an incorporated administrative agency with non-civil servant status. It resulted from the reorganization and rationalization plan developed for Special Public Corporations and represents a consolidation of the services of the Pharmaceutical and Medical Devices Center of the National Institute of Health Science and the Organization for Pharmaceutical Safety and Research and part of the Japan Association for Advancement of Medical Equipment.

Initial staffing of the PMDA organization in 2004 was 256 and has grown to 521 as of 2009 in response to efforts to increase the speed for carrying out its review processes. Financial support for this organization includes contributions toward both the compensation system and the application review process. Licensed manufacturers contribute directly to PMDA. There is also funding from the Ministry of Health, Labour and Welfare.

Reviews and Related Services Performed by PMDA

The reviews and related services performed by the PMDA include:

- Approval reviews of applications for drugs and devices based on the Pharmaceutical Affairs Law
- Guidance and Advice relating to clinical trials or other issues related to drug development and licensure
- Review for compliance to GCP and GLP standards
- Review for compliance to GMP and QMS standards
- Confirmation of re-examinations and re-evaluations based on the Pharmaceutical Affairs Law.

Post-Marketing Safety Measures

The post-marketing safety measures include:

- Collection, analysis, and provision of information related to quality, safety, and efficacy
- Consultations with consumers
- Guidance and advice for marketing authorization holders to enhance the safety of their products
- Research related to the development of standards

The results of reviews of applications are forwarded to the MHLW for final action.

PANDEMIC INFLUENZA PROGRAM

In 2005, the “Pandemic Influenza Preparedness Action Plan of the Japanese Government” was prepared based on the avian influenza threat and then updated in 2006. The current plan will allow Japan to be self-sufficient in providing influenza vaccine supplies for its entire population, if needed, during a pandemic. The goal is to have production capacity that will allow for manufacturing of vaccine for the entire population within 6 months of initiating production. The plan includes an overall investment of $1 billion ($1=120Yen) during the
next 5 years to support the construction of manufacturing facilities and associated development of a cell culture-based influenza manufacturing process. Effort will also be devoted to developing third generation vaccines that will include adjuvants or alternative delivery systems to permit a lower antigen use and possibly provide broader protection. The plan was initiated in 2009 and requires that manufacturers who want to participate (about 4-5 are eligible) submit proposals for construction of vaccine pilot plants, test the non-clinical vaccine product quality (Phase 1), and then initiate initial clinical testing of the test product (Phase 2). Two or three companies will be selected to continue the program to large-scale production, validation, and rapid examination (Phase 3). The goal is to have the capability in place by around 2013.

The H1N1 pan program was managed by procuring vaccine from both domestic and foreign manufacturers. Based on the WHO director general’s announcement in April 2009 of a raised alert to level 4, domestic manufacturers were requested to produce vaccines and overseas companies were solicited for vaccine provisioning. In May the SAGE group of WHO provided recommendations on vaccination and a decision on the strain was made in July. At that time domestic production was initiated and import negotiations started. The contract for vaccine importation was signed on October 6. Vaccination with domestic product began on October 19. The domestic manufacturers supplied 54 million doses. Contracts with Novartis and GSK were completed to provide another 99 million doses, with approval for import given on January 20, 2010. As of the end of February, 35 million doses were supplied to patients. Vaccine uptake was less than expected and thus strategies to use the surplus vaccine are under discussion.

The following special measures were implemented for this program. An exceptional approval system was used to license the imported vaccine. Clinical studies from other countries, mainly in Europe, were used to support the licensure, with a small number of subjects tested in Japan. In addition, special legislation was enacted in December of 2009 to provide compensation for adverse reactions to vaccination and to indemnify the vaccine companies.

Vaccine administration was prioritized in rank order as follows: health care workers, pregnant women, people with underlying disease, infants (1 year) to pre-schoolers, first to third graders, guardians of infants under 1 year of age, fourth to six-graders, with the final group being the junior high, high school and elderly, in order. Uptake was less than expected. This may be due to the fact that the disease was not perceived to be very severe, and due to possible concerns over the safety of the vaccine.

OVERVIEW OF THE JAPANESE VACCINE INDUSTRY

The MHLW in conjunction with other government agencies, industry, and the medical community conducted a review of the vaccine industry in Japan beginning in 2005 and summarized their findings in March of 2007 in a report entitled “Vaccine Industry Vision: Aiming at realizing an image of the industry that supports infection control and meets social expectations.” The report included the following information.

There are seven domestic organizations that supply vaccines which protect against diphtheria, tetanus, polio, measles, rubella, Japanese encephalitis, tuberculosis, influenza, mumps, hepatitis A, hepatitis B, leptospirosis, and rabies. Except for Takeda and Meiji Dairies, where vaccine sales are less than 2% of their overall business, vaccines sales represent either one-third or nearly all of their sales volume. Vaccines for pneumococcal pneumonia (infant and adult), yellow fever, Haemophilus influenzae b and human papilloma virus are provided by foreign manufacturers. As of 2007, the annual market for vaccines was valued at 90,000
million yen (about $900 million), more than double that of 1995 (see Figure B.10). Exports are only 3% of the total. Comparisons with the United States indicate that the market is less than 1/3 of that of the United States and that the United States spends 10 times more in research and development than does Japan. The United States has introduced 15 new or combination vaccines over the 20 years preceding 2007, whereas Japan has introduced 8. A newly developed Japanese vaccine has not been put on the market since 1995 (although in 2009 Biken received a license for an improved JE vaccine).

Figure B.10. Annual production of vaccines in Japan (from a survey by the Association of Biologicals Manufacturers of Japan, Saikin Seizai Kyoukai; courtesy of the Ministry of Health, Labour, and Welfare of Japan).

Challenges in introducing new vaccines into Japan include the following:

- Immunization schedules in Japan differ significantly from those in the United States and other countries.
- The relatively small size of the Japanese vaccine companies when compared to the multi-nationals that supply the United States and Europe make it difficult for them to compete in vaccine development and in entering the global marketplace.
- The costs to bring a vaccine to market that is demonstrated to be safe and effective are high (translational research) and any individual small company will have difficulty in finding the resources.

Difficulties also arise from the fact that the birth rate is declining, and the culture of Japan requires that vaccines be extraordinarily safe before the public will accept them. Return on investment may also be limited by limited use of the vaccines if the vaccine is not required by law. Vaccine manufacturers facing uncertain future prospects for sales may not want to undertake such large investments.

The Japanese Ministry of Health recognizes the importance of maintaining both a viable domestic vaccine industry and the ability to source vaccines internationally. Recommended actions include strengthening research and development by for example, providing centers
for human clinical studies support, encouraging the alliance of Japanese companies with foreign manufacturers, subsidizing orphan drugs, and providing subsidies for manufacturing and stockpiling prepandemic vaccines.

More public education and outreach is needed on the usefulness of vaccines, especially those that are not required by law. This education and communication needs to be provided to both the medical community and the public. Publishing guidelines for vaccine development and participating in international harmonization of guidelines and regulations can help promote export and licensing out of vaccines from Japanese manufacturers. Collaboration between public and private organizations should be fostered to make the best use of limited resources. In addition, market expansions can also come from participating in alliances that will provide vaccines and technology for developing nations. Japanese companies already participate in programs for training and technology transfer to developing countries within Asia.

**MHLW DISCUSSION OF SPECIFIC QUESTIONS SENT IN ADVANCE**

**The Broad Issues**

As demonstrated by the H1N1 pandemic influenza accomplishments, Japan was able to secure sufficient vaccines for the population using some exceptional methods for licensing vaccines from outside suppliers.

Depending upon the situation, clinical study in humans can be the most rate limiting step. For influenza vaccine, the process of making the vaccine (strain selection and production testing through final steps) was most rate limiting.

Japan has a wealth of excellent technology for current and future vaccines that may not always be able to be translated into a product based on the limited resources of small Japanese vaccine companies.

**Science and Engineering**

Cell culture technologies offer a great deal of promise. Development and harmonization of guidelines, including guidelines for adjuvants will be helpful.

Japan is making a major $1 billion investment in cell culture and other new production technology for influenza vaccines.

Improved and more rapid technologies for strain selection will be helpful.

**International Collaboration**

Japan supports the training of scientists from other Asian countries in vaccine technology through the Japanese International Cooperation Agency (JICA) in addition to transferring technology to manufacturing plants in these countries.

They participate in the WHO influenza surveillance programs. Improved global influenza surveillance in developing countries is considered a high priority.

**Training and Education**

It has not been so easy to obtain staff, requiring the use of staff from other parts of the organization to complete programs.

Training and education of new personnel are mainly provided through on the job experience.

The National Institute of Infectious Diseases has an excellent monitoring program to ensure that any new outbreaks in Japan are quickly identified.
Clinical and Regulatory Issues

Compared to the United States, timing of approval time for new drugs/vaccines is 2-3 years behind. The PMDA has an active “drug-lag” program to shorten these time frames substantially.

Guideline development and international harmonization would help facilitate human clinical studies without compromising safety.

Working with WHO and bilateral cooperation among countries is helpful in limiting the spread of disease.

REFERENCES

Ministry of Health, Labour and Welfare. 2007 (March). Vaccine industry vision: Aiming at realizing an image of the industry that supports infection control and meets social expectations (report).


Pharmaceuticals and Medical Devices Agency. 2010. Profile of services, fiscal year 2009, Pharmaceuticals and Medical Devices Agency, Japan.

**Mogam Biotechnology Research Institute and Green Cross Company**

**Site Address:** Mogam Biotechnology Research Institute and Green Cross Company  
341 Bojeong-Dong, Giheung-gu  
Yongin, 446-799, Republic of Korea  
http://www.mogam.re.kr/  
http://eng.greencross.com/rd/intro_04.asp?id=1

**Date Visited:** March 5, 2010

**WTEC Attendees:** N. Iyer (report author), J. Bielitzki, C. Gay, R. Kumagai

**Host(s):**  
Yeup Yoon, PhD, Director, Mogam Biotechnology Research Institute  
Tel: +82-31-260-9833  
yy@mogam.re.kr  
Song-Yong Park, PhD, Vaccine Team, Research Director  
Mogam Biotechnology Research Institute  
Tel: +82-31-260-9766  
songpark@greencross.com  
Jin Won Youn, PhD, Vaccine 2 Team, Head  
Mogam Biotechnology Research Institute  
Tel: 82-31-260-9823  
jwyoun@mogam.re.kr  
Ahn Dong Ho, PhD, Central Research Center, Vaccine Group Leader  
Green Cross Company  
dhahn@greencross.com

**BACKGROUND**

Mogam Biotechnology Research Institute (MBRI) was founded in 1984 as the first non-profit research institute in South Korea focusing on research and development from basic innovation through processing. It was funded by Green Cross Corporation (GCC). MBRI has been designated as a World Health Organization Collaborating Centre for the Research and Development of Vaccines and Diagnostic Reagents since 1989. MBRI has focused on fundamental research in biomedical fields, especially on the biological approaches to medically unmet needs. GCC has been a partner for the development of the R&D products by supporting commercial manufacturing and distributions.

GCC, founded in 1967, is an R&D-oriented pharmaceutical company that leads the biotechnology industry with annual sales over $700 million, one of the biggest pharmaceutical companies in the country. About 200 scientists are employed at MBRI and GCC Research Unit, the Central Research Institute, including 39 PhDs. GCC’s manufacturing systems utilize recently renovated state-of-art facilities. The company is publicly traded on the Korean Stock Exchange.

Korea is located on the East Asian/Australian flyway for migratory birds, making influenza, and in particular avian influenza a national concern.
PRODUCTS
Of many products licensed by GCC, vaccine related products are as follows: Hepatitis B vaccine was licensed in Korea in 1983; in 1988 a Hanta virus vaccine (Korean GMPs) for hemorrhagic fever was licensed. In 1993, as an achievement of MBRI’s research, a Varicella vaccine was licensed and is now sold in Southeast Asia, Central and South America.

The company produced 3.5 million doses of the first lot of seasonal influenza vaccine in 2009, using a manufacturing plant at Hwasun which had started the flu vaccine project in 2005 and can produce 25 million doses (45 μg/dose) per season. It has ancillary suppliers that provide 135 thousand eggs/day for this operation. GCC has also produced a vaccine against pandemic H1N1pan in 2009, which contributed to pandemic preparedness of Korea. The production facilities were designed to meet the production standards currently used in the European Union.

The following vaccines are on the pipeline: adult Td (phase II/III), highly pathogenic avian influenza (phase I/II), and anthrax (phase I).

DISCUSSION
Prior to 2009, influenza vaccines were mostly imported in Korea. With the release and domestic production of influenza vaccine by GCC, imports have been greatly reduced.

Development of the pandemic influenza H1N1 vaccine was aggressive and fast tracked. A seed stock was obtained in June 2009 and went through the optimized process of manufacturing, followed by the initiation of a clinical study in September and an NDA approval in October, 2009. Studies typically had about 500 adult subjects and 250 in a pediatric cohort (march-down) clinical study. The end point was set to meet at least two defined criteria (seroconversion, seroprotection and GMT response).

Following the success of the seasonal influenza vaccine development, GCC has produced 25 million doses of H1N1pan vaccines for the 2009 pandemic. The total number of vaccinees has been estimated up to 10 million population within 6 month period without any significant adverse events. The population analysis of the benefits from the nationwide vaccination is under evaluation.

Korea has a population of 48 million situated in 9 provinces. The country’s relatively small size (approximately that of Texas) makes vaccine distribution efficient.

Other General Information (Dr. Yoon)
MBRI is investing in basic and applied research to ensure Korea has the capability to meet the medical needs of their country.

Specific needs include greater international collaboration to ensure the supply of vaccines for emerging diseases. Additional research on platform technologies, such as gene expression, fermentation systems, purification systems, and in vitro assays, is needed. Fundamental science is focusing on oncology, anti-cancer antibodies, recombinant protein therapeutics, cell therapy, and cell culture vaccine platform for influenza.
National Institute for Control of Pharmaceutical and Biological Products of the People’s Republic of China (NICPBP)

Site Address: National Institute for Control of Pharmaceutical and Biological Products of the People’s Republic of China
2 Tiantan Xili, Beijing, 1000050, P.R. China
http://www.nicpbp.org.cn/cmsweb/

Date Visited: March 2, 2010

WTEC Attendees: N. Iyer (report author), J. Bielitzki, J. Zhang

Host(s): Wang Junzhi, PhD, Professor, Deputy Director
National Institute for the Control of Pharmaceutical and Biological Products
Tel: +8610-67014382, +8610-67095782
wangjz@nicpbp.org.cn
Several other Chinese scientists also attended the meeting.

BACKGROUND

The National Institute for Control of Pharmaceuticals and Biological Products (NICPBP) is China’s premier agency for quality control of medicine. It has been a subordinate agency of the State Food and Drug Administration (SFDA) since 1950. Its major areas of function are as follows:

- Drug testing and retesting required for drug approval and drug quality surveillance regulations
- Calibration and management of national reference standards
- Organizing sample testing of pharmaceutical products and medical devices for the Quality Sampling Program, providing technical data for the Quality Bulletin, and submitting the report of drug quality information and technical analysis
- Providing technical assistance and guidance regarding laboratory testing technologies at provincial, autonomous and municipality level and for the institutes authorized to import drugs as well as for the testing units within the pharmaceutical manufacturers, drug supply companies and medical institutions
- Managing the batch release of biological products
- Reviewing the requirements and specifications of direct-contact packaging materials and containers of pharmaceuticals and pharmaceutical expedients and providing the relevant review report
- Providing the technical identification of active pharmaceutical ingredients, assays and impurities in counterfeit drugs suspected of causing harm to human health when entrusted by judiciary agencies
- Registration testing of pharmaceutical products, biological products, and medical devices and assistance to the SFDA in administrative supervision of pharmaceutical products and medical devices
Appendix B. Site Reports

- Technical supervision of advertisements regarding drugs, medical devices, and health products
- Registration of specifications of the pharmaceutical products and biological products, and providing verification opinions
- Organizing and evaluating the promotion of technical qualifications for senior technical positions in the areas of drug research and engineering; undertaking the daily work of the Science and Technology Office of the SFDA
- Collection, identification, classification, preservation, management, and distribution of bacterial, viral and cell strains, and standard medical type cultures that are used in quality control and manufacturing in the country
- Preservation, breeding, and supplying of experimental rodent animals and the quality control of experimental animals
- National drug safety evaluations
- Other tasks assigned by the SFDA and relevant agencies

NICPBP has 52 Divisions and about 820 employees. There are 10 laboratories for biological products and about 170 staff in these labs. These laboratories include:

- Three divisions for viral vaccines
- Type culture collections
- Cell biology
- Two divisions for bacterial vaccines
- Sera
- Blood products
- Recombinant technology products
- Biosafety

NICPBP provides a complete outlook for science and development. It is primarily responsible for interactions with WHO and other agencies, including the USP to gain access to reference standards and produce and maintain national reference standards and reagents.

NICPBP has been ISO accredited for its process, and it works closely with the SFDA in development of China’s cGMP guidance.

NICPBP is the publisher of China’s Pharmacopeia, which has been divided into the 4 main parts of biologics: vaccines, diagnostics, plasma-derived products (e.g., anti-toxins), and recombinant proteins (e.g., Interferon)

For all marketed products in China (i.e., the 37 vaccines marketed in China) the lot release is done by NICPBP typically in the local labs where the manufacturer is located.

The national stockpile is managed by China’s CDC, and distribution occurs via provincial and local CDC representatives, who run the clinics.

For emerging diseases that threaten the public, there are series of National Laws (regulations) that allow NICPBP to work together with the SFDA in generating seed stocks, QC reagents, reference reagents, and reviews, all under a “fast track” status. Their key role in release of H1N1 pan vaccine launch was reported in WHO Biologics that also published the
methodology. The Ministry of Health put significant emphasis on the development of this vaccine. NICPBP and SFDA see fast track approval as critical in times of emergent diseases.

**GENERAL DISCUSSION OF CHINA’S CURRENT CHALLENGES AND OUTLOOK**

The WTEC team’s hosts concur that animal-based potency tests are outdated and must change to *in vitro*-based methods. Development of new adjuvants is recognized as very important. China does not have any approved adjuvant other than alum. Chinese universities do conduct research, but are more focused on products as drivers rather than towards basic research. One example given was the new Hepatitis C vaccine developed by a university professor and tested for efficacy and safety in 100,000 human subjects. The clinical trial for dose determination and efficacy was reviewed by the SFDA.

China’s CDC conducts all clinical studies including design and execution. The provincial CDCs conducting the studies do not seem to face major hurdles in recruitment. Results are evaluated by their equivalent to a Data Safety Management Board (DSMB) whose membership is appointed from a pool of national and local governmental institutions and university investigators (similar to the system of conducting audits by SFDA).

NICPBP is monitoring the progress of SFDA toward obtaining WHO Certification. WHO certification is seen as essential to progress in the international marketplace.

Regarding new technologies, institute personnel are looking forward to the development of cell-based flu vaccine technology. There are a few ongoing projects in this area. In addition, they are working on:

- New adjuvants
- New technologies for expansion and scale-up
- Standardization of reference materials internationally
- Improved calibration of reference materials, tests, time, temperature, plates, materials, and reagents across international testing facilities to reduce time to assess comparable products
- Animal model for development of infectious diseases
- *In vitro* models for efficacy testing
- Quick availability to standards and reagents as well as mechanism for “harmonizing of all testing methods”
- Seeking greater international collaboration on areas relevant to harmonizing methods and reagents

**General Notes Relevant to This Area**

Vaccines (on the national list = Category 1 under the Expanded Program on Immunization [EPI] of WHO) purchased and distributed via CDC as noted elsewhere. Provincial governments (e.g., Beijing and Shanghai) buy additional vaccine (Category 2) for their citizens for which there is a co-pay. Vaccines are without cost for senior citizens and available at a lower price for children.

**CONCLUSION**

NICPBP has significant impact on vaccine availability and is responsible for batch release, including testing, reagent quality, and other governmental interactions.
National Institute of Infectious Diseases

Site Address: National Institute of Infectious Diseases
1-23-1 Toyama, Shinjuku-ku
Tokyo, 162-8640, Japan
http://www.nih.go.jp/niid/index-e.html

Date Visited: February 26, 2010

WTEC Attendees: M. Ritchey (report author), T. Leighton, R. Kumagai

Host(s): Koji Ishii, PhD, Section Chief, Department of Virology II
4-7-1 Gakuen, Musashi-murayama, Tokyo 208-0011, Japan
Tel: +81-42-561-0771
kishii@nih.go.jp
Kazuhiko Katayama, PhD, Section Chief, Department of Virology II
4-7-1 Gakuen, Masashi-murayama, Tokyo 208-0011, Japan
Tel: +81-42-561-4729
katayama@nih.go.jp
Ichiro Kurane, MD, PhD, Director, Department of Virology I
Tel: +81-3-5285-1169
Kurane@nih.go.jp
Keiko Tanaka-Taya, MD, PhD, Chief, Division of Immunization Program, Infectious Disease Surveillance Center
Tel: +81-3-5285-1111 ext.2536
ktaya@nih.go.jp
Nobuyoshi Tani, Director, Division of International Cooperation
Tel: +81-3-5285-1111 ext.2910
Tani-nob@nih.go.jp
Haruo Watanabe, MD, PhD, Deputy-Director General
and Professor, Tokyo University
Tel: +81-3-5285-1337
haruwata@nih.go.jp

BACKGROUND
This organization was established in 1947 in response to the urgent need to control infectious diseases after World War II. The National Institute of Health, which was later renamed the National Institute of Infectious Diseases (NIID) was established as a research institute attached to the Ministry of Health. Its mission is to conduct fundamental and applied research on infectious diseases and national control tests for lot release and development of antibiotics and vaccines. Prior to this date, a series of private institutes and public agencies were responsible for managing infectious disease problems within Japan. Beginning in the 1950s and going forward, the Institute focused on establishing control laboratories for dealing with infectious disease issues and related vaccines and conducting research and surveillance in support of control of infectious diseases.

The current functions of the Institute include the following:
• Basic and applied research on infectious diseases, including molecular analysis, methods for rapid diagnosis and new concept vaccines, e.g., DNA vaccines. Areas of investigation include a broad range of viral and bacterial pathogenic reagents.

• Reference services, which include storing and supplying pathogenic agents and their products, standardizing and supplying reagents and reference materials for diagnosis and surveillance of infectious diseases.

• Infectious disease surveillance, which includes collection, analysis, feedback and distribution of information on infectious diseases. Epidemiological investigations of outbreaks of disease are carried out.

• National control of biological products and antibiotics, which includes lot testing to assure potency and safety requirements are met along with development and supply of testing reagents and standards.

• International cooperation activities that include designation as a WHO Influenza Collaborative Center in addition to participation in many other WHO vaccine related programs for research, reference and surveillance activities.

• Training programs for groups and individuals from both within and outside Japan in technical areas related to controlling infectious diseases.

Departments within the NIID include the following:

• The Department of Virology I includes laboratories for special pathogens, arboviruses, neurovirology, herpesviruses, rickettsia and Chlamydia.

• The Department of Virology II includes laboratories for study of gastroenteritis viruses, enteroviruses, tumor viruses, hepatitis viruses

• The Department of Virology III includes laboratories for measles virus, rubella virus, mumps virus, acute viral respiratory infections and cytokines

• The Department of Bacteriology I includes laboratories for the study of enteric infections, emerging infections, systemic infections and oral bacterial infections.

• The Department of Bacteriology II includes laboratories for the study of antibiotics and antimicrobial resistance, mycoplasmas and haemophilus, bacteria toxins, toxoids and antitoxins, tuberculosis, pertussis and endotoxin

• The Department of Parasitology includes laboratories for Protozoa, platyhelminthes and nematodes, imported parasitic diseases.

• The Department of Pathology includes laboratories for diagnostic functions and infectious animal models, experimental pathology and molecular pathology.

• The Department of Immunology includes laboratories for viral infection and immunity. Bacterial infection and immunity, vaccine development, immune-based therapeutic intervention.

• The Department of Chemotherapy and Mycoses includes the laboratories for mycoses, cell growth and control, immune regulation, antibiotics and actinomycetology.

Additional departments include Biochemistry and Cell Biology, Medical Entomology, Mycobacteriology, Veterinary Science, and Safety Research on Blood and Biological Products.

Additional divisions include International Cooperation, Biosafety Control and Research, Radiological Protection and Biology, Experimental Animal Research, and Quality Assurance,
Other centers include Infectious Disease Surveillance, Aids Research, Pathogen Genomics, Influenza Virus Research, and Leprosy Research

DISCUSSION

Our meeting hosts provided insights into how the NIID supports disease prevention programs through research programs, surveillance of disease activity and contributions to making policy decisions and licensing vaccines.

The NIID has approximately 1000 employees with around 300 at the PhD/MD level. They have a broad range of experience with infectious diseases and their causes, with functions similar to both FDA and CDC in the United States.

Vaccine Licensing and Control

With respect to licensing vaccines for use in Japan, the NIID will work with the Pharmaceutical and Medical Device Agency (PMDA) to review applications when requested. They can also participate in inspections if requested. The PMDA is an independent agency that is charged with review of applications for pharmaceuticals and medical devices and post-marketing follow-up. (See MHLW site report for more details on the PMDA). NIID also acts as the National Control Authority, as noted in the functions listed above to perform lot release testing for marketed products and reference sera and reagents for testing.

Responsibility for animal vaccines resides with the Ministry of Agriculture, but the NIID in its Department of Veterinary Science does study Zoonoses with the aims of understanding the mechanisms of pathogenesis, transmission modes, and means for controlling their spread.

Surveillance

The Institute has an extensive program for infectious disease surveillance that includes gathering information on the frequency of more than 60 diseases. These diseases are sorted into 5 categories depending upon the severity and each category has a specific set of reporting requirements. For example, for some diseases, only a specific set of hospitals provide surveillance information. Many local surveillance operations contribute to the generation of information. The NIID can assist with diagnoses, if needed and can investigate outbreaks when necessary.

NIID also conducts an annual serosurvey to look at the level of antibodies in the population that protect against diseases for which vaccination is on the recommended schedule.

The website of NIID provides results of surveillance reports that can be accessed by the general public.

The surveillance data gathered contributes to world-wide understanding of disease patterns.

Immunization Policy

Immunization Policy is established by the Ministry of Health, Labor and Welfare. At present, the Ministry does not have a standing committee like the ACIP in the United States to recommend vaccination policy, although it does form advisory groups for review of vaccine issues. A standing committee that would act like the ACIP in the United States is a possibility for the future.

Within the NIID’s Infectious Disease Surveillance Center, there are divisions that review epidemiological data and make technical recommendations for control of infectious diseases. This Center also monitors and reviews immunization adverse event data with the goal of
providing accurate information on immunization practice and effective use of immunization to control disease. The NIID can therefore make policy recommendation for the Ministry of Health.

Other groups that can influence immunization policy include the pediatricians and their professional associations and the Japanese Association of Vaccinology.

The Japanese Association of Vaccinology was established more than 10 years ago and includes representatives from the vaccine industry, academia, and regulatory agencies. It is not for the benefit of any one group and is able to provide a balanced analysis of immunization issues.

On some specific issues we learned the following: Japan does not routinely immunize for hepatitis B whereas many other nations include this vaccine in the routine immunization schedule. The Japanese data to date indicate a lack of horizontal transmission of this disease (possibly based on the genetics of the population) and so routine immunization is not warranted. However, this policy can be changed if additional data in the future changes the overall picture.

Japan used to routinely immunize children for influenza as a means of stopping the spread of disease. An analysis of this data during the 90’s indicated that it was not effective in preventing disease in the elderly. The policy was changed to make immunization routine for the population that most seriously affected by disease, i.e., those over 64. Immunization of children then became voluntary.

**Pandemic H1H1**

The NIID contributes its expertise to development of molecular test kits for typing of strains, analysis and characterization of strains isolated in Japan and overseas, assay and pilot production of vaccines, standards and reference reagents in addition to developing candidate vaccine strains. Research on production of influenza vaccines using cell culture methods is also conducted.

Extensive surveillance was conducted across Japan with the help of the local centers in the prefecture using test kits to tract disease. Reports and disease tracking are published and available on their website.

The Ministry of Health was active in promoting the development of vaccines for this pandemic, including procuring enough vaccine from companies outside Japan to ensure that supply was sufficient (see site report on the MHLW).

**International Collaboration**

Japan is a member of the World Health Organization (WHO) and the NIID collaborates with WHO on many disease prevention efforts. In 1951, NIID was assigned as a WHO Collaborative Influenza Center and since then, many other centers and reference laboratories have become part of this effort. Many laboratories within NIID participate in efforts to isolate and identify infectious agents, investigate outbreaks, prepare and maintain supplies of reference reagents, and standardize laboratory diagnoses.

These activities are undertaken for a broad range of pathogens including Japanese encephalitis virus, polio, measles, rubella, SARS, influenza viruses, including H5 influenza, human papilloma viruses, and bacterial phages.

The NIID trains various groups and individuals on technical aspects of AIDS, polio, and leprosy.
Challenges

Japan does not currently have centers for clinical studies where novel vaccine concepts can undergo initial clinical evaluation in humans. The initial hurdles of testing a new vaccine concept for the first time are high. Since vaccines are given to healthy individuals, a large amount of safety data is required. Compared to the multi-national companies that serve the United States and Europe, Japanese companies that make vaccines are small and must carefully consider costs before taking a new vaccine concept into the clinic. Future development of government funded sites that financially support new vaccine ideas would be helpful in keeping the Japanese companies competitive and allowing good ideas to be tested sooner rather than later.

Exportation of Japanese vaccines to other countries would be helpful in generating income for additional vaccine development (but this can be difficult if regulations are not harmonized).

The Japanese culture is such that vaccines must have the highest safety profile in order to be accepted by the public. There is a need to develop better mechanisms of communication to ensure that the public and the medical community have all of the information that allows them to make good decisions regarding acceptance of vaccination.

Compensation for vaccinees and companies was required to get the population to accept vaccination for the H1N1 pandemic influenza strain. Even though laws were passed to provide compensation, uptake of the H1N1 vaccine was not as high as expected. Reasons for this included the fact that the population did not perceive the severity of the disease to be high and the vaccine may not be as safe as the ordinary seasonal flu vaccine.

Japan has a wealth of educated individuals who could make excellent contributions to the vaccine field if money were available to fund research. The NIID does not have trouble recruiting staff as there are many well-qualified researchers coming out of the Japanese universities. Our hosts noted that today there is actually an underutilization of educated individuals. Additional funds for R&D would help this situation and contribute more toward solving some of the infectious disease problems.
Osaka University, WPI Immunology Frontier Research Center (IFReC)

Site Address: Osaka University, WPI Immunology Frontier Research Center (IFReC)
3-1 Yamada-oka, Suita City
Osaka 565-0871, Japan
http://www.ifrec.osaka-u.ac.jp/index-e.php

Date Visited: February 26, 2010

WTEC Attendees: S. Jacobson (report author), S. Drew

Host(s): Professor Shizuo Akira, Director/Principal Investigator
Laboratory of Host Defense, IFReC, Osaka University
Tel: 81-6-6879-8302
sakira@biken.osaka-u.ac.jp

Professor. Ken J. Ishii, MD/PhD, Principal Investigator, Laboratory of Vaccine Science, IFReC; Project Leader, Laboratory of Adjuvant Innovation, National Institute of Biomedical Innovation (NIBIO), Program Officer; Grants in Aid for Scientific Research (KAKENHI), Program Officer, Ministry of Education, Culture, Sports, Science and Technology
Tel: 81-6-6879-8303 (IFReC)
kenishii@biken.osaka-u.ac.jp

BACKGROUND

Professor Akira heads a world class research program in the broad area of immunologic response to vaccines. He is the Director of the Laboratory of Host Defense and of the WPI (World Premier International) Immunology Frontier Research Center of Osaka University. He received his M.D. in 1977 and his Ph.D. in 1984 from Osaka University. After postdoctoral work in the Department of Immunology, University of California at Berkeley, he studied IL-6 gene regulation and signaling at the Institute for Molecular and Cellular Biology, Osaka University, and cloned transcription factors NF-IL6 (also known as C/EBP beta) and STAT3. He is one of the most widely cited scientists in immunology and has received many awards of distinction for his research, including the 2003 Takeda Medical Prize (2003), the Robert Koch Prize (2004), the Emperor's Purple Ribbon Medal (2005), the 2006 Asahi Prize (2006), the Milstein Award (2007) and the 2009 Person of Cultural Merit from the government of Japan. In 2009, he was elected a Foreign Associate of the U.S. National Academy of Science. He is a frequent lecturer at scientific gatherings around the world.

Professor. Ken J. Ishii, M.D./Ph.D. joined our meeting with Professor Akira. Professor. Ishii is a program officer for the Ministry of Education, Culture, Sports, Science and Technology (MEXT). He is also a key member of the WPI Immunology Research Center. His laboratory focuses on understand the physiological roles and the molecular mechanisms of immune recognition of nucleic acids in the innate and adaptive immunity systems. His team in Professor Akira's center also studies the mechanisms of vaccines and adjuvants through recognition by innate immune receptors such as Toll-like Receptors (TLRs), nucleotide-binding oligomerization domains or NOD-like receptors (NLRs), retinoic acid-inducible protein-I-like receptors (RLRs), and double-stranded DNA sensors.
The Host Defense Laboratories and the WPI Immunology Frontier Research Center study the fundamental mechanisms of innate immunity. The innate immune system senses invading microbial pathogens and plays an essential role in the induction of inflammatory responses and sets the stage for adaptive immune responses. Germline-encoded pattern-recognition receptors (PRRs) expressed on innate immune cells such as macrophages and dendritic cells are responsible for recognizing pathogen-associated molecular patterns (PAMPs), which represent conserved molecular features in microbial pathogens. Through generation of knockout mice, Professor Akira has demonstrated that a family of Toll-like receptors (TLR) recognizes a variety of PAMPs such as lipopolysaccharide, lipoprotein and nucleic acids derived from bacteria, viruses and protozoa to elicit innate immune responses. Professor Akira’s laboratory has also demonstrated that a family of RIG-I-like RNA helicases (RLR) participate in TLR-independent recognition of nucleic acids derived from different types of RNA viruses in the cytoplasm. He has also found a sensor function that is not yet fully understood that recognizes double-stranded DNA in the cytoplasm.

Professors Akira and Ishii envision creation of novel vaccines, adjuvants, and immunotherapies for intervention in infectious diseases and other immunological disorders. They believe that a deeper and more thorough understanding of the basic science of immunological host defense mechanisms at the molecular, cellular, and system levels will accelerate the design, development, scale-up and manufacturing of new safe and effective vaccines and adjuvants.

**ACTIVITIES AND FINDINGS**

Our discussion focused around a novel vaccine paradigm described by Professor Akira. Professor Akira’s work strives to develop a fundamental understanding of immunity, immune response, and vaccines at the most basic level using basic science research to unlock the physiological secrets of how the human body elicits an immune response. Professor Akira utilizes the engineering principles of monitoring outputs as a function of input parameters to probe the complexities of immune response. Vaccines and adjuvants are the inputs to the human body immune response system; a “black box” of extraordinary complexity. The levels of immunogenicity and adverse reactions that develop provide the measurable outputs of this system and suggest the structure and dynamics of the system. The approach being taken by Professor Akira hopes to uncover the secrets within this “black box”, with the goal of gaining a higher level of understanding of how vaccines and adjuvants work in the human body and elicit immune responses. Such an understanding will be invaluable in the design of new (and better) vaccines and adjuvants that provide greater immunity with minimal adverse reactions. It will also provide a more transparent understanding of how to evaluate vaccines. Along these lines, an issue frequently raised during our discussion was vaccine safety.

Both vaccine efficacy and vaccine safety were discussed as equal hallmarks in this research. Professor. Ishii explained that adjuvants may be powerful stimulants of innate immune response, but may also stimulate inflammatory response or more rarely be linked to neurologic side effects. Thus the desirable effect of increasing vaccine effectiveness may be balanced by the potential to generate adverse effects. Only by understanding more about the molecular aspects of adjuvant interaction with pattern recognition receptors (PRRs), specifically Toll-like receptors (TLRs), are we likely to understand the mechanisms by which they produce their effects. We were impressed by the intense focus of Professor Akira’s teams on both safety and efficacy of vaccine and adjuvant development.

Our hosts posited that by gaining a basic understanding of how vaccines and adjuvants work at the molecular level, vaccine development and manufacturing can be simplified, effectively
reducing the time required to create, evaluate, and produce vaccines. A deeper understanding may also support prediction of vaccines’ safety and efficacy, individual biomarkers, or surrogate markers for vaccine efficacy and safety in human populations. As the granularity of understanding improves it may be possible to predict vaccine potency across individuals, allowing a more effective approach to personalized vaccines. Professor Akira provided an example of how a single gene deletion in test mice can result in loss of vaccine efficacy. Their studies with gene deletion are already unraveling the complexities of innate immunity and its communication with adaptive immunity.

Professor Akira provided a list of research directions that would provide important advances in vaccine development:

- Advances in the basic understanding of how immunity memory is achieved and maintained will elucidate the complexities of immune response to pathogens.
- Research on biomarkers or surrogate markers to predict vaccine efficacy and safety will provide a critical step towards developing personalized vaccines.
- Bioinformatics research that analyzes data and develops mathematical models to help identify biomarkers and establish reliable surrogates of immune response would provide much needed value. Stochastic functional transformations may be at the core of such models. Initial work on statistical prediction modeling may be a fruitful first step in this direction.
- Research on vaccine delivery systems (i.e., mechanisms that transfer the vaccine into the human body) will require interdisciplinary efforts to facilitate advances and breakthroughs in this domain.
- Social science research that works to better explain and educate the population on the importance, effectiveness, and safety of vaccines will eliminate many of the current barriers to rapid vaccine development.

**SUMMARY AND CONCLUSIONS**

Our meeting with Professor Akira provided a clear and candid picture of his world-class research into the mechanisms of innate immunity. The next frontier will be at the interface of innate immunity and adaptive immunity where funding and focus are critically needed. The basic approach of understanding vaccine immune response at the molecular level provides the potential to change the way in which vaccines are designed, evaluated, and manufactured. The seminal ideas under investigation by Professor Akira will require input from an interdisciplinary group of microbiologists, physicians, mathematicians, and others to meet its full potential in accelerating the development and manufacture of new safe and effective vaccines. Unique collaborations between the BIKEN Foundation and Osaka University foster an environment where discovery and development flourish.

**REFERENCES**


Panacea Biotec Ltd.

Site Address: Panacea Biotec Ltd
B-1 Extn./ A-27, Mohan Co-op
Indl. Estate, Mathura Road,
New Delhi-110 044, India
www.panaceabiotec.com

Date Visited: October 19, 2010

WTEC Attendees: J. Bielitzki, M. DeHaemer (report author), F. Heineken, M. Ritchey

Host(s): Dr. Sanjiv Sharma, Vice President, Regulatory Affairs
Tel: +91-11-4167 8000; Fax: +91-11-4167 9063
sharmasanjiv@panaceabiotec.com
R. K. Suri, Chief Executive Biologicals
Tel: +91-11-4167 8000 (ext. 2064); Fax: +91-11-4167 9027
rksuri@panaceabiotec.com
Kapil Mishra, Business Manager – InLicensing
Tel: +91-11-4167 9000 (ext. 2048); Fax: +91-11-4167 9027
kapilmishra@panaceabiotec.com
M. S. Rehman, General Manager – Regulatory Affairs
(Vaccines & Biopharmaceuticals)
Tel: +91-11-4167 8000 (ext. 2334; Fax +91-11-4167 9063
shafiqurrahman@panaceabiotec.com

BACKGROUND

Panacea Biotec is a mid-size corporation (about $200 million revenue in recent years) with business lines in pharmaceuticals, biopharmaceuticals, and vaccines. It ranks among the largest vaccine and biopharmaceutical companies in India with about 5000 employees, including the sales force. It has been listed by Business Week among the 100 fastest growing companies in Asia. Panacea has representatives in North America, Europe, and Africa and engages in international collaborations for marketing, manufacturing, and research with corporations and governments. Among them are Novartis Vaccines & Diagnostics, Sanofi Aventis, U.S. National Institutes of Health, NVI, GSK, National Institute of Immunology of India, Biotech Consortium India Ltd, and PT Bio Farma, Indonesia. Panacea Biotech Ltd. has product sales in 55 countries.

With vaccine production facilities in Delhi and in North India, Panacea has the capacity for 50 million doses per year of bulk antigens (diphtheria, tetanus, whole cell/acellular pertussis, Haemophilus influenzae type b conjugate, recombinant hepatitis B); and 2 billion doses per year of vaccine formulations.

Panacea claims 10 leading brands among pharmaceuticals and biopharmaceuticals in India, with a strong (No. 1 or No. 2) leading position in organ transplantation, diabetes and pain management. Pharmaceutical production facilities are certified by USFDA, German and Brazilian regulatory agencies.
Having begun vaccine manufacturing in 1988, there are two leading brands in Panacea's vaccine line: Easy Five (DTP-Hep B-Hib), one of three fully liquid PQ pentavalent vaccines globally; and Polprotec (joint venture with Novartis) polio vaccine. Panacea has nine WHO pre-qualified vaccines, enabling it to be among the largest suppliers to United Nations programs. UNICEF recently awarded a multiyear contract for vaccines valued at $23 million.

TECHNOLOGIES
Panacea Biotec employs 391 persons in research and has five research and development centers for drug discovery, drug delivery, and vaccines. Research centers have good access to the academic community to engender support for work on computer simulation or other tasks. Research focus areas are as follows:

- NCE research: Metabolic disorders, anti-infectives, CNS
- NBE research: Autoimmune diseases, dermatology, metabolic disorders
- Drug delivery research: Oral modified release, nanotechnology, depot injections, transdermal systems
- Vaccine research: New generation combination vaccines, new prophylactic vaccines (pediatric and adult)

The Saha Vaccines Research Center is in Delhi. New approaches for vaccines include work on dengue fever, virus like particles "VLP", and "depot injection" (injections that release vaccine over 30 days or more).

DISCUSSION OF ISSUES RELATED TO VACCINE MANUFACTURING
Our hosts saw advantages in India for pharma and vaccine research, specifically the availability of scientifically trained manpower, a climate for high R&D investment (5-6% of returns), and favorable regulatory environment in India. In addition, due to favorable labor conditions, production in India will be cost competitive.

With the growth of vaccine production and new facilities coming online, there is a challenge to get experienced manpower. However, this problem will subside as new workers in the field gain experience.

Beyond the home market of India, qualification by governments in targeted market areas of Southeast Asia, Africa, and South America caused additional expense and delays before products could be sold. Although there is talk of accomplishing some "harmonization" of national certification requirements among various nations, such is not in the foreseeable future. Nevertheless Panacea expects growth in international sales.

With some pride Panacea takes responsibility for distributing vaccines, managing shippers, and providing special temperature controlled shipping containers. Panacea has its central warehouse at Delhi. The company uses its expertise in cold chain management for storage and distribution of vaccines under monitored conditions using a system of vaccine vial monitors, data loggers, ice boxes, coolant, cold rooms, and refrigerated vehicles. This ensures that the vaccines remain safe and effective despite changes in ambient temperature conditions.
TRENDS DISCUSSED IN THE PANACEA BIOTEC LTD ANNUAL REPORT

- Vaccines will be a more lucrative business than pharmaceuticals over the next 5 years.
- While pharmaceutical products' revenues are projected to grow at 14% per annum in India, vaccine revenues will grow about 18% for the next 5 years.
- Panacea Biotec Ltd will invest 9% of net turnover in R&D
- A 13% annual growth in vaccine sales is forecast worldwide for 5 years
- A worldwide vaccine market of $36 billion is predicted by 2013
- Pediatric vaccines will dominate the market
- The developing world requires 124 million doses per year for newborns
- India exports 50% of its vaccine production

REFERENCES

Panacea Biotec Ltd Website: http://www.panaceabiotec.com
PATH (China)

Site Address: PATH, People's Republic of China Field Office
Suite 2113 Ruoy Chai International Building
No. 8 Yong An Dong Li Jian Guo Men Wai
Chaoyang District, Beijing 100022, P.R. China
http://www.path.org/index.php

Date Visited: March 3, 2010

WTEC Attendees: N. Iyer (report author), J. Bielitzki, C. Gay, R. Kumagai

Host(s): Jiankang (Jack) Zhang, Representative, China PATH
Tel: +86-10) – 85288211
jzhang@path.org

BACKGROUND ON PATH

PATH (known by the acronym but standing for Program for Appropriate Technology in Health) is an international nongovernmental organization (NGO) that administers international health programs by working with government and industry to mature the infrastructure necessary to accelerate availability of vaccines, accessories, and delivery systems in areas of need. A key component is providing recommendations to develop the infrastructure necessary to distribute products that meet international standards.

- PATH manages collaborations (Meningitis A vaccine development with India)
- PATH assists in finding vaccines from manufacturers certified by the World Health Organization

PATH’s goals are to utilize the existing infrastructure to upgrade vaccine production systems and capacity, including development of new vaccines. PATH in China, with the Chinese government, maintains numerous relationships with international groups such as Global Alliance for Vaccine and Immunization (GAVI), IVI, and the UN Foundation.

CHINA’S VACCINE DEVELOPMENT SYSTEM

Mr. Zhang offered an extensive background on the structure, function, and operational aspects of the Chinese vaccine development system. China sees the 21st century as the century of bioscience. Basic research investment and priorities are established by the Ministry of Science and Technology.

China’s population of 1.3 billion, with an annual birthrate of 16 million, requires significant commitment of resources on the part of the government. There is significant focus on HIV/AIDS vaccine, tuberculosis (especially with respect to the Multiple Drug Resistant (MDR) strains), malaria vaccine, and continued interest on endemic infectious diseases. At present, there are about 750,000 HIV positive individuals in China and 1,000,000 tuberculosis new cases per year, about 7-8% of which are MDR. Childhood vaccinations include those on the Expanded Program for Immunization (EPI) and eight additional common infectious agents.

The Chinese program has achieved success in the areas of childhood vaccination and in family planning. China has invested 3 billion RMB for the acquisition of childhood vaccine.
China does not qualify under the “list of poor countries” to receive the vaccines listed in the standard protocol from Global Alliance for Vaccine and Immunization (GAVI) and those on the EPI. The immunization needs of a population that includes approximately 250 million people under the age of 16 years represent a significant expenditure for the Chinese government. Some vaccines (e.g., DPT) are given multiple times to infants and children. There is interest in manufacturing methods that can reduce production costs associated with the total amount of vaccine needed annually.

Much of China’s EPI vaccine is produced by the Chinese National Biotec Group (CNBG), a consortium of State Owned Enterprises (SOEs). This consortium consists of 6 regional vaccine institutes focusing vaccine production that recently (2009) merged with another SOE, Sinopharm, which is China’s largest manufacturer of pharmaceuticals. The merger of these SOEs is coordinated by the State-owned Assets Supervision and Administration Commission (SASAC). By manufacturing different vaccines, CNBG meets about 80% of China’s domestic need for EPI vaccination series. The remaining 20% is manufactured by other local vaccine manufacturers.

China classifies its vaccine needs into 2 categories:

- **Category 1**: EPI vaccines, which are mandatory for children and required prior to enrollment in the educational system
- **Category 2**: Vaccines that are not mandatory and can be purchased by the general population; in some population centers the local government may supply vaccines for its residents

A policy change now allows both SOEs and privately held companies to manufacture and sell vaccines for both categories. Today there are about 30 different companies (privately owned, SOEs and joint ventures) in China plus imported products that are overseen by the Chinese FDA, SFDA. The base population requires a vaccine infrastructure that is capable of meeting national needs. Government structure and support can rapidly redirect resources to SOEs and private industry to meet needs. Since the site visit, China’s SFDA and affiliated institutions have met WHO indicators as a functional vaccine regulatory system, which will enable Chinese companies to apply for WHO pre-qualification. This, in turn, will permit them to sell vaccines to United Nations agencies and other countries (see [http://nbr.org/research/activity.aspx?id=141](http://nbr.org/research/activity.aspx?id=141)). At the present time, China (i.e., the Chengdu Institute of Biological Products) exports some Japanese encephalitis (JE) vaccine to India, Lao PDR, Sri Lanka, and other countries. These sales are made on a country to country basis, not through the WHO system, although WHO pre-qualification is planned for the future. PATH has been very involved in efforts to control JE outbreaks in India and elsewhere in Asia (PATH et al. 2009).

Production costs and price to the government are key elements in the government's acquisition strategy. The Chinese CDC is responsible for the purchase and acquisition of vaccines. Vaccines are distributed from the national CDC to the provincial CDC to local districts. All 14 vaccines listed under the EPI are administered and distributed by the local CDC governed and operated clinics.

China’s CDC has another important function. It conducts clinical trials for vaccines. It works with local CDCs but designs clinical studies at an acceptable power-level, conducts the clinical studies and provides the results to the vaccine manufacturers. The system supports rapid testing of vaccines during periods when vaccine testing and release is a national imperative.
This has a tremendous advantage in costs for smaller manufacturers and uniformity within the clinical studies (e.g., when comparing multiple H1N1pan vaccines). Clinical trials may typically involve 10,000 subjects. China has recently been credited with successfully conducting a 100,000 person clinical trial for a new Hepatitis E vaccine that was developed at a Chinese academic institution (Zhu et al. 2010).

Vaccines manufactured in China are tested by the National Institute for the Control of Pharmaceutical and Biological Products (NICPBP, which also provides reference reagents and seed strains and develops the tests necessary for product validation and release. The Chinese Pharmacopeia, which is published by a special committee, includes four categories of biologics: vaccines, diagnostics, plasma-derived products (e.g., anti-toxins), and recombinant proteins (e.g., Interferon). Products include those associated with both Chinese traditional medicine and Western medicine. The Chinese FDA (SFDA) relies heavily on the expertise of NICPBP, university, and industry personnel for conducting audits and inspections.

INTERNATIONAL ISSUES

At present, Chinese regulations and structure meet national needs, but these processes are maturing to the global level and are moving towards meeting the ICH and cGMP standards. China recognizes that to have a presence in the international vaccine marketplace, it must be able to participate in the WHO-approved process. This internationally recognized process reviews policies, procedures, and practices used to manufacture vaccine products. Now that the Chinese SFDA and related agencies have been accepted (in March 2011) as a functioning regulatory system, the door is open to Chinese companies that want to seek WHO pre-qualification for their products.

Participation in the WHO-approved process is seen as a high-priority national goal by the Ministry of Health that will permit China to contribute its share in supporting Africa and other developing nations where vaccine needs are significant. In addition to immediate benefit to the SOEs, significant benefit will go to commercial producers, since WHO pre-qualification opens the door for Chinese vaccine products to enter the international marketplace.

REFERENCES


PATH (India)

Site Address: PATH
A-9 Qutab Institutional Area
New Delhi 110 067 India

Date Visited: October 18, 2010

WTEC Attendees: J. Bielitzki, M. DeHaemer, F. Heineken, M. Ritchey (author)

Host(s): K.A. Balaji
Program Manager-India, Advancing Rotavirus Vaccine Development
PATH
A-9 Qutab Institutional Area
New Delhi 110 067, India
Tel: +91 11 2653 0080
bananath@path.org

Dr. Kamini Walia, PhD, MPH
Director, Research & Development
PATH
A-9 Qutab Institutional Area
New Delhi 110 067, India
Tel: +91 11 2653 0080 (211)
Kwalia@path.org

PATH (Program for Appropriate Health Technology), a catalyst for global health, was established more than 30 years ago for the purpose of making contraception available to women in developing nations. This non-profit has since evolved into an organization whose focus is to provide sustainable, culturally relevant solutions to health problems in developing nations at affordable costs. They are headquartered in the United States with offices around the world and programs that affect 70 countries. Partnerships with both public and private organizations are used to accomplish their goals.

One area of focus for PATH is to assist developing nations in acquiring the technology to make vaccines locally for diseases that have significant impact for their own and surrounding nations. At present, it takes many years longer than it should to introduce a newly available vaccine to developing countries. A rotavirus vaccine program was established in 2003 to shorten this time frame. Three vaccine manufacturers in India are involved in this program, with one ready for Phase III clinical studies. The role of the PATH organization is to provide access to relevant technology, materials and expertise to the vaccine companies. Some of the assistance they provided in this program is access to starting materials, expertise from NIH and training in laboratory assays. PATH is also able to assist with arranging for clinical studies. Joint meetings among the participants were helpful in accelerating the process as the companies learned from each other. Engaging more than one participant in this program has been more cost effective and faster than other programs where only one partner was selected.

Other programs underway include vaccine development for malaria. This program is at the preclinical stage and PATH is working with partners in India to perform preclinical studies and prepare clinical supplies. There is also a program in India for a pneumococcal conjugate
vaccine to protect against serotypes relevant to India. Other diseases for which vaccines are needed include HIV and cholera among others.

The market in India for vaccines includes both a private and public sector, with 80% in the public sector. Newly developed vaccines available as imports would only be used in the private sector because of the cost. When local companies begin to produce these vaccines, it will be possible to make them more accessible to the population at large.

Regulations for vaccines involve both state and central authorities and additional oversight for genetically engineered products. Although there is not a clear path for expedited approval, an EMEA or FDA approved product can be reviewed more quickly. PATH has developed a tutorial on CD to provide some guidance on the regulatory pathways.

Input into vaccine policy can come from the Indian Academy of Pediatrics and the National Advisory Group on Immunization.

Challenges in vaccine development also include intellectual property (IP) issues.

There is an anti-vaccine lobby group that most recently targeted Hib vaccines on the basis that the disease is not of sufficient prevalence to require an immunization program. In India it is relatively easy to file litigation that is in the public interest.

PATH’s role in facilitating access to technology, materials and training for vaccine companies in India provides a means of reducing costs and shortening the time frame to development and use of vaccines important for the region.

REFERENCES

www.path.org
Serum Institute of India Ltd.

**Site Address:** Serum Institute of India Ltd.
212/2, Hadaspar
Pune-411028, India
www.seruminstitute.com

**Date Visited:** October 22, 2010

**WTEC Attendees:** J. Bielitzki (report author), M. DeHaemer (report author), F. Heineken, M. Ritchey

**Host(s):** Dr. S.V. Kapre, Executive Director
212/2, Hadaspar
Pune-411028, India
Tel: +91-20-26602394; Fax: +91-20-26993921
skapre@seruminstitute.com
Mr. S.M. Dodwadkar, Senior Director, International Business
Tel: +91-20-26993900; Fax: +91-20-26993924
serumexports@vsnl.com

**BACKGROUND**

Serum Institute of India Ltd. (SII) is one of the top two large biotechnology companies in India, with revenues of about $200 million reported for 2010. The fifth largest manufacturer of vaccines in the world, SII was founded in 1966 in response to a dire national need for large volumes of vaccine at affordable prices. The company produces 15 products, including recombinant, conjugate, and combination vaccines as well as anti-cancer vaccines. SII is WHO certified and exports large volumes of vaccines to 140 countries, predominantly in South America, Africa, and Southeast Asia. The company does not export to the heavily regulated markets of the United States, the European Union, Australia, or New Zealand.

SII’s mission includes the requirement to manufacture large quantities of vaccines at affordable and competitive prices, successfully handling perishable product, and maintaining quality. SII is the world’s largest producer of the measles and DTP group of vaccines. Notable are its measles-rubella vaccine and DTB-HB combination vaccine. SII was contracted by the World Health Organization in 2009 to begin manufacturing of H1N1pan vaccine, resulting in production of a nasal spray type vaccine.

SII produces approximately 400 million doses per year, with 200 million doses of rubella vaccine and 100 million doses of mumps vaccine.

The company recently received an award from the Pan-American Health Organization for its contributions to health in South and Central America—specifically for the elimination of rubella.

**TECHNOLOGIES**

SII is working on novel vaccines and improving vaccine delivery with emphasis on meningitis, rotavirus, and monoclonal antibodies for rabies. The company has an active program to develop vaccines using in house developed conjugate technology, for example, a pneumonia
vaccine that will contain the specific serotypes that cause disease in the region. They are also working in the cancer vaccine area.

SII has USFDA approval for its oncology vaccine facility. Its production lines are automated, state-of-the-art with respect to finish and fill, as well as having continuous automated quality monitoring and quality testing.

Serum Institute of India has set up Serum Bio Pharma Park, India’s first biotech special economic zone (SEZ). The SEZ park of 55 acres is adjoining the company’s manufacturing unit in Pune and will produce biotechnology products. Planned investment is approximately $300 million. A vaccine production rate of one billion doses of vaccine annually is projected for the SEZ.

DISCUSSION OF ISSUES RELATED TO VACCINE MANUFACTURING

SII hosts general comments for advancing the field of vaccine manufacturing include:

- The need for **uniform standards for conduct of clinical studies** of prospective products, suggesting an international standards body should be developed and sanctioned by all interested governments.

- The need for **international harmonization of regulations**. They observed that there was frequent inconsistency appearing in the approval processes, perhaps incorporating political considerations and other local, non-scientific interests.

- The need for improvement/reduction in **export/import barriers** for vaccines.

- The need for **standards and qualification of base materials**, as well as standards for control and characterization of base materials.

- Public reaction in India against a vaccine for fear of **Guillain-Barré Syndrome** effect. In spite of government campaign in the case of the H1N1 pandemic and although 800,000 doses were available free, the public did not respond.

- **Bioinformatics advancement.** In particular appropriate 3D modeling needs to be commonly available to assist antibody research, enabling better prediction and selection of research approaches.

- **Reduction in litigation** about vaccine effects and reduction of the fear of litigation.

REFERENCES


Company presentation to WTEC delegation, October 22, 2010. [http://www.seruminstitute.com](http://www.seruminstitute.com)
Figure B.11. WTEC Team at Serum Institute (*left to right*: F. Heineken, M. DeHaemer, M. Ritchey, J. Bielitzki, Exec. Dir. S.V. Kapre, Senior Dir. S. M. Dodwadkar).
Sinovac Biotech Ltd. (China)

**Site Address:** Sinovac Biotech Ltd. (China)
No. 39 Shangdi Xi Road, Haidian District
Beijing, 100085, People’s Republic of China
http://www.sinovac.com/

**Date Visited:** March 2, 2010

**WTEC Attendees:**
N. Iyer (report author), J. Bielitzki, C. Gay, R. Kumagai, J-Y. Zhang

**Host(s):**
Chris Lee, International Business Development
Tel: +86-10-82799659
icd@sinovac.com

Weining Meng, International Business Development
Tel: +86-10-82799378
mengwn@sinovac.com

**BACKGROUND**

Sinovac is a private, publicly traded company, currently traded on the NASDAQ exchange. It focuses on the research and development, manufacturing, and marketing of both human and animal vaccines. Tangshan Yian Biologicals was the original research and development component of Sinovac, but it was converted to an animal vaccine company in 1993; it now manufactures rabies vaccine.

**VACCINE DEVELOPMENT AT SINOVAC**

**Products**

Sinovac’s primary products are:

- Healive, an inactivated vaccine against hepatitis A
- Bilive, a combined vaccine for hepatitis A and B
- Anflu, an inactivated split-virion vaccine for annual influenza; it is a non-adjuvanted vaccine without preservatives

In addition Sinovac has produced vaccines against swine influenza, Panflu 1, H1N1pan, and human and animal rabies. In 2008, Sinovac successfully registered pandemic influenza A/H5N1 vaccine in Mexico and Hong Kong. In 2009 it licensed EUVAX-B and BILIVE, Hepatitis A and B, in Korea.

Research efforts are underway at Sinovac to produce approved vaccines for Japanese encephalitis (JE), hand foot and mouth disease, HIV, and epidemic meningitis. Company researchers are also working on the production of a vaccine against enterovirus 71 (EV71), which affected 480,000 children in China in 2008, with about 300 deaths in children.

Upon direction from the Ministry of Health, Sinovac focused resources on the development of a vaccine against severe acute respiratory syndrome (SARS). Scientists worked closely with
CDC from isolation to manufacture. In 3 years they were able to conduct a Phase 1 clinical study (safety). This vaccine was placed on hold following the early testing and is available should future epidemics occur. While SARS remains a potential threat, stockpiling of vaccine has not occurred.

In 2009 Sinovac manufactured and released 12.5 million doses of H1N1pan using conventional egg-based technology. It had fast-track review and release priority based on national directives. Preliminary information on production of H1N1pan was shared with other vaccine manufacturers to facilitate meeting the national needs. Ten companies were directed by the national government to produce the vaccine. Sinovac was among the first to share information on the use of a single-dose non-adjuvanted vaccine for protection against H1N1pan. Clinical trials for dose determination and efficacy were conducted on a fast track through the Chinese CDC and reviewed and approved by the SFDA. In its 2009 H1N1pan production, Sinovac participated in the Influenza Vaccine Supply Taskforce (IVSTF) with GSK, Sanofi, and Novartis, under the coordination of the WHO.

Sinovac was one of the early private entrepreneurial ventures that started developing the Category 2 non-mandatory vaccines that can be purchased by the general population. Because the distribution for these vaccines is limited to domestic use, Sinovac management focused on expanding the company's market reach within China.

**National Vaccine Distribution**

Vaccines on the national list (i.e., Category 1 under the Expanded Program on Immunization of the WHO) are purchased and distributed by CDC. The provincial level of CDC buys additional vaccines in Category 2 and distributes these to local clinics for its residents. For non-pediatric Category 2 vaccines there is a co-pay, but Category 2 vaccines are provided without cost to senior citizens and at a reduced cost for children.

**Production**

At the time of the WTEC visit, Sinovac was following China's GMP guidelines, but during 2010 new guidelines are expected that will be similar to European standards. An audit is scheduled by IVI.

Manufacturing schedules and priorities for non-emergency use is determined by market factors. Actual production time (e.g., Anflu) is around the standard 4 to 5 months.

Sinovac has both a syringe-fill and vial fill/finish capability.

Production capacity for Sinovac's Hepatitis A vaccine is at 10 million doses/year, for influenza at 8 million doses/year, with additional fill/finish capacity for 20 million doses/year.

The company recently acquired a facility for live virus vaccine production. Sinovac is receptive to acting as a contract manufacturing organization/contract research organization (CMO/CRO). Company management plans to expand current capacity by acquisition; a second plant has been acquired for influenza vaccine production.

Company managers are very keenly watching the progress of SFDA to get WHO certification; they consider national certification to be of benefit to the entire vaccine industry.
Appendix B. Site Reports

Therapeutic Goods Administration (TGA), Australian Government Department of Health and Aging

Site Address: Therapeutic Goods Administration (TGA)
Australian Government Department of Health and Aging
136 Narrabundah Lane,
Symonston, ACT 2069, Australia

Date Visited: February 23, 2010

WTEC Attendees: M. Ritchey (report author), S. Drew, T. Leighton, S. Jacobson

Host(s): Dr. Graham Dickson, MGGS (Hons), MHA, Director, Clinical Evaluation Section 2,
Office of Prescription Medicines
Tel: +61 2 6232 8113; Fax: +61 2 6232 8140
grahame.dickson@health.gov.au
Dr. Gary Grohmann, FASM, Director of Immunobiology, Office of Laboratories and Scientific Services
Tel: +61 2 6232 8490; Fax: +61 2 6232 8564
gary.grohmann@tga.gov.au
Chris Rolls BSc (Hons), Principal Scientist, Immunobiology Section,
Office of Laboratories and Scientific Services
Tel: +61 2 6232 8498; Fax: +61 2 6232 8481
chris.roolls@tga.gov.au

BACKGROUND

The Therapeutic Goods Administration of Australia (TGA) is the regulatory authority to conduct assessment and monitoring activities to ensure that therapeutic goods are of acceptable standards with the aim of ensuring that the population has access to advances in technology in a reasonable timeframe. It regulates medicines, medical devices, blood and tissues for the human population. Therapeutic goods include goods and devices intended to prevent, diagnose, cure or alleviate disease, test for susceptibility to disease, pregnancy related goods, or any good intended to influence a physiological process. These goods must be licensed and when they complete the process they are listed on the Australian Registry of Therapeutic Goods (ARTG).

Regulation is based on risk management to ensure safety and free industry from unnecessary regulatory burden. The three main functions of this organization are (1) auditing and assessing the quality of the manufacturing process, (2) pre-marketing assessment, and (3) post-marketing surveillance for compliance. Regulations are very close to those of the European Agency for the Evaluation of Medicinal Products (EMEA).

The TGA consists of a Business Management Group, an Executive Support Group, and the following Offices: Complementary Medicine; Devices, Blood and Tissues; Laboratories and Scientific Services; Manufacturing Quality; Medicines Safety Monitoring; Non-prescription medicines; and Prescription Medicines.

Individuals we met with were involved with WHO and had worldwide access to information on vaccines, especially in the influenza field. This facilitates their ability to provide efficient
and meaningful oversight for vaccines in Australia. For example, Dr. Grohmann serves on the WHO committees for strain selection for flu vaccines and the Global Action Plan group that is assisting developing country manufacturers in their efforts to manufacture influenza vaccine. Mr. Rolls serves as a WHO expert on review of regulatory systems.

**RATE-LIMITING STEPS FOR DEPLOYMENT OF INFLUENZA VIRUS VACCINES**

1. Getting in the field strains to make selections for reassortants is the first rate-limiting step. There is a world-wide network to do this, but it takes time.

2. The second bottleneck is the generation of reassortants that is the first step in providing seeds for manufacturers to use in production. There are only three places in the world that do this. The reassortants then need to be screened for the proper characteristics, including sufficient yield in the manufacturing process. (The manufacturers do this step.) It is interesting to note that production strains prepared by reverse genetics instead of the classical reassortant methodology have yet to yield strains that give a sufficient yield for production purposes.

3. Reagents and standards need to be made, which is a partnership between the manufacturers and regulatory authorities.

Figure B.12 describes the process steps involved in deploying pandemic influenza vaccines, and the average timeframes.

![Figure B.12. Steps involved in the development and approval of southern hemisphere inter-pandemic and pandemic influenza vaccines (from Grohmann 2009).](image-url)
PANDEMIC H1N1
The TGA attribute the success of timely registration and distribution of the H1N1 pan vaccines in Australia to rapid, good communication with all of the involved organizations that are involved in the entire process from strain selection and monitoring through packaging and distribution. It meant that decisions needed to be made in the absence of complete information, e.g., standard dose, without adjuvant, and to use multidose vials as the capacity to produce all single doses was not practical because of supply and storage limitations. The vaccine completed registration requirements at the beginning of September and began to be distributed a few days later.

Despite the availability of 22 million doses, only 2 million were used in the voluntary immunization program. This could be attributed to the fact that it required a separate immunization and the perception that the pandemic H1N1 pan vaccines were not as safe as the seasonal vaccine. This coming season the H1N1 pandemic strain will become part of the seasonal vaccine product.

H5N1 AND OTHER POTENTIAL PANDEMICS
With respect to H5N1, preparedness for an outbreak includes gaining experience with the potential vaccines strains by manufacturing candidates and studying them in clinical trials. There is agreement among regulatory authorities in developed countries to accept each others’ dossiers and data. The TGA has adopted EU guidelines which facilitates this process

One gap that was identified in the influenza program was the lack of a program to develop candidate production strains from the group of H2 strains that are circulating in animals, e.g., pigs. These strains have not been circulating in the human population for many years, so individuals under 50 are at increased risk. Programs to generate potential candidates for H5, 7 and 9 types exist, but not for H2 strains

WORLDWIDE ASSISTANCE
We were also informed about a WHO program to assist vaccine manufacturers in developing countries to begin manufacturing influenza vaccines. Seed money is provided with the goal of getting matching or multiples of the WHO contribution to get the manufacturers started. Thus far, five manufacturers have had successful start-up programs in regions in Asia, Indonesia and South America. WHO is actively promoting new, more rapid technologies for manufacturing influenza vaccine. Figure B.13 depicts technologies selected by a number of different Asian manufacturers, with their timelines to production.
Figure B.13. Technologies chosen by six WHO grantees (red) to build in-country influenza vaccine production capacity, in addition to technologies being deployed by other manufacturers (black), with relative time and investment projections for the technologies (from Grohmann 2009).

Stockpiles have also been developed for H5N1 vaccines. The WHO has 50 million doses, and Australia has stockpiled 3M doses. The WHO has a virtual stockpile of AV drugs, and Australia has 6 M doses of Tamiflu and Relenza.

LIMITATIONS ON TGA RESOURCES

The section of the TGA that is responsible for vaccines is small, with 25 individuals participating as compared to the U.S. FDA where there are around 250 individuals available for performance of similar functions. The organization is a Cost Recovery Organization, meaning that the amount of money in their yearly budget is based on fees that they receive from the product licensing and inspection processes. As a result, they do not have any research capabilities as does the FDA. They do have a future goal of being able to participate in making reassortants for influenza vaccines, as this could contribute to more rapid identification of suitable production strains. They are also looking toward expanding the number of inspectors to relieve the extensive travel and workload of the current group. Recruitment of qualified individuals can also be limited because of their limited resources.

POTENTIAL TO EXPAND CAPACITY

In discussion of the possibility of using animal vaccine facilities to expand capacity for human vaccines in an emergency situation, it was noted that these vaccines are under different regulatory agencies within Australia, but there may be some opportunities, especially with respect to filling areas.

REFERENCES


TGA. 2010. Website: http://www.tga.gov.au
University of Melbourne, Department of Microbiology and Immunology, David C. Jackson Laboratory

Site Address: University of Melbourne, Department of Microbiology and Immunology
David C. Jackson Laboratory
Parkville, Melbourne
Victoria, 3010, Australia
http://www.microbiol.unimelb.edu.au/
http://www.microbiol.unimelb.edu.au/research/groups/jackson.html

Date Visited: February 21, 2010

WTEC Attendees: T. Leighton (report author), S. Drew, S. Jacobson, M. Ritchey

Host(s): David C. Jackson, PhD, Professor and Principal Research Fellow
Department of Microbiology and Immunology
Faculty of Medicine, Dentistry & Health Sciences
Tel: +61 3 8344 9940; Fax: +61 3 9347 1540
d.jackson@microbiology.unimelb.edu.au
davidcj@unimelb.edu.au

BACKGROUND
Dr. Jackson is an immunochemist whose research interests focus on the mechanisms controlling vaccine antigenicity and immunogenicity.

VACCINE DEVELOPMENT
Dr. Jackson was awarded the David Syme Prize in 2004 for creating synthetic self-adjuvantizing vaccines that target dendritic cells (DCs) and are effective against viruses, bacteria and tumors. The synthetic vaccine scaffold contains Pam2Cys-S-[2,3-bis(palmitoyloxy)-propyl]-cysteine and a DC activating danger signal (e.g., lipopolysaccharide) targeting a Toll-like receptor (Figure B.14).
What else is attractive to DCs apart from geometry? (from Zeng et al. 2002).

The synthesis of Pam2 peptides (30-40 residues) is rapid and scalable. DC uptake of Pam2 synthetic vaccine constructs is rapid and quantitative (Figure B.15).

These lipopeptide constructs cause DCs to mature through a TLR2 targeting and loading mechanism (Figure B.16). Antibody responses are T helper cell dependent. The technology is also capable of breaking self antigen tolerance (e.g., an anti-LHRH vaccine that can down-
regulate testosterone production, which could be of use in treating hormonal-dependent cancers)

**What branched lipopeptides do to DCs**

D1 cells: murine splenic-derived DC maintained in immature state

Figure B.16. What branched lipopeptides do to dendritic cells (courtesy of D.F. Jackson).

**Lipopeptide Vaccines**

A Group A Streptococcal M protein vaccine administration by an intranasal route was very effective in inducing humoral and secretory opsonizing antibody production (Figure B.17).

**Figure B.17.** Secretory IgA is elicited by lipopeptide vaccines (from Batzloff et al. 2006).
The opsonizing antibodies produced by this lipoprotein vaccine were protective against a bacterial challenge and reduced bacterial load (Figure B.18).

Figure B.18. Lipopeptides vaccination with Group A streptococcal (GAS) lipopeptide vaccine reduces bacterial load and allows survival (from Batzloff et al. 2006).

Incorporation of the human papilloma virus (HPV) L2 peptide into the lipoprotein scaffold induced antibody production against multiple HPV strains. Intranasal vaccination allowed protection against HPV-16 or HPV-45 challenges (Figure B.19).
Figure B.19. Novel intravaginal human papilloma virus (HPV) challenge using a fluorescent reporter (from Alphs et al. 2008).

Intranasal administration of a lipopeptide influenza vaccine reduced untreated viral titers by 99.7% and provided complete protection from a lethal viral challenge (Figure B.20).
Figure B.20. (Right) Lipopeptides induce strong anti-‘flu CD8+ T cell-mediated viral clearing responses; (Bottom left) ... and prevent death following lethal challenge (from Jackson et. al. 2004).

The acute protective antibody responses are also retained as enduring memory responses (Figure B.21).
CONCLUSIONS AND VACCINOLOGY IMPLICATIONS

Dr. Jackson summarized his conclusions about lipopeptide-based vaccines as follows:

- They work
- Defined mechanism
- Simple and robust
- Easily characterized
- Safe: minimum toxicity and site reactions; accepted by TGA
- Better alternative to weak and/or toxic adjuvants
- Attractive to dendritic cells; unusual geometries are advantageous
- Induce Ab or CMI
- Defined specificity
- Longevity: Ab, memory – CTL
- Applicable to multiple indications

These results suggest that this innovative influenza vaccine modality, utilizing conserved viral epitopes, could bypass the necessity of having prior availability of emergent pandemic or seasonal strains to achieve vaccine protection. This potential is also reflected in the broad range of anti-HPV (HPV-15, -5, -18, and -45) cross-reacting antibodies elicited by a single L2 lipopeptide vaccine.
The barriers to advancing Dr. Jackson’s very promising vaccine platform are the lack of government supported translational vaccine clinical trial centers and the nascent state of Australian venture capital.

REFERENCES
Zhejiang Tianyuan Bio-Pharmaceutical Co., Ltd.

Site Address: Zhejiang Tianyuan Bio-Pharmaceutical Co., Ltd.
56 Tianhe Road, Linping, Yuhang District,
Hangzhou City, Zhejiang Province
PC 311100, People’s Republic of China

Date Visited: March 4, 2010

WTEC Attendees: C. Gay (report author), J. Bielitzki, N. Iyer, R. Kumagai, J. Zhang

Host(s): Qinglang Li, MD, Deputy General Manager, Research and Development
Tel: 0571-2628-6028
Chen Xue Kui, Deputy General Manager, Operations
Tel: 0571-2628-6027
chenxuekui@hotmail.com
chenxuekui@126.com
Xiang (Sam) Liao, Head, Business Development & Licensure Asia
Novartis Vaccines and Diagnostics, Inc.
350 Massachusetts Ave., Cambridge, MA 02139-4182
Tel: +1 617 871 8130
Sam.liao@novartis.com
Mr. Guo, Head of Manufacturing

BACKGROUND

Zhejiang Tianyuan Bio-Pharmaceutical Co., Ltd. is one of the largest private pharmaceutical companies in China. The company started in 1989, initially as a diagnostic facility for the diagnosis of hepatitis B. It has 10 senior scientists and 20 scientists and technicians dedicated to vaccine development. At present the facilities include 27,000 square meters.

Novartis is currently negotiating with the Chinese government the acquisition of Tianyuan Bio-Pharmaceuticals for $125 million. Xiang Liao will become the new COO following completion of the acquisition. The intention is to couple Tianyuan’s strengths with Novartis technology without losing the essential identity of the original Chinese company.

VACCINE PRODUCTION

Tianyuan was one of the first of China’s private pharmaceutical companies to comply with China’s cGMP standards. It produces or is developing vaccines against influenza, meningitis A and C, diphtheria-pertussis-tetanus, Hantavirus (HFRS), Japanese encephalitis virus (JE), a conjugated polysaccharide meningitis, H1N1pan and rotavirus. It can produce a maximum of 200 million doses of vaccine within its facilities.

One of the vaccines currently under development is a quadrivalent influenza vaccine that includes influenza A/H5N1 and seasonal influenza viral strains. The company obtained a license to market pandemic Influenza A/H1N1 in 2009.
Tianyuan has the ability to produce 120 million doses of (monovalent) A/H1N1 per year or about 15 million doses of seasonal flu, 3 million doses of HFRS, 5 million doses of JEV, up to 30 million doses of meningitis vaccine, and 15 million doses of DPT.

Seasonal influenza vaccine is sold to India and Chile.

Tianyuan Bio-Pharmaceuticals was able to develop its pandemic A/H1N1 vaccine in a record 3½ months, with the following timeline:

- June 18, 2009 – Obtained A/H1N1 virus strains from Chinese CDC
- June 28, 2009 – Completed the preparation of master seed bank
- July 10, 2009 – Completed the manufacture of four batches of final bulk
- July 30, 2009 – Initiated clinical trials
- August 30, 2009 – Clinical trials completed
- September 4, 2009 – Applied to Chinese FDA for batch release
- September 10, 2009 – Manufacturing process approved
- September 25, 2009 – Registration approved
- September 28, 2009 – GMP process approved
- October 1, 2009 – 5 million doses produced and released

The Chinese government procured 23 million doses of A/H1N1 from Tianyuan Bio-Pharmaceuticals in 2010.

Eight other companies have been licensed to produce A/H1N1 vaccines in China. Tianyuan Bio-Pharmaceuticals Company’s pandemic A/H1N1 vaccine was tested by the National Institute for Control of Pharmaceutical and Biological Products (NICPBP) and found to have the best potency and quality (residual albumen, etc.) of the 8 manufacturers. One of the reasons for this success was the addition of a second purification step in the manufacturing process.

Among Tianyuan’s biggest challenges, according to Mr. Guo, are access to new technologies for improving speed, cost, and quality of the manufacturing process; Mr. Chen added that other challenges include the ability to market vaccines’ attributes compared to competitors.

Once a vaccine is approved for release the Chinese government can provide the master seed and manufacturing process for Category 1 products to other manufacturers to improve distribution.

**GENERAL REVIEW OF VACCINE DEVELOPMENT IN CHINA**

The NICPBP provides master seed stocks to biologics manufacturers.

To distribute and sell vaccines in China the clinical trials to support the release of product must be conducted in China. The Category 1 vaccines fall into this category.

Many of the clinical trials for vaccine evaluation are conducted by the Chinese CDC. Vaccine manufacturers provide the clinical materials and any specifications they would like to see integrated in the clinical trial. Sponsoring institutions can finance the independent monitoring of the clinical trials if desired.

There are 31 provincial CDCs in China. Two of the 31 specialize in vaccine clinical trials but a company can seek the execution of clinical trials in any of the provincial CDCs. The data
generated from a clinical trial in a provincial CDC will allow the vaccine to be distributed anywhere in China; that is, there are no requirements to test the efficacy and safety of a vaccine in more than one province. The two provincial CDCs that conduct vaccine trails specialize in this type of study; this experience facilitates design and execution of the trial.

In the past, vaccine acquisition, storage and distribution was handled by the 31 provincial CDCs. Since 2008, local level CDCs may store and distribute vaccines. There are approximately 2600 local level CDCs in China. Vaccine distribution is facilitated by the number and ability to focus these local CDCs to provide products to the local hospitals and clinics. Local hospitals and clinics purchase vaccine from the local CDC. Adverse event reporting goes back to the CDC. For severe adverse events, reports are forwarded to the CDC within 2 hours and an investigating team is on site within 24 hours.

Vaccines in China fall into two categories: (also see PATH report):

- **Category 1**: required “expanded protocol for immunization (EPI)” MMR, DPT, Polio, Hepatitis A and B, and other vaccines (total of 14 required), which are provided to the population at no cost.
- **Category 2**: vaccines that are not required and the cost is an obligation to the patient in total or as a copayment. Some rich provincial cities can procure directly from the company.

GSK, Sanofi, Novartis are among the multinational companies that market vaccine in China. Novartis is considering a fill/finish facility for 20-45M doses.

Engineering needs include improved filtration/purification methodologies and scaled density gradient centrifugation. Tianyuan management firmly believes that China’s (Ministry of Health/SFDA) efforts to obtain WHO certification will expand access to international markets.
Zydus Cadila

Site Address: Zydus Cadila
Sarkhej-Bavla N.H. No 8A, Moraiya
Sanand taluka, Ahmedabad
Gujarat 382 210, India
http://www.zyduscadila.com

Date Visited: October 20, 2010

WTEC Attendees: J. Bielitzki, M. DeHaemer, F. Heineken, M. Ritchey (author)

Host(s):
Dr. Reihhard Glueck, CSO
Zydus Cadila
Sarkhej-Bavla N.H. No 8A, Moraiya
Sanand taluka, Ahmedabad
Gujarat 382 210, India
Tel: +91 2717 666458
reinhard.glueck@zyduscadila.com

Dr. P.Y. Guru, General Manager, Animal Research Facility
Zydus Cadila
Sarkhej-Bavla N.H. No 8A, Moraiya
Sanand taluka, Ahmedabad
Gujarat 382 210, India
Tel: +91 2717 250801
purushottamguru@zyduscadila.com

Dr. Amaresh Sinha, Sr. General Manager-Head (Vaccines)
Zydus Cadila
Sarkhej-Bavla N.H. No 8A, Moraiya
Sanand taluka, Ahmedabad
Gujarat 382 210, India
Tel: +91 2717 250319
asinha@zyduscadila.com

Dr. P.M. Patel, Vaccine Production
Zydus Cadila
Sarkhej-Bavla N.H. No 8A, Moraiya
Sanand taluka, Ahmedabad
Gujarat 382 210, India

Dr. Gaurav Gupta, Virology
Sarkhej-Bavla N.H. No 8A, Moraiya
Sanand taluka, Ahmedabad
Gujarat 382 210, India
Dist: Ahmedabad 382 210, India

Zydus Cadila is an innovative global pharmaceutical company that discovers, develops, manufactures and markets a broad range of healthcare products. The group's operations range from active pharmaceutical ingredient (API) production to formulations, animal health products and cosmeceuticals. Headquartered in the city of Ahmedabad in India, the group has
global operations in four continents spread across the United States, Europe, Japan, Brazil, South Africa, and 25 other emerging markets. Zydus Cadila’s vision for vaccines is to produce the best quality, cost effective and affordable vaccines in state-of-the-art GMP facilities.

The vaccine market in India is challenging. Disposable income per capita is low, making high sales dollar volumes difficult to achieve, despite the large population. Government support for vaccines other than the essential pediatric vaccines is limited and forecasts for long term growth of this market are lacking. Despite this, Zydus Cadila is dedicated to developing and providing relevant vaccines at affordable prices. It has acquired Etna Biotech in Italy, which will provide the company a research center along with technologies and seed materials for both viral and bacterial vaccines, in addition to an export market for their vaccines.

Zydus Cadila currently produces a globally marketed duck embryo rabies vaccine that is WHO pre-qualified and being supplied to UN agencies. An inactivated Influenza vaccine for pandemic H1N1 was offered for sale on June 10, 2010, 9 months after receiving the starting materials. This was the first one available in India. The company also currently sells a typhoid vaccine. Vaccines in the pipeline include human papilloma virus, malaria, hepatitis B, nasal influenza, measles, mumps, varicella, and DTP-Hib. Some of these involve international collaborations. A combination of DTP-Hib (conjugated to tetanus) with Hepatitis B to form a pentavalent vaccine is planned and will include a future acellular pertussis component to replace the whole cell pertussis component. A protein conjugated typhoid polysaccharide vaccine that improves on the currently marketed vaccine is also being developed. A purified chicken embryo cell culture vaccine for rabies to replace the duck embryo vaccine has been developed and awaits market authorization. A patented chick embryo cell culture technology and adaptation of the duck embryo strain was developed in house.

The company plans to employ patented technology for a measles reverse genetics platform to produce vaccines for HPV and malaria. There is proof of concept in animals for a number of antigens (Hepatitis B, HIV, mumps, etc.). This platform has the advantages that it requires a lower dose since it is a replicating vector and preferentially infects antigen presenting cells and lymphoid tissues. It is also based on a currently used measles virus attenuated vaccine that has an extremely good safety record.

The company is in the final stages of developing a seasonal influenza vaccine and plans to use reverse genetics to enhance its ability to produce influenza vaccines. This platform will also be useful for future viral vaccines such respiratory syncytial virus and parainfluenza virus.

Future programs will encompass other vaccines important for the area such as dengue, JE, shigella, hepatitis A and meningitis (using conjugate technology). WHO prequalification will be sought for the new vaccines.

Zydus has constructed state-of-the-art facilities to support its vaccine programs. A chick embryo cell culture facility, with BSL-3 areas, was built to support influenza and rabies vaccines. Facilities for production of the pentavalent vaccine are under construction and others are planned for vaccines in the pipeline. The Quality Unit also has modern facilities with a state-of-the-art animal facilities that are accredited by AAALAC (Association for Assessment and Accreditation of Laboratory Animal Care International). Zydus is well-positioned to provide new vaccines for India and other global markets.

REFERENCES

www.zyduscadila.com
## APPENDIX C. GLOSSARY OF ACRONYMS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAALAC</td>
<td>Association for Assessment and Accreditation of Laboratory Animal Care International</td>
</tr>
<tr>
<td>AAFP</td>
<td>American Academy of Family Physicians</td>
</tr>
<tr>
<td>ACIP</td>
<td>Advisory Committee on Immunization Practices (U.S.)</td>
</tr>
<tr>
<td>AIDS</td>
<td>acquired immune deficiency syndrome</td>
</tr>
<tr>
<td>APHIS</td>
<td>Animal and Plant Health Inspection Service (USDA)</td>
</tr>
<tr>
<td>API</td>
<td>active pharmaceutical ingredient</td>
</tr>
<tr>
<td>APVMA</td>
<td>Australian Pesticides and Veterinary Medicines Authority</td>
</tr>
<tr>
<td>AQIS</td>
<td>Australian Quarantine and Inspection Service</td>
</tr>
<tr>
<td>ARS</td>
<td>Agricultural Research Service (USDA)</td>
</tr>
<tr>
<td>BSE</td>
<td>bovine spongiform encephalopathy</td>
</tr>
<tr>
<td>BSL</td>
<td>Biosafety Level</td>
</tr>
<tr>
<td>CBER</td>
<td>Center for Biologics Evaluation and Research division (USFDA)</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention (U.S.)</td>
</tr>
<tr>
<td>CDL</td>
<td>Central Drugs Laboratory (India)</td>
</tr>
<tr>
<td>CDSCO</td>
<td>Central Drugs Standard Control Organization (India)</td>
</tr>
<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
</tr>
<tr>
<td>CFSE</td>
<td>CarboxyFluorescein Succinimidyl Ester</td>
</tr>
<tr>
<td>cGMP</td>
<td>current good manufacturing practice</td>
</tr>
<tr>
<td>CHMP</td>
<td>Committee on Medicinal Products for Humans (EU/EMEA)</td>
</tr>
<tr>
<td>CMO</td>
<td>contract manufacturing organization</td>
</tr>
<tr>
<td>CNBG</td>
<td>Chinese National Biotec Group</td>
</tr>
<tr>
<td>CRO</td>
<td>contract research organization</td>
</tr>
<tr>
<td>CTD</td>
<td>Common Technical Document (EU/EMEA)</td>
</tr>
<tr>
<td>CVB</td>
<td>Center for Veterinary Biologics (USDA)</td>
</tr>
<tr>
<td>CVMP</td>
<td>Committee for Medicinal Products for Veterinary Use (EU/EMEA)</td>
</tr>
<tr>
<td>DBT</td>
<td>Department of Biotechnology (India)</td>
</tr>
<tr>
<td>DC</td>
<td>dendritic cell</td>
</tr>
<tr>
<td>DHS</td>
<td>Department of Homeland Security (U.S.)</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>DOD</td>
<td>Department of Defense (U.S.)</td>
</tr>
<tr>
<td>DTaP</td>
<td>diphtheria-tetanus-acellular pertussis</td>
</tr>
<tr>
<td>ECDC</td>
<td>European Centres for Disease Prevention and Control</td>
</tr>
</tbody>
</table>
Appendix C. Glossary of Acronyms

ELISA enzyme-linked immunosorbent assay
EMEA European Agency for the Evaluation of Medicinal Products
EPI expanded program on immunization (WHO)
EU European Union
FDA Food and Drug Administration (U.S.)
GAO Government Accountability Office (U.S., until 2004 called the General Accounting Office)
GAVI also, the GAVI Alliance, formerly known as the Global Alliance for Vaccines and Immunisation; only the acronym is used now
GCP Good Clinical Practice
GLP Good Laboratory Practice
GMOs genetically modified organisms
GMP Good manufacturing practice
GSK GlaxoSmithKline Biologicals
HA hemagglutinin (or haemagglutinin)
HAV hepatitis A vaccine [virus]
HBV hepatitis B vaccine [virus]
HCD high cell density (bioreactor)
HHS Department of Health and Human Services (U.S.)
HI hemagglutination inhibition
Hib or Hflu Haemophilus influenzae type b
HIV human immunodeficiency virus
HPAI high pathogenic avian influenza (HPAI)
ICH International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IND Investigational New Drug application process (USFDA/CBER)
IP intellectual property
IPV inactivated polio vaccine
ISO International Standards Organization
IVI International Vaccine Institute
IVSTF Influenza Vaccine Supply Taskforce
JEV Japanese encephalitis vaccine
JICA Japanese International Cooperation Agency
MAFF Ministry of Agriculture, Forestry and Fisheries (Japan)
MHC major histocompatibility complex
MHLW Ministry of Health, Labor and Welfare (Japan)
MMR measles-mumps-rubella
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA</td>
<td>New Drug Application (USFDA)</td>
</tr>
<tr>
<td>NIBIB</td>
<td>National Institute of Biomedical Imaging and Bioengineering of NIH (U.S.)</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health (U.S.)</td>
</tr>
<tr>
<td>NICPBP</td>
<td>National Institute for the Control of Pharmaceutical and Biological Products (China)</td>
</tr>
<tr>
<td>NIP</td>
<td>National Immunization Program (U.S.)</td>
</tr>
<tr>
<td>NLRs</td>
<td>nucleotide-binding oligomerization domains or NOD-like receptors</td>
</tr>
<tr>
<td>NRC</td>
<td>National Research Council (part of the U.S. National Academies)</td>
</tr>
<tr>
<td>NSF</td>
<td>National Science Foundation (U.S.)</td>
</tr>
<tr>
<td>NVAC</td>
<td>National Vaccine Advisory Committee</td>
</tr>
<tr>
<td>NVRQS</td>
<td>National Veterinary Research and Quarantine Service (Korea)</td>
</tr>
<tr>
<td>ORA</td>
<td>Office of Regulatory Affairs (USFDA)</td>
</tr>
<tr>
<td>OTGR</td>
<td>Office of the Gene Technology Regulator (Australia)</td>
</tr>
<tr>
<td>PAMP</td>
<td>pathogen-associated molecular pattern</td>
</tr>
<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
</tr>
<tr>
<td>PCV7</td>
<td>pneumococcal conjugate vaccine</td>
</tr>
<tr>
<td>PMDA</td>
<td>Pharmaceutical and Medical Devices Agency (Japan)</td>
</tr>
<tr>
<td>PMED™</td>
<td>Particle Mediated Epidermal Delivery device (PowderMed, Ltd.)</td>
</tr>
<tr>
<td>PRR</td>
<td>pattern-recognition receptor</td>
</tr>
<tr>
<td>QMS</td>
<td>Quality Management System [standard, ISO]</td>
</tr>
<tr>
<td>RIG</td>
<td>intracellular retinoic-acid-inducible-gene-like (receptors)</td>
</tr>
<tr>
<td>RLRs</td>
<td>retinoic acid-inducible protein-I-like receptors</td>
</tr>
<tr>
<td>RNA</td>
<td>ribonucleic acid</td>
</tr>
<tr>
<td>RSV</td>
<td>respiratory syncytial virus</td>
</tr>
<tr>
<td>RT-PCR</td>
<td>reverse transcription polymerase chain reaction</td>
</tr>
<tr>
<td>S&amp;T</td>
<td>science and technology</td>
</tr>
<tr>
<td>SARS</td>
<td>severe acute respiratory syndrome</td>
</tr>
<tr>
<td>SEC</td>
<td>Securities and Exchange Commission (U.S.)</td>
</tr>
<tr>
<td>SFDA</td>
<td>State Food and Drug Administration (People’s Republic of China)</td>
</tr>
<tr>
<td>SPF</td>
<td>specific pathogen-free</td>
</tr>
<tr>
<td>TB</td>
<td>tuberculosis</td>
</tr>
<tr>
<td>TCR</td>
<td>T-cell receptor</td>
</tr>
<tr>
<td>TGA</td>
<td>Therapeutic Goods Authority of the Department of Health and Aging (Australia)</td>
</tr>
<tr>
<td>TLR</td>
<td>Toll-like receptor</td>
</tr>
<tr>
<td>USDA</td>
<td>U.S. Department of Agriculture</td>
</tr>
<tr>
<td>USFDA</td>
<td>U.S. Food and Drug Administration</td>
</tr>
<tr>
<td>Acronym</td>
<td>Definition</td>
</tr>
<tr>
<td>---------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>USP</td>
<td>United States Pharmacopeia</td>
</tr>
<tr>
<td>VAR</td>
<td>varicella</td>
</tr>
<tr>
<td>VLP</td>
<td>virus-like particle or pseudovirion</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>WTEC</td>
<td>World Technology Evaluation Center, Inc.</td>
</tr>
<tr>
<td>YLL</td>
<td>years of life lost</td>
</tr>
</tbody>
</table>
APPENDIX D. DEFINITIONS OF TERMS

Note: Definitions here are largely derived from open online sources Wikipedia (http://en.wikipedia.org) and/or Dictionary.com (http://dictionary.reference.com), chiefly its Merriam-Webster's Medical Dictionary entries.

adaptive immunity – the ability of the vertebrate immune system to generate immunity to and also recognize and remember specific pathogens in order to prepare itself to mount a stronger attack should the pathogen be encountered again

adjuvant – a vaccine ingredient that is mixed with an immunogen in order to facilitate or enhance immune response

antigen – any molecule or portion of a molecule that can induce an immune response (such as of a toxin)

attenuated – rendered less virulent

B cell(s) – lymphocytes produced in the bone marrow of most mammals that play a large role in the humoral [bodily fluids] immune response; their principal function is to make antibodies against soluble antigens; they are an essential component of the adaptive immune system

bacterial ghosts – nonliving bacterial cells that are useful as vaccines because they retain the morphology and structural integrity of their living counterparts without their properties, and they have intrinsic adjuvant properties

BHK – baby hamster kidney cells, an immortalized cell line often used in molecular genetics

CD4 – (cluster of differentiation 4) a cellular surface glycoprotein expressed by mature Th (helper) cells, regulatory T cells, monocytes, macrophages, and dendritic cells. On T cells, CD4 is the co-receptor for the T cell receptor and amplifies the signal generated by the TCR

CD8 – (cluster of differentiation 8) a transmembrane glycoprotein that serves as a co-receptor for the TCR. Like the TCR, CD8 binds to a major histocompatibility complex (MHC) molecule, but is specific for the class I MHC protein; it is predominantly expressed on the surface of cytotoxic T cells, but can also be found on natural killer cells

cytokine(s) – a group of proteins and peptides that function in organisms as signaling compounds and are important in both innate and adaptive immune responses; due to their key role in the immune system, they are involved in a variety of immunological, inflammatory and infectious diseases

disposable manufacturing line – a vaccine production system that has many single use components, thereby enabling shorter product turnover time and lower costs (see also wave bioreactor)

epitope – a region on the surface of an antigen capable of eliciting an immune response and of combining with the specific antibody produced by such a response

H3N2 – a subtype of the influenza A virus that contains the proteins hemagglutinin (H) and neuraminidase (N) on its surface coating; H3N2 viruses infect humans and pigs, and in each species, the virus has mutated into many strains

H5N1 – a subtype of the influenza A virus that can cause illness in humans and many other animal species; a bird-adapted strain of H5N1 is the causative agent of what is commonly known as “avian influenza” or “bird flu”; it is endemic in many bird populations, especially in SE Asia

humoral – the part of the immune response that involves antibodies secreted by B cells and circulating in bodily fluids
Appendix D. Definitions of Terms

**immunogen** – any substance, cell, or organism introduced into the human body in order to provoke an immune response

**MCH** – major histocompatibility complex, a large genomic region or gene family found in most vertebrates that plays an important role in the immune system, autoimmunity, and reproduction; the proteins encoded by the MHC are expressed on the surface of cells to T cells that have the capacity to kill or coordinate the killing of pathogens or infected or malfunctioning cells

**morbidity** – the symptoms of or rate of sickness and spread of a disease

**NFkB** – a protein complex found in all cell types that helps regulate the cell’s response to bacterial or viral antigens, thus helping orchestrate its immune response

**split/subunit** – a vaccine prepared by growing a virus strain in the conventional egg-based process then

**vaccine** – treating the recovered virus to remove the core, leaving only the outer antigenic determinants; most egg-based vaccines today are split or subunit vaccines; they are less likely to cause adverse reactions than vaccines containing the whole virion

**Tamiflu** – the trade name of an oral antiviral drug Oseltamivir marketed by Hoffmann-La Roche (Roche) and generally available by prescription only that is used in the treatment and prophylaxis of both Influenza virus A and B; it acts as a transition-state analogue inhibitor of influenza neuraminidase, preventing new viruses from emerging from infected cells

**T helper (Th)** – (also known as effector T cells) cells that are a subgroup of lymphocytes that play an important role in establishing and maximizing the capabilities of the immune system; although they cannot themselves kill infected host cells or pathogens, they are actively involved in activating and directing other immune cells

**T cell(s)** – a subgroup of white blood cells known as lymphocytes, produced by the thymus, that play a central role in cell-mediated immune response; they can be distinguished from other lymphocyte types, such as B cells and NK cells, by the presence of a special receptor on their cell surface that is called the T-cell receptor (TCR)

**Toll** – a key component of the innate immune system of the fruit fly; in the mid-1990s, the mammalian equivalent, Toll-like receptors (TLR), were identified

**tumorigens** – agents capable of causing tumors

**variolation** – the deliberate inoculation of an uninfected person with the smallpox virus (as by contact with pus) to protect against severe forms of smallpox, widely practiced before the era of vaccination

**Vero cell(s)** – lineages of cells used primarily in virus cell cultures/replication that were isolated from kidney epithelial cells extracted from African green monkeys; they constitute a continuous cell lineage that can be replicated through many cycles of division and not become senescent

**virion** – a complete virus particle that consists of an RNA or DNA core with a protein coating and that is the extracellular infective form of a virus

**wave bioreactor** – a form of disposable manufacturing system that uses a large disposable poly bag in which components are combined and then agitated with a rocking motion, causing an observable wave action
whole-virus – a vaccine produced from the intact virus that has been rendered inactive or attenuated

vaccine – including killed and split virus preparations; a vaccine for pandemic influenza is likely to be a whole-virus vaccine

zoonotic – pertaining to or describing an infectious disease that has originated in animals and/or is able to be transmitted from animals to humans
WTEC Books:


Other Selected WTEC Panel Reports:

(Imperial College Press will publish the first three reports)

Research and development in simulation-based engineering and science (1/2009)

Research and development in catalysis by nanostructured materials (11/2008)

Research and development in rapid vaccine manufacturing (12/2007)

Research and development in carbon nanotube manufacturing and applications (6/2007)

High-end computing research and development in Japan (12/2004)

Additive/subtractive manufacturing research and development in Europe (11/2004)

Microsystems research in Japan (9/2003)

Environmentally benign manufacturing (4/2001)

Wireless technologies and information networks (7/2000)

Japan’s key technology center program (9/1999)

Future of data storage technologies (6/1999)

Digital information organization in Japan (2/1999)

Selected Workshop Reports Published by WTEC:

International assessment of R&D in stem cells for regenerative medicine and tissue engineering (4/2008)

Manufacturing at the nanoscale (2007)

Building electronic function into nanoscale molecular architectures (6/2007)

Infrastructure needs of systems biology (5/2007)

X-Rays and neutrons: Essential tools for nanoscience research (6/2005)

Sensors for environmental observatories (12/2004)

Nanotechnology in space exploration (8/2004)

Nanoscience research for energy needs (3/2004)

Nanoelectronics, nanophotonics, and nanomagnetics (2/2004)

Nanotechnology: Societal implications (12/2003)

Nanobiotechnology (10/2003)

Regional, state, and local initiatives in nanotechnology (9/2003)

Materials by design (6/2003)


Nanotechnology research directions (1999)

All WTEC reports are available on the Web at http://www.wtec.org.