

***Economics of vaccine development and implementation: changes over
the past 20 years***

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Introduction

Twenty years ago, vaccine developers were for the most part the public sector cousins of the pharmaceutical industry. Vaccines in use in 1980 included BCG, DTP, measles, and OPV, all of which had been on the market for more than a decade, and some for the better part of a half-century. The Food and Drug Administration (FDA) had overseen regulation of vaccines in the United States (US) for only eight years. The vaccine industry in the US was feeling the impact of adverse reactions and potential liability issues with pertussis and swine flu vaccines, and prices for established vaccines were <\$1-\$3/dose (see Table 1). Plasma-derived hepatitis B vaccine was not yet licensed, and recombinant products were still under development. The era of increased major expansion of vaccine R&D support¹ was just beginning. GMP was far from an industry-wide concept.

Table 1. US vaccine prices – 1980 vs 2000, US\$ per dose

Year/Product	Public sector	Private sector
1980		
DTP	0.15	0.30
OPV	0.35	1.60
MMR	2.71	7.24
2000		
DTaP	9.25	16.64
IPV	6.99	15.42
MMR	14.69	28.19
Varicella	35.41	45.56

(source: Bob Snyder, CDC, personal communication, 2001)

Today, with blockbuster products like *Haemophilus influenzae* type b (Hib) and pneumococcal conjugate vaccines, vaccines are big business. Vaccine selection has changed and prices are now much higher (Table 1); the new 7-valent pneumococcal vaccine Prevnar® costs \$232 for a four dose series.² The major vaccine producers are divisions of global pharmaceutical houses. Annual vaccine sales have gone from about \$2 billion in 1982³ to an estimated \$5.4 billion today.⁴ While still only a fraction of the \$337.3 billion pharmaceutical market,⁴ the vaccine market is projected to increase 12% per year.² This paper explores some of the major change areas in the economics of vaccine development.

Cost components

The cost components of vaccine development include research and development, production, and regulation, including clinical trials. We have focused on patents relating to the development of or access to a particular technology, on process standardization and scale-up as an example of production costs, and on clinical trials, licensing and testing to highlight some of the cost components of regulation.

The impact of TRIPS

When Jonas Salk developed the first polio vaccine, he was asked if he intended to patent it. He replied, “It would be like patenting the sun.”⁵ In the 1970s, many European countries were not giving patents on pharmaceutical products. Today, accessing intellectual property is a major factor in the product development cycle. However, for vaccines, it may not be an important barrier. For five new vaccines, acellular pertussis, hepatitis B recombinant, Hib conjugate, pneumococcal conjugates,

and rotavirus vaccines, only the first two had exclusive licenses that limited access. The conjugation technology used for Hib and pneumococcal vaccines is in the public domain⁶ (although alternative conjugated products exist) while the rotavirus vaccine technology, developed by the National Institutes of Health and licensed solely to Wyeth, is unlikely to be further developed.

DNA recombinant hepatitis B vaccine is produced in yeast or mammalian cells using bioengineering technology. The British firm Biogen obtained a broad patent covering all methods of making the vaccine antigens using recombinant technology. Biogen granted licenses to Merck and SmithKline Beecham, who put the recombinant vaccine on the market by the mid-1980s for \$30-\$40/dose. By 1993, due to the competition from the plasma-derived vaccine, the price decreased to only marginally above that of the plasma-derived product - \$1.25 – 2 per dose.⁷ Biogen started infringement procedures against Medeva who, beginning in 1992, had wanted to market a recombinant DNA vaccine, even though it was based on a different production process. Following a counterclaim by Medeva, the House of Lords, in 1996, revoked the patent on the basis of the enablement provisions, which allow an attack on an overly broad claim: “the court stated that to grant a monopoly to the first person who has found a way of achieving an obviously desirable goal for every way of doing so would, stifle further research and health competition in the post grant phase.”^{8 9}

While the price had come down significantly, access to the technology was still limited. By the mid-1990s the Biogen patent expired in many parts of the world, and this, coupled with the House of Lords decision in 1996 to revoke the patent, resulted in new manufacturers entering the market. By 1999, two Korean manufacturers (KGCC and LG Chem) were selling recombinant vaccines on the global market and

prices decreased to below \$1/dose. Currently, recombinant hepatitis B vaccine can be obtained by international bulk procurement for under \$0.30/dose.¹⁰ There are at least 10 manufacturers, five of which are prequalified for sale to United Nations agencies.¹¹

Another case study is that of the pertactin antigen of *Bordetella pertussis*, called P69. Evans Medical Limited* asserted that their P69 patent, licensed exclusively to SmithKline Beecham Biologicals, covered the pertactin antigen in Chiron's acellular pertussis vaccines. In a final non-appealable decision made in March 1998, the European Patent Office Technical Board of Appeal revoked the Evans patent.¹² This decision, applicable to most European countries, ended patent infringement litigation against Chiron in the United Kingdom, Italy and the Netherlands and cleared the way for sale of other acellular pertussis vaccines containing pertactin.

The impact of patents on technology access will now spread to most developing countries as they join the World Trade Organization and thus agree to uphold TRIPS, the Agreement on Trade-Related Aspects of Intellectual Property Rights, which established minimum universal intellectual property standards. A recent study¹³ carefully analyzed the projected impact of TRIPS on the pharmaceutical industry in Thailand. The study did not reveal a price change due to the patent protection act in Thailand, but proposed a number of proactive strategies to avoid limitation of technology access and price rises.

It is not possible to predict the full impact of TRIPS on vaccine development costs. However, vaccine development requires not only the patentable technology but also

the know-how to consistently produce a safe and effective biological product. It is this dependence on know-how, not covered under TRIPS, which may attenuate its impact.

Process standardization and validation

In 1980, Good Manufacturing Practice (GMP) was just being introduced into vaccine production. Today, investments in facilities, staff, and processes to maintain GMP compliance are driving production costs up.¹⁴ The ever-increasing “GMP spiral” demands more and more investment. Each step of the production process must be documented and validated. Vaccine manufacturers now contract out parts of the process to contract manufacturers, particularly production scale-up. A recent study carried out at WHO assessed 28 manufacturers capable of performing under contract some part of the vaccine development process.¹⁵

Clinical trials

Clinical trials have become a major expense in vaccine development. Following preclinical testing of a product, clinical trials of increasingly larger size are performed to establish clinical tolerance and acceptable safety, as well as to quantify immune response and demonstrate protective efficacy.¹⁶ In parallel, consistency of production must be demonstrated by showing comparable levels of clinical response to different vaccine batches. Factors impacting trial conduct and thus their costs include the characteristics of the study population, the power of the trial needed to detect potential

* Note the changing names of the vaccine manufacturers due to mergers: SmithKline Beecham is now

safety problems, the increasing amount of documentation required to ensure that appropriate quality assurance and ethical procedures are in place, and the trend toward use of Contract Research Organizations (CROs) to manage these aspects.

Traditionally, vaccines available on the international market were developed, produced, and authorized for marketing in industrialized countries, on the assumption that the data were applicable to most infant populations, at least for the traditional vaccines. For industrialized countries this procedure seemed obvious and appropriate. But populations are changing and even homogeneous populations have groups which may respond differently. Because of the potential differences in safety, immunogenicity and efficacy between populations, safety and immunogenicity data should be obtained using the candidate vaccine in the specific population in which the efficacy trial will be performed.^{17 18} This has applied, for example, to pneumococcal 9- and 11-valent conjugate vaccines developed in the US and designed to benefit individuals in countries outside the United States as well as special high-risk groups, e.g. Eskimos and Native Americans.¹⁹ The potential globalization of vaccines means that population characteristics must be even more carefully considered in developing clinical trial protocols.

A second factor impacting trial costs is the number of subjects needed to ensure sufficient power to demonstrate the potential safety and efficacy of the product. The story of RotaShield®, a tetravalent rhesus-based recombinant rotavirus vaccine licensed by the FDA on 31 August, 1998, is illustrative. At that time clinical trials included over 10,000 vaccine recipients, sufficient for demonstration of efficacy, but

Glaxo SmithKline; Evans/Medeva is now part of Powderject; and KGCC is now Green Cross Vaccine Corp

not enough to demonstrate a statistically significant increase in intussusception.²⁰ The Advisory Committee on Immunization Practices of the US Centers for Disease Control and Prevention (CDC) recommended post-licensing surveillance for this adverse event,²¹ and by June 1999, following distribution of 1.8 million doses of vaccine,²² the CDC had noted increased reports of intussusception in recipients of the vaccine. This event could not have been picked up in any reasonably-sized clinical trial. Especially for vaccines for universal use in children,²³ the US FDA is considering requiring expanded phase III trials with more attention to safety monitoring, a direction which could increase time to market and thus raise development costs significantly. Other regulatory authorities, for example, in Europe, seem likely to impose instead more formal phase IV post-marketing safety studies to carefully monitor potential adverse events for vaccine candidates.²⁰ There are benefits and drawbacks to either approach; both will impact costs.

In the effort to ensure the rights of clinical trial subjects Investigational Review Boards and Ethics Committees require more documentation and independent trial monitoring. This increase was considered at the Global Vaccine Research Forum held in Montreux, Switzerland in June 2000,²⁴ where increased trial costs with little return on investment were cited.

Because of the complexity of complying with expanding guidelines on conduct of clinical trials, more sponsors are using CROs to conduct trials. According to PricewaterhouseCoopers,²⁵ about 60% of big pharmaceutical manufacturers are outsourcing some part of their drug development, which adds up to a \$5 billion

market, growing at 20+% per year and projected to account for 45% of the total R&D budget for drug development in 2003.

An important outcome of efficacy trials can be the determination of serological correlates of protection - the type and quantity of a specific immune response associated with vaccine protection. The identification of these determinants can facilitate future trials, as immune response is easier to measure than efficacy, and can help development of an appropriate lot release test. Although identification of such a correlate is not a requirement for US licensure,¹⁷ failure to identify one adds complications and expense to subsequent trials, consistency demonstration, and lot release testing.

One approach used for acellular pertussis vaccine is to develop a large well-characterized production lot shown to be effective or identical in all quantifiable respects to an effective product, as a reference and to demonstrate consistency of each lot to the reference. This approach requires standardization and validation of tests and full characterization of the reference. In any case, all final product tests for vaccine release must be appropriately standardized and validated.

Harmonization and mutual recognition

Preparation of applications for marketing authorization is hampered by differing requirements across countries. Many manufacturers now have huge regulatory divisions to prepare files and data in a multitude of languages and formats. Several initiatives are in place which may eventually reduce registration costs. The

International Conference on Harmonisation (ICH) involves regulatory agencies of the US, Japan and Europe working with manufacturers to harmonize aspects of dossier requirements. So far the ICH has addressed issues more applicable to pharmaceutical products, but more recently aspects applicable to vaccines, such as safety issues for biotechnological products, Good Clinical Practice guidelines, viral safety evaluation of cell substrates, and a Common Technical Document for all products including biologicals have been addressed.²⁶

Mutual recognition agreements are in place between the European Union and Australia, New Zealand, USA, and Canada, and more are being developed.²⁷ The Pharmaceutical Inspection Convention, involving Australia, Austria, Belgium, the Czech Republic, Denmark, Finland, France, Germany, Hungary, Iceland, Ireland, Italy, Liechtenstein, Norway, Portugal, Romania, the Slovak Republic, Sweden, Switzerland, and the United Kingdom, promotes joint GMP inspections, networking, training, and a move toward global harmonization of inspections.²⁷

Many countries receiving vaccines through United Nations agency procurement use WHO prequalification (a system of ensuring a well-functioning regulatory process, coupled with assurance of compliance of the product with certain product specifications)²⁸ as a mechanism to fast-track national registration.

A major issue now confronting US and European manufacturers of products designed for developing markets is the increasing difficulty of finding appropriate regulatory pathways. The regulatory agencies involved, the FDA and the European Medicines Evaluation Agency, have a primary responsibility to their home markets,⁴ and the use

of scarce regulatory resources to evaluate products for different epidemiological situations is of low priority. Nevertheless, this problem must be addressed if manufacturers are to invest in development of future vaccines against diseases such as malaria and AIDS.

Pricing considerations

The pricing of vaccines has been characterized by heavy tiering across markets, which is possible because of highly scale sensitive manufacturing economics and product life cycles. The product life cycle has three distinct phases, as seen in Table 2: new product launch, market penetration, and product maturity. Most price tiering has been seen with mature products. The challenge for bringing new products to market is to ensure effective management of the life cycle²⁹ so that both manufacturers and the market will benefit.

Table 2. Managing the product life cycle³⁰

Factor	New Product Launch	Market Penetration	Product Maturity
Number of producers	1	Multiple, industrialized countries	High, industrialized and developing country
Available capacity	Low	High	Potential surplus
Market	Low	High, industrialized	High, all markets

demand		countries and private sector	
Costs	High	Medium	Low
Prices	High uniform	Tiered within and across markets, high average	Tiered within and across markets, low average

On launch, there is typically only one producer, who owns product and process intellectual property. This phase will have limited capacity, low demand, high production costs and high prices. During market penetration, new manufacturers will enter the market, either through their own development efforts or through licensing of the original manufacturer's patent, and capacity will increase. Limited price tiering will be possible. Once the product reaches maturity and the intellectual property protection expires, there may be many manufacturers, both in the developing as well as the industrialized world. Production costs are low and often there will be overcapacity so that availability is high and demand is global. Prices will be heavily tiered.³⁰

This paper will examine the impacts of capacity, market characteristics, and competition on pricing.

Capacity

A critical decision in vaccine development is that of scale. The price impacts depend on the risk inherent in the decision to make a specific capacity investment and the ultimate utilization of that capacity. A vaccine company will have to take the decision

to invest in production capacity at an early stage, well in advance of knowing the real demand and before revenues are available to offset investment costs.

In the past in the US, capacity decisions were fairly straightforward as US manufacturers knew the US market and their likely export market. The global market however, depends on excess capacity. Manufacturers can choose between two extremes: to focus only on the core market, which implies low availability, high cost, high price, and a risk of competition from manufacturers offering lower prices; or a global market focus, with low cost and high revenues through market segmentation, but running the risk of threatening the domestic price structure through price tiering. Data analysis suggests that for manufacturers the most profitable route is to maximize production volumes, serving all segments of the market at appropriate price points.³¹ However, unused capacity will have a cost. Capacity decisions are relatively immutable as the GMP requirements for biologicals make capacity expansion both very expensive and time consuming. Thus capacity investments imply higher prices because of high risks incurred by manufacturers.

Markets

The vaccine market is really a series of markets, including private markets in all countries and the public sector markets in both industrialized countries and those countries that are mostly donor dependent. Managing pricing (tiered pricing) over the product life cycle will depend on the segmenting of these markets.

Recently there has been much discussion on mechanisms that can be used to manage markets, including “push” mechanisms to accelerate product development for specific markets or “pull” mechanisms to create more attractive markets. “Push” mechanisms include direct financing of or tax credits for product development, and facilitation of clinical trials. They tend to reduce risk for product developers and have a proven track record.⁴ They influence the earlier segments of product development activities and provide a credible indication of public sector will to encourage specific research and development.^{1 32} “Pull” mechanisms, including innovative IPR protection and market assurances are stronger later in the value chain.⁴ They are a safer form of intervention for the funder because they are not given until the product is available, and can be of larger direct value to the product developers. On the other hand, they tend to lock the funder into an outcome, and they are currently untried. Both types are needed.

Competition

We have earlier touched on the role of competition in reducing prices. There are two competing tensions in play that impact competition: the consolidation of large multinational vaccine producers and the growing importance of vaccine manufacturers in developing countries and emerging economies (DC/EE). Table 3 shows the impact this has on the number of manufacturers serving United Nations procurement agencies.

Table 3. UN agency purchase – a changing mix of suppliers¹⁴

Year	Number of vaccines	Number of suppliers	% located in developing countries or emerging economies
1986	4	7	0
1996	5	14	50
2001	6	12	58

Note: BCG not included

The extent to which this mix of manufacturers can positively impact new product development depends on their ability to develop R&D capacity or to access technologies. Recent developments indicate that DC/EE manufacturers will play an increasingly important role:

- The Developing Country Vaccine Manufacturers Network, a new alliance of manufacturers, represented on the Board of the Global Alliance for Vaccines and Immunization, is comprised of manufacturers, both private and public sector, meeting or on track to meeting international standards of quality and viability;

- A limited number of joint ventures has been initiated between multinational manufacturers and developing country manufacturers, and more are under consideration. While some of these are for the express purpose of leveraging market access or regulatory pathways, their existence will enhance the impact of DC/EE manufacturers.

Future changes impacting the economics of vaccine development

A number of potential changes will impact vaccine development activities in the future:

- **Product lines** – In the past vaccines have been produced in industrialized countries and used on a global basis. In the future many vaccines are likely to be developing market- or at least region-specific, which will in turn impact capacity decisions and market sizes.
- **The regulatory spiral** – There is a trend toward substantially increasing regulation. This will increase product development costs with uncertain gains. Moreover, it could impact possible regulatory pathways.
- **Increasing role of outsourcing** – The current product development model, where a large pharmaceutical company carries out the entire process, may be outmoded. Product development may in future be co-ordinated by virtual organizations, with more emphasis on outsourcing at all stages – basic research, early preclinical and clinical work, manufacture, and even sales.
- **Competition** – Any vision of the future must take into account the changing face of the vaccine production industry, from increasingly consolidated global manufacturers to a new breed of developing country manufacturers reaching high standards of excellence. This group is already a major source for production of already existing products; time will tell if it will also serve as a source for innovative developing market products as well.
- **New funding sources** – With the formation of the Global Alliance for Vaccines and Immunization and increasing investment into the Vaccine Fund, there is likely to be a large funding increase for vaccine development, especially those for developing markets. Many of these are being implemented by Public-Private-Partnerships, a new mechanism for accelerating R&D. Current vaccine developers are watching these initiatives closely.

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