In November 1984, the World Health Organization and the Rockefeller Foundation initiated a collaborative program to assist key developing countries to produce tissue culture-based rabies vaccine (1). The Veterinary Products Company of Colombia (VECOL) was selected as the first technology transfer recipient. The program wended its way through many obstacles. But, finally, in 1999, a license was granted to VECOL to produce and sell VERO-based human rabies vaccine in Colombia. A short review of this remarkable history is in order.

Beginning of the Effort

Rockefeller Foundation Programs.

In 1978, Kenneth S. Warren was appointed Director, Health Sciences Division with a mandate to stimulate basic and applied research on parasitic diseases through a program called “The Great Neglected Diseases of Mankind (GND).” Soon, Dr. Warren became an advocate for the accelerated vaccination of the world’s children. Early in 1984, he was the prime mover in the creation of the Task Force for Child Survival, a committee formed to raise funds for the purchase of vaccines and to coordinate the vaccination programs of WHO, UNICEF, UNDP, the World Bank and the RF. Also in 1984, the RF co-founded the WHO Programme for Vaccine Development (PVD), an effort that continues to this day to fund vaccine research in six major infectious disease areas. The PVD and the GND focussed on the research and development of vaccines and the Task Force raised funds to supply the six existing vaccines of the Expanded Programme on Immunization (EPI) to poor countries. This left an important gap in a comprehensive program to meet the vaccine needs of developing countries. In November 1984, the author proposed that the Health Sciences Division of the RF initiate a long-term program to support the transfer of tissue culture-based vaccine production technology to selected large or medium-sized developing countries (1). The vaccines proposed for inclusion were rabies, Japanese encephalitis, dengue and yellow fever. This program was complemented in 1990 by the Children’s Vaccine Initiative that was an attempt by development agencies and industry to distribute at low price newly licensed vaccines to developing countries or to develop and produce new vaccines to meet developing country needs.
What was the rationale behind the 1984 program?

“Most large and medium-sized developing nations should acquire the capacity to produce inexpensive, safe and efficacious vaccines. These are needed to sustain preventive health programs and to gain effective control over the sale and distribution of biological products. For viral vaccines, this necessarily implies mastery of large-scale tissue culture production techniques. As of 1984, only China, Vietnam, Iran and Brazil produce some or all of their needs of viral vaccines required for the EPI program.

The ability to produce tissue culture viral vaccines has two important secondary benefits: 1) the techniques for production of human viral vaccines are virtually identical to those for making veterinary vaccines. If technology transfer can be shared between the health and agriculture sectors there should be effects on both human health and improved food production. 2) mastery of all steps in the production, safety and efficacy testing of vaccines will produce a team experienced in the basic techniques of biologics quality control. Quality control is a responsibility for safeguarding national health that few developing nations have acquired.

Finally, the ability to make vaccines successfully may permit countries to decide not to manufacture certain products themselves, but to depend on imports. Unless both vaccine production expertise and some experience with the cost of vaccine production is acquired, nations will not have a data base to make a rational cost-effective decision regarding source, quality and other factors relating to vaccine manufacture.”

The proposal went on to describe rabies as causing 28-36,000 human deaths per year with 4 million persons receiving post-bite rabies vaccination. It noted that safe and efficacious tissue culture-based human rabies vaccines manufactured in the USA and Europe were too expensive to be used widely in developing countries. Instead, most developing countries produced in animals a Semple-type vaccine that often lacked potency and resulted in neurological side effects. In addition, dog and cat populations required annually 250 million doses of rabies vaccines. In short, there was a need in many countries for an inexpensive yet potent tissue culture-based rabies vaccine.

Then the proposal described opportunities for increasing the use in developing countries of improved Japanese encephalitis vaccines – but that is another story.

WHO Programs.

During the 1960s and 70s, the Veterinary Public Health offices of WHO and PAHO promoted the production of veterinary rabies vaccines in tissue culture, principally on BHK-21 cells. When the Pasteur Institute and Pasteur Vaccines developed and licensed a human veterinary vaccine in the stable cell line, VERO, it seemed that a technology affordable by developing countries was at hand.
In October 23-26, 1984, WHO held a Consultation on Transfer of Technology for Production of Rabies Vaccine (2). Following this meeting, the Director-General of WHO approved the establishment of a Group of Experts to implement the recommendation of the Consultation that the technology of producing human rabies vaccines be transferred to larger developing countries.

A Meeting of the WHO Group of Experts (GOE) on Rabies Vaccine Production Techniques was held almost immediately, in 20-22 December, 1984 (3). The GOE included S.B. Halstead (Chair), G. Baer (Rapporteur), Professor H. Lundbeck (Sweden), Dr. P. Reculard (France), G.S. Schild (England), A.L. van Wezel (Netherlands), G. Letchworth (USA) and the WHO staff, Dr. F. Assaad, K. Bogel, J.F. Dunne, P. Sizaret and Mr. T. Topping.

The GOE recommended use of the PV tissue culture-adapted strain of rabies virus and VERO cells as the substrate for manufacture of veterinary and human rabies vaccines by developing countries. Site visits were to be made to selected countries with a target of choosing two to participate in technology transfer projects which were to begin in 1985 with funds provided by the Rockefeller Foundation. Members were tasked to provide advice on standards for the production and control of tissue cultures and viruses needed for human rabies vaccines and for quality control testing of vaccine and to devise a means to train personnel in the production of rabies vaccine.

Progress.

1985. In this year, three of the GOE’s laboratories, Rijksinstitut voor Volksgezondheid en Milieuhygiene (RIVM), Bilthoven, Netherlands, Federal Research Institute for Animal Virus Diseases, Tubingen, Germany and Centers for Disease Control (CDC), Atlanta, Georgia initiated an effort to produce a WHO rabies seed virus. Each lab grew various tissue culture-adapted rabies virus strains in VERO cells, testing yield of infectious virus and rabies glycoprotein.

Members of the GOE visited Burma, Colombia, Egypt, China, India and Indonesia to assess present methods of production of human rabies vaccines and the capability of these countries to participate in a technology transfer project. With the assistance of Dr. Tom Yuill, the Minister of Health of Colombia agreed in principal to a rabies vaccine technology transfer project that had as its aim the production of human rabies vaccine in a veterinary biological products facility. In August, the Directors of VECOL and PAHO signed an agreement for technical cooperation with regard to the production of biologicals for “veterinary and human use.”

1986. On 16-17 January, a WHO Consultation was held on Transfer of Technology for Production of Rabies Vaccine (4). In attendance were: S.B. Halstead (Chair), G. M. Baer (Rapporteur), F. Brown, L. Crawford, G. Letchworth, H. Lundbeck, J.R. Mitchell, P.
Reculard, L.G., Schneider, A.L. van Wezel and WHO staff, F. Assaad, K. Bogel, T. Fujikura, V. Gratchev, F.X. Meslin, J. Petricciani and P. Sizaret. Site visit reports to the above countries were presented. Colombia (VECOL) was selected as initial transfer recipient with RIVM chosen as transfer R&D and training site. The RF allocated funds to RIVM to purchase equipment for a training facility, purchase equipment for production and quality control testing in Colombia, produce a virus seed and a VERO cell bank and send engineers to Colombia to design a Good Manufacturing Practices human rabies vaccine production facility at VECOL. The first meeting was held in Bogota of the Technical Advisory Group (S.B. Halstead, F. Assaad, G. Baer, P. Reculard, P. Sureau, A.L. van Wezel, T. Yuill).

October 1986. Dr. A.L. van Wezel died unexpectedly at age 54. He was co-inventor with W. Thilly of the microcarrier system in which tissue culture monolayers on sepharose beads are grown in suspension cultures.

1987. The vaccine production facility construction at VECOL was begun with the assistance of Ray and Joan McMahan. The RF contract with RIVM was concluded and a new collaboration begun with the Institute Armand Frappier (IAF), University of Quebec, Montreal, Canada. Included in the new team were Robert Dugre, Pierre Trepanier and Bill Thilly. This collaboration provided access to Thilly’s new ultra-high density microcarrier culture system that comprises the current efficient continuous harvest virus production methodology. Technical Advisory Group meets in Montreal.

1988 – 89. Ultra-high density microcarrier cultures were tested at pilot scale at MIT and adapted to commercial scale fermenters at IAF. A VERO cell bank was established. Studies were initiated on rabies virus seeds that yielded high quantities of antigenic glycoprotein. Technologists from VECOL were trained at IAF, Montreal. Technology assistance was received from Ray and Joan McMahan. The Technical Advisory Group met in Montreal and Bogota.

1990. IAF was privatized, creating a new company, IAF-BioVac. IAF-Biovac technologists visited Bogota. Technology transfer process continues, but, with the requirement of protecting the intellectual property rights owned by IAF-Biovac. The Technical Advisory Group met in Bogota. CDC (Dr. George Baer) donated rabies hybridoma cells to produce the monoclonal antibodies needed for the rabies fluorescence focus antibody assay.

1991-94. P. Reculard provided technical assistance on optimizing rabies glycoprotein yield and reducing DNA concentration in final product. INPPAZ (Dra Ana Maria Diaz) assisted with tests required for rabies vaccine potency testing. A Confidentiality Agreement is negotiated between IAF, VECOL and the Government of Colombia. At issue is the limitation in the length of intellectual property protection under Colombian law. Negotiations are conducted by Patterson, Belknap Webb & Tyler, the New York law firm retained by the RF and by the firm of Castillo, Grau & Assoc., Bogotá. Once signed (March 1994), the complete Standard Operating Procedure (SOP) for rabies vaccine production and quality assurance developed by IAF BioVac was transferred to VECOL.
With partial funding from the RF, the National Institute of Health (INS), Bogotá, Colombia completed the renovation of a limited-access laboratory suite for performing quality control tests on biologicals, including rabies vaccines. VECOL began applied research to produce VERO cell banks and virus seeds, find dose of virus needed to infect cell suspensions to achieve optimal yields of rabies glycoprotein, optimize fermenter yields at high altitude, lyophilization, heat stability, DNA quantification and to develop quality assurance protocols and tests.

1995-96. VECOL prepared rabies vaccine consistency lots and fine tuned potency and safety tests and developed assays to measure residual VERO DNA in candidate vaccine. First drafts of plan for immunogenicity and reactogenicity trials in human volunteers are prepared. At an international meeting, WHO limits on VERO DNA are removed. Manufacturing countries are to set their own standards.

1997-99. With collaboration of INS, VECOL conducted VERO-based rabies vaccine immunogenicity and reactogenicity tests in 59 human volunteers. Rabies fluorescent focus antibody assays performed. INS reviewed and upgraded its potency and safety test procedures. A new large-scale fermenter was purchased and adapted to the ultra-high density microcarrier culture system (by Thilly). VECOL submitted vaccine lot consistency data, quality assurance records and human immunogenicity data to INS and Ministry of Health for review. Human rabies vaccine was licensed for use in Colombia.

The hard work of many people at VECOL should be acknowledged: Adriana Sierra, Clara Turriago, Nelson Mora, Raymond Rubin, Walter Ocampo, Fernando Andrade, William Suarez and Oscar Robin.

Discussion.

As the world enters the new millennium, what is the availability of vaccines to or production by developing countries to meet national needs? In 1990, the United Nations celebrated the achievement of “universal childhood immunization.” In fact, “universal” was defined as 80% of children receiving a full course of the six EPI vaccines. This achievement proved the reliability and extent of the global vaccine distribution systems of the WHO and UNICEF. It was agreed that new vaccines were needed for the pipeline. Hepatitis B, Hemophilus influenzae and Rotavirus vaccines went to the top of the list. But, these new vaccines were costly. Something had to be done to divert funds from purchase of the old to new vaccines. As a step in this direction, the Children’s Vaccine Initiative and its companion the WHO Global Programme for Vaccines have been helping developing country manufacturers improve the amount and quality of vaccines produced. This has worked well.

Recently, with leadership from the United Nations Development Program, several countries in Asia have co-sponsored an International Vaccine Institute (IVI) in Seoul, Korea. The IVI plans to help countries upgrade manufacturing methods and quality control of vaccines produced in domestic facilities as well as to budget for the import of adequate supplies of high quality vaccines. More recently, Bill Gates of Microsoft has provided $200 million to support a Children’s Vaccine Program whose mission is to increase the
distribution of currently licensed new vaccines to developing countries and invest in research and development on vaccines against important causes of mortality such as malaria and HIV. The World Bank has approached the large industrialized countries with the idea of creating a large fund to guarantee the purchase of new vaccines as a way to encourage pharmaceutical companies to invest in the necessary R&D.

Another trend is to move away from manufacture of vaccines in government plants and toward the private sector. Some successful private sector vaccine technology transfer projects have been completed. The strategy preferred by most manufacturers is to add capacity to their central base and export vaccines, often at concessional prices for developing countries. A huge portion of consumer goods is produced in factories that were set up by technology transfer. Success usually follows if the following principals are in place: transfer of technology to recipient country with a capable and inexpensive workforce, maintain continuous quality control and achieve profitability, principally through exports.

We are here to celebrate. Admittedly, the completion of the VECOL technology transfer project has been delayed. Delayed but not stopped. There are reasons for these delays. Already mentioned was the tragic, project-transforming impact of the sudden death of A.L. van Wezel during its first year. The privatization of IAF had a similar delaying impact. In all candor, the internal security conditions in Colombia imposed many overt as well as invisible delays in the scheduled visits of training staff, in the import of equipment and supplies and in visits by consultants. Perhaps most importantly, time was required for VECOL to complete the applied research needed to achieve high quality production of human rabies vaccine. As detailed above, dozens of different and difficult problems were encountered and overcome. For example, it was necessary to obtain supplies of beta-propiolactone - a toxic human carcinogen manufactured only in limited quantities and nearly impossible to transport. The parties had to come to grips with the need to protect rights to manufacturing processes. In the final analysis, the production of quality vaccines requires a solid infrastructure, adequate logistics and a high-caliber multi-disciplinary team.

Today, a review of the initial planning documents makes comic reading. Cost estimates were ridiculously low. It was thought that human rabies vaccine could be produced in large flasks or roller bottles in conventional laboratories. The need for and the expense of GMP facilities were underestimated. The difficulty of obtaining high yields of antigenic viral glycoprotein from available tissue culture-adapted rabies virus strains was not understood. The complexity of the problem of limiting VERO DNA to less than 100 picograms per dose of final vaccine produced at commercial scale was missed. The difficulty of a completing a parallel strengthening of a national quality control authority was only dimly understood.

Against this backdrop of technical, logistical and legal complexities a less determined institution and less tenacious program manager would have given up. VECOL did not give up. Above all, Eduardo Aycardi, the Manager of Research and Production at VECOL did not give up. The world should acknowledge in the completion of this project
an act of true courage and determination. The field of Public health and the country of Colombia have a new hero.

The completion of this project immediately raises broader questions. Price has always been an impediment to the widespread use of high quality tissue culture-based human rabies vaccines. A question for VECOL to answer is whether it may be possible to market this product at a price that can be afforded by all persons exposed to suspect bites. Another question is whether this product can be made available to other countries in the region. Rabies has never risen to a high priority on lists of vaccines for distribution to developing countries prepared by WHO, UNICEF or other global vaccine proponents. This is still an orphan disease. Only national health authorities understand the frustration of being unable to deal effectively with the problem of rabies year after year. Can VECOL help? This hard won victory should inspire plans and dreams.

Meanwhile, may the VECOL rabies vaccine join an elite list of high quality biologicals that can be expected to serve the needs of human beings for generations to come.

Vaccines are forever.

References.


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