

**Demand Policy Instruments for R&D:  
Procurement, Technical Standards and the Case of Indian  
Vaccines**

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## ABOUT THE AUTHOR

Dr. Smita Srinivas is Associate of the Science, Technology and Globalization Project and Science, Technology, and Public Policy Program of BCSIA, and UNIDO Fellow. Her research focuses on economic development, industrial organization and labour, and the role of science and technology policies in development. Recent research and policy work have involved the study of cross-country biotechnology and pharmaceutical capability, laboratory to industry scale-up, innovation taxonomies, metrics for relevance of local science, and comparative national histories of technological change. Dr. Srinivas is currently leading a research effort supported by the United Nations Industrial Development Organisation on technical advance and local capabilities in developing countries within the framework of the Uruguay Round agreements. The core issues relate to capacity and “upgrading” in response to the technical standards and regulations of the SPS, TRIPs and other agreements.

Apart from her academic and policy research, she has had over 6 years of prior experience as a staff member and research consultant within the UN system and to Indian NGOs on various issues of economic and industrial development. She is primary author and co-author of two ILO books on industrial organization and labour protections. More recently, she has been a Task Force Fellow with the United Nations Science, Technology, and Innovation Task Force (TF10) of the Millennium Project. She is a Visiting Fellow with the Institute of Bioinformatics and Applied Biotechnology in Bangalore as part of a research and planning exercise for biotechnology development, and an affiliate researcher at the MIT Industrial Performance Centre (IPC, LIS project) studying Finland’s biopharmaceutical development. She has experience teaching and supervising both graduate and undergraduate students at MIT and elsewhere in microeconomics and research design and methods.

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## 1. Introduction

Vaccines represent a nearly \$8 billion global industry today, which is projected to grow to \$10 billion in 2010 (PhRMA, 2001). In 2001, worldwide spending on R&D for “biologicals,” of which vaccines are the largest segment, was \$1.1 billion (about 4% of total private pharmaceutical R&D) (PhRMA, 2001). Although vaccines comprise only 2% of the global pharmaceutical market, it is indispensable for public health immunization the world over. Yet, at the same time, the number of private vaccine suppliers in advanced industrialised countries is shrinking (in the US alone, there were over twenty vaccine suppliers until the 1970s and now approximately five exist); firms in developing countries must pick up some of this slack, especially for vaccines that are especially important for diseases prevalent in developing countries.

A slew of regulations surround the domestic production as well as subsequent export of the products and processes of this sector. Technical regulations and standards are important for the production and use of biological substances, such that not only do such products and processes have to be compatible with domestic standards, but a country that chooses to administer nationwide vaccine programs often has to comply with international standards, even if the vaccines are not being exported. In addition, as if there were not enough challenges facing developing countries, the World Trade Organisation’s various Agreements, preclude entirely open-ended support by developing country governments for domestic firms. Public health has some limited flexibility in the current multilateral regime as an issue of national interest. It should thus be investigated further in terms of its technological and institutional implications for R&D and innovation.

The research for this paper was conducted using a combination of primary data collection in India in 2001-2003, from collection of various quantitative indicators and from structured, open-ended interviews.

Among those interviewed were vaccine suppliers in the Indian biotechnology concentrations within the Southern cities of Bangalore and Hyderabad, as well as potential producers of vaccines i.e. those with some vaccine R&D efforts. Detailed interviews were also carried out with vaccine scientists in public research institutes and universities. All interviewees were assured confidentiality because of the sensitive nature of the processes and products as well as the competition among suppliers worldwide. Therefore, details of the process or product discussed during interviews are omitted, but publicly available information is used where relevant to showcase the progression of capabilities. In addition, secondary sources were used such as World Health Organisation (WHO) and United Nations Children’s Fund (UNICEF) publications, government, industry and news reports and medical, economic and development journal articles. The following variables were used to track process upgrading: the increase in the number of private Indian firms who are international vaccine suppliers in absolute terms, and in relative terms compared to other international suppliers, the increase in the range and production output of vaccines, and the range of process development capabilities in vaccine production. In addition, the research involved analysis of data on timelines of production, stages of production and “firsts.”

This paper focuses on international procurement policies in vaccines and other biologicals that have relevance for products deemed in the public interest. Section 2 provides a theoretical background to discussing public procurement and the link between demand instruments and technological learning. Sections 3 and 4 discuss the peculiar characteristics of vaccines that makes procurement powerful to ensure high-quality supply and that requires specific process

capabilities of suppliers. Section 5 assesses evidence of advances made by Indian firms in process development capabilities related to vaccine and biological manufacture. Section 6 highlights the continued gaps in Indian capability vis-à-vis other geographic distributions of vaccine capabilities. The next section, Section 7, briefly describes some institutional benefits for innovation arising from procurement. Section 8, Discussion, lays out the findings from and discusses why demand alone is insufficient. It also discusses some technological elements that need further attention. The paper concludes with some observations about the current international climate for technological advance and the need for revisiting procurement as an instrument for industrial development.

## **2. Theoretical framework:**

### **2.1. Demand policy instruments and public procurement**

What impact do demand-side policy instruments have on technological learning and R&D in the industrial sector? Demand-side policies have been investigated in various ways. Earlier economic literature (Hirschman, 1961 was one early starting point) has highlighted demand conditions as an innovation-inducing mechanism, later underscored again by Von Hippel (1988) on the importance of user-interactions with the innovator. Over time, Landes (1970), the SAPPHO study and others identified success and failure in innovation across industries (Freeman et al 1971, 1972) and identified factors influencing innovation. Seven broad areas of S&T advances, raw materials, market demand, competition, societal needs, government legislation and companies S&T and market specialisation were identified as influencing innovation. Market demand and government legislation continued to play an important role in studies focusing on national systems of innovation and which studied procurement among them (Edquist, 1999), and found the “system” with interactive learning at its core outperformed others. The interactive process induces firms to engage with both suppliers (Dore, 1986, for example) and users (Von Hippel 1988; Schmitz and Cassiolato, 1993) or with their counterparts, i.e., other firms (Dosi et al 1988; Lundvall, 1992). Achilladelis et al. 1982, 1990 and others have studied the chemical and pharmaceutical industry more particularly.

Most of the past attention for vaccines has focused almost entirely on demand-incentives for R&D to combat a supply problem for neglected diseases (for example, Mrazek and Massiolo, 2003), with little attention paid to the development of specific laboratory or industrial capabilities in developing countries as such. Those who link health policies to technological advance (such as Finkelstein, 2003) are invariably interested in advanced industrialised countries and in broad data aggregates. Few cases exist with interest in the micro-details of advance. Furthermore, the literature on procurement has evolved from its early role as an instrument for infant industry protection and not much beyond this. Vocal opponents have argued that government intervention must be minimized in development (Lal, 1985, Krueger, 1974, Bhagwati, 1982). However, once the argument was accepted that markets themselves might be competitive yet inherently imperfect or underdeveloped, the role of government became more defensible. The evidence is mixed on whether or not, in what timeframe, and how exactly government intervention improves the nation’s welfare. (extensively discussed for example, in Grossman, 1990, Tybout, 1992 and Rodrik, 1994). Others have suggested (Harrison, 1994) that even with data, analysis and interpretation become challenging. While from an empirical standpoint, it appears that few countries other than Hong Kong, developed industrial bases without a series of infant industry protections, including public procurement (for example, Chang, 2002, Shafaeddin, 1998). Indeed, although functional and selective government intervention (Lall, 1987) has been widespread in the histories of the early industrializing countries such as the UK, Germany and USA, it has been a much-debated tool for industrial development in the 20<sup>th</sup> century. Nevertheless, there is emerging agreement that government policies continue to be important for industrial development, but the devil is in the details.

Critics argue that even if national procurement policies hold potential, they are unnecessarily interventionist, being unable to gauge when firms have “matured,” and worse, are rife with biases in the selection of firms and awarding of contracts. Nevertheless, whatever one’s position vis-à-vis national public procurement, the role of international procurers is relatively understudied for technological and industrial development. The argument of this paper is that because the standard critiques of national protectionism do not apply straightforwardly to international schemes, they provide a system by which firms can find reliable (and large) markets. The firms, however, must demonstrate high levels of product quality, consistency of batches and the ability to supply large volumes on demand.

On the one hand, theory predicts that “easy” markets and government protection will result in firms stagnating and suggests that competition and free markets are the solution. Others suggest that procurement has its place in helping firms learn. Public health procurement is unique for the global scale in which acquisitions are made. While only a limited number of industries allow such possibilities, procurement from private suppliers can occur in some sub-sectors of energy, education (e.g. educational materials, including innovative software), public services (e.g. waste removal or recycling), health (e.g. medical equipment, for example, in public hospitals) and defense and related industries (e.g., bomb detonators, land mine clearing machines). While public procurement is often automatic for public suppliers, the focus here is on procurement for private companies, where technological learning and upgrading requirements can be linked to the demand for their products. In vaccines, for example, both public and private suppliers exist in India, but the private suppliers in emerging segments, such as recombinant Hepatitis B and combination vaccines, are primary recipients of the advantage. The widespread nature of public procurement means that it continues to be an important, if understudied tool for technology access and advance. Clearly, while any public agency can, in principle, be a consumer, it is of particular value for developing countries that the public procuring agency link its demand to standards of technological advances (including efficacy, quality and safety) and even institutional change in the way the standards are set, assessed and disseminated. However, the dynamics of how the procurement instrument is structured become important.

## **2.2. Demanding learning through standards and regulations**

Regulations and standards govern the broader environment today in which developing countries’ industries operate. Health, environmental and sanitary requirements all create significant challenges for developing country institutions related to science and technology and industrial development. The mandatory component (the regulations) is required under all circumstances, while the voluntary requirement (the standards) provides options that developing countries (and others) elect to uphold. This global trading system was established by the original Uruguay Round agreements, which specified technical standards and regulations for the environment, and health and sanitary requirements, known as the Sanitary and Phytosanitary (SPS) and Technical Barriers to Trade (TBT) measures. For relevance to developing countries, see for example, Finger and Schuler, 2000, Henson and Loader, 2001, Athukorala and Jayasuriya, 2003 and various United Nations Conference on Trade and Development (UNCTAD) case studies on horticultural export sectors.

To date, the discussions on standards primarily focus on the economic benefits of access to export markets, treating these technical requirements as non-tariff barriers to trade, and less on the domestic technical and institutional impact of meeting such standards. In other words, the focus has primarily been on the needs of the buyer, and less on the needs of the selling environment. Second, the debate of supply of high quality, affordable vaccines is a slightly different one from the cry for access to affordable drugs. Quality, efficacy, safety and affordability are technical and

institutional challenges in both the case of vaccines and drugs, but market incentives are structured differently in the case of vaccines and for a variety of reasons having to do with mass immunization, the stakes are extremely high. Certainly, price regulation and patent considerations are important as in the case of drugs, but the technical development challenges and the broader institutional setting in which such development occur, are considerable. Thus, vaccine suppliers are unlikely to miraculously appear unless some attention is given to the problem as a part of industrial policy, as much as it is a public health policy matter. To what extent, how are demand-side incentives affect technological learning and R&D in the domestic industrial sector?

An important reason to shift the lens from these standards as purely barriers is more than simply normative. The institution of the buyer need not remain a passive link between demand and supply, but merely a transaction cost-creating institution (Bardhan, 1991). It can further industrial development under a constrained set of circumstances. Past research in this latter trend with the focus on development and upgrading has been vast (see for example, Bauer, 1991, Glasmeir, 1990, Lall, 1991, Schmitz, 2000). This paper returns not to the question of whether buyers promote industrial development, but to an investigation of how standards and regulations *while acting as the buyer's demand instrument* act in ways that benefit local industry. While past work has fleshed out the elements of industrial organization, specifically the vast and informative value chains literature (Gereffi, 1994, Kaplinsky, 1998, and many others), this article focuses on innovation, through process development upgrading and manufacture. Given the increasing importance of such external standards and regulations, it is useful to study cases where developing countries have had to respond within a technically challenging domain of R&D and manufacturing. The case is particularly useful because the international agency is itself a procurer (in conjunction with the governmental request) and thus is able to respond to the needs of developing country suppliers more directly than simply as an observing party. Indeed, the WHO, for example, has a variety of measures in place to interact with suppliers of vaccines.

### **3. Vaccines and other biologicals: Unique technical and social challenges**

Vaccines are a means to boost the body's immunity to certain disease-causing microorganisms<sup>1</sup>. There can be traditional and newer vaccines. Before biotechnological tools were available, vaccines were still made. Vaccines contain killed microorganisms (bacteria/viruses) or attenuated live microorganisms and contain antigens (proteins) that induce antibody formation (the body's proteins). These antibodies are able to render harmless the vaccine's antigens as well as various microorganisms that can cause disease. The body thus gains resistance, i.e., is immunized. The early smallpox vaccine arose in the late 1700s through Jenner's efforts. More recently, the first recombinant vaccine (Hepatitis B) has been publicly available since 1982. This is an important date because India's first locally manufactured recombinant Hep B vaccine emerged in 1997, and provides a rich timeline of efforts to build private capability in the interim.

Vaccines and sera are not like other drugs. They fall under a broader class of therapeutics called "biologicals," which includes vaccines, serums, and toxins. Vaccines are the largest sub-class. Their quality and control considerations are significantly different, as are their procurement guidelines. For vaccines, procurement cannot be made based on price since quality considerations are of utmost importance. Furthermore, vaccine efficacy and safety cannot be determined solely

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<sup>1</sup> Vaccines are active immunization because they contain the killed/attenuated microorganisms themselves and the human body then produce their own antibodies (or animals do). Passive immunization refers to the process when antibodies (from animals, more often than not) are directly given to the patient instead of the microorganisms themselves.

in the laboratory, thus making the uncertainties and technical challenges for manufacturers acute. Scaling up, manufacture and regular batch supply are complex tasks. Only a few companies worldwide make vaccines of high enough quality to be procured internationally for expanded immunization programs (EPI). The fact that vaccines are highly temperature sensitive means that both the manufacturer and the procurement agency rely on considerable support infrastructure to keep the vaccines effective and safe.

Vaccine development of interest to developing countries today primarily involves (a) finding and manufacturing improved versions of existing vaccines and (b) developing combination vaccines and manufacturing them. Some, like India, have set their sights on new vaccines but the majority do not have this capability. Therefore, process development and manufacturing capabilities are extremely important both in making slight improvements to existing vaccines and in developing combination vaccines, but also in developing entirely new vaccines.

The emphasis on process development arises from all the interviews and from secondary data on Indian “firsts. The definition of process development is that capability within a firm to develop a viable manufacturing method for a given proposed (product) outcome. The capabilities particularly important for vaccines are *process chemistry, biology and process engineering*.

The following social and economic characteristics of vaccines shape institutions of R&D as well as procurement: (Adapted from WHO/VSQ/98.05): 1. They have a large national impact on public health 2. They are biological products and production is a biological process. Good Laboratory and Good Manufacturing Practices are thus absolutely necessary given the prevalence of living organisms. Furthermore, vaccines are difficult to handle because of their heat-sensitivity and limited shelf life. 3. The mandatory nature of immunisation means that consumers are captive to the product and procedure. In most cases, they have neither the choice to opt out of the program nor the ability to judge the quality of the product. Thus, the government is invariably an important intermediary consumer who checks safety, quality and efficacy. The credibility of such programs is important so that people do not opt out and endanger its efficacy. 4. Economically, the vaccine market is a semi-captive one. Currently, fewer than 20 vaccine suppliers of important categories of vaccines dominate the worldwide market. 5. They must be affordable, yet low costs can also make people perceive them to be of low value. From these characteristics, there is a clear rationale for public involvement, and a less studied but equally clear rationale for upgrading and innovation in process development.

#### **4. International demand policies: understanding the technological implications**

Since the start of such programs, centralized international procurement has been continually used in various innovative ways for improved access to drugs, for example. The Global TB Drug Facility (GDF) is a case in point for procurement being an incentive tool for broader health policy aims. The GDF is a new initiative to give tuberculosis patients greater access to high quality medication. The GDF is innovative in its intelligent use of market signals: linking demand and supply, using service partners and providing incentives for well-functioning TB programmes. (Kumaresan, Smith, Arnold and Evans, 2004). Overall, access to drugs is only one goal of procurement in pharmaceuticals. Some others are procurement of medical equipment and the public procurement programs for the rational use of drugs. However, essential drug and vaccine programs, particularly for pediatric medicines, vaccines and various biologicals, provide a continued rationale for public procurement programs.

In recent years, this procurement role has been increasingly dominated by international organizations. These organizations have two functions. First, they provide a launching pad into new markets through the certification system for public health procurement, particularly for



vaccines; and secondly (and more importantly), they act to procure large volumes of certified drugs from strictly selected manufacturers. Interviewees stated repeatedly the importance of public procurement for vaccines, and guaranteed markets (despite slow growth) for antibiotics.

Two international agencies with large procurement programs are the World Health Organisation (WHO) and the United Nations Children's Fund (UNICEF). UNICEF alone supplies vaccines to 40% of the world's children. It spends US\$220 million on vaccines and immunization supplies (the largest group expenditure on commodities) out of a total budget for supplies of \$541 million for children in 162 countries and territories. UNICEF works with both governments and other partners to strengthen and increase in scale and scope existing immunization programs and has co-founded the Global Alliance for Vaccines and Immunization (GAVI), "a partnership dedicated to strengthening immunization systems and increasing access to new and under-used vaccines" for the poorest nations. GAVI includes hepatitis B, Hib (for some types of meningitis and pneumonia) and yellow fever. "Priority is given to the 40 nations where routine immunization coverage is lowest and to the districts within those countries where children are least protected." ((UNICEF reports). The explicit goal of procurement from these two agencies is public goods delivery.

The role of such steady demand, where possible, becomes more important when one considers the number of suppliers leaving developing country markets for different vaccines. In 2001, BCG lost three suppliers, and DTP and tetanus toxoid lost three. Measles was the biggest loser, with seven fewer suppliers (Source: McKinney, Jarrett, 2002 SAGE/UNICEF/WHO). The international procurers have made a determined effort to correct this trend, with UNICEF alone going from no suppliers or 0% (1992) to 53% (2000), not including OPV (Milstien, Munira and McKinney, 2002).

Suppliers pre-qualify by registering in their home countries through the National Control Authority (NCA)<sup>2</sup> and through an International Competitive Bidding (ICB) procedure<sup>3</sup>. They also furnish additional information to the NCA and WHO/UNICEF. The supplier must be a manufacturer (or importer of bulk product for filling, labelling and repackaging) and must provide: 1) A certificate of registration /licensing in country of origin, 2) documentation on quality control (QC) and sampling procedures, 3) copy of most recent GMP certification, 4) production and quality control summary protocols, 5) certificate of analysis from NCA in country of origin, and 6) statement of licensing status in other countries. (Source: WHO/VSQ/98.05, "Guidelines for the international procurement of vaccines and sera", Global programme for vaccines and immunization, Vaccine supply and quality, World Health Organization, Geneva 1998).

For UNICEF, companies must show qualification for - EN ISO 9001 / EN 46001 and EN ISO 9002 / EN 46002 standards.<sup>4</sup> The technical challenges can be considerable depending on the type of vaccine, the extent of use and the speed of response time needed for supply. They also depend on how stable the vaccine type is to external conditions. The role of the international procurers is also to coordinate worldwide agreement and uniformity on methods, substrates and virus strains; supply and demand, licensing, standards setting and regulatory guidelines for packaging, distribution and return, among others.

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<sup>2</sup> See "Regulation and licensing of biological products", *WHO Technical Report Series* No 858, 1995

<sup>3</sup> The NCA reviews all bids and acts as a selector.

<sup>4</sup> See also WHO/GPV/VSQ at [www.who.int/gpv-supqual/unprequalprod.htm](http://www.who.int/gpv-supqual/unprequalprod.htm)

The vaccine industry is compartmentalized into five segments by manufacturers: US and European multinational companies (MNCs), OECD local manufacturers, emerging worldwide suppliers, developing country local suppliers and biotechnology companies. The mandate of international agencies in sourcing vaccines from developing countries has gained in importance. In 1986 there were seven suppliers of four vaccines; none were located in developing countries/emerging economies. Ten years later, in 1996, through deliberate procurement policies, there were 14 suppliers for five internationally procured vaccines; 50% were located outside the First World. This number has continued to increase to 58% for six vaccines, but the suppliers have dropped to 12, partly as a function of stricter guidelines (Milstien et al. 2001). In addition, there is a shortening lifespan of product development cycles for pediatric vaccines (For example, in the US, DTP, introduced in 1948, took 48 years to find a replacement, DTaP; while DTP-Hib, introduced in 1993, took only seven years to be replaced by DtaP combination vaccines. The shortest period of replacement was two years, for Hib polysaccharide, introduced in 1985, which was replaced by Hib conjugate).<sup>5</sup>

Three elements are vital for procuring agencies: quality, reliability, and availability. A high quality manufacturer that cannot deliver large quantities of the vaccine on short notice also fails the test on availability. Clinical trials must also be rigorous in methods and testing, and conducted on appropriately sized trial populations.

The control of vaccines for quality, in turn, depends on three elements: control of input materials, production process control and stipulations on the final product. While the second element involving actual manufacture is predominantly the concern of the firm, in reality all three processes closely involve both firm and the National Regulatory Authority (NRA).

Table 1 Quality considerations for vaccines

CONTROL STAGES	BROAD TASKS
Control of input materials	Characterisation of inputs (homogenous quality and purity, specified origin), such as cells, production bacteria/virus seeds <sup>6</sup>
Production process control at firm-level	Validation, certification for reproducibility and consistency for varied production lots
Controls on the final product	Lot release checks and monitoring for safety and efficacy of product both at trials and in final target population.

Adapted from Dellepiane, Griffiths, Milstien (2000)

The table below highlights the process development challenges of chemical and biological varieties facing firms in different sub-categories of vaccines and biologicals. The “how to” hurdles are outlined in the third column and range from fermentation, filtration and chemical processing, to conjugation, purification, stabilization, and so on. Companies that are able to accomplish all these tasks and pass muster with various standards and regulations for vaccine development are relatively few worldwide.

<sup>5</sup> Ibid. DTP=Diphtheria and tetanus toxoid, DTaP= Diphtheria and tetanus toxoid with acellular pertussis vaccine, Hib=Haemophilus influenzae type b, TT=Tetanus toxoid

<sup>6</sup> This is particularly challenging for viral contamination and imply attention to biological reagents, which may be contaminated, contaminations during laboratory work, cell source contamination from infected animal tissue and viral contamination from the viruses creating the cell line itself (Dellepiane, Griffiths and Milstien, 2000).

Table 2: Process challenges in vaccine development

VACCINE/BIOLOGICAL TYPE	TECHNOLOGICAL GOAL	PROCESS DETAILS
<u>Attenuated microbial cells</u>	Growth and purification of microbial cells adapted or engineered to delete pathogenicity, retaining immunogenicity.	Fermentation in defined media; recovery of whole microbial cells by centrifugation/washing or ultrafiltration methods; formulation, filling.
<u>Live microbial vector</u>	Growth and purification of non-pathogenic microbial cells carrying added gene for an immunogenic protein.	Fermentation in defined media; recovery of whole microbial cells by centrifugation/washing or ultrafiltration methodology; formulation, filling.
<u>DNA vaccine</u>	Extraction and purification of plasmid DNA from bacterial cells containing desired gene in the plasmid.	Fermentation in defined media; recovery of whole microbial cells by centrifugation/washing or ultrafiltration methodology; cell lysis and removal of cell debris (filtration, centrifugation or expanded bed chromatography); removal of host impurities, RNA, genomic DNA, proteins and endotoxins (salting out, PEG precipitation); concentration (ultrafiltration methodology, PEG precipitation); purification of plasmid DNA by IEC and/or SEC; concentration and buffer exchange; sterile filtration of final bulk; formulation, filling.
<u>Purified protein, excreted or cell associated</u>	Growth of recombinant bacteria, yeast or cell culture where recombinant protein, cell lysis (for cell associated proteins), isolation and purification of the protein.	Fermentation in defined media; removal of microbial cells by centrifugation or filtration; mechanical disruption of cells, removal of cell debris, solubilization (if necessary); concentration of soluble protein by ultrafiltration methodology; protein purification by chromatography, concentration, buffer exchange, sterile filtration and stabilization; formulation, filling.
<u>Conjugated polysaccharides</u>	Growth of bacterial culture, extraction and purification of capsular polysaccharides, preparation of carrier protein, conjugation to carrier protein.	Fermentation in defined media; primary recovery of cells; isolation/extraction of polysaccharide by chromatography or precipitation; chemical characterization of the polysaccharide; concentration and drying of bulk. Purification of carrier protein (see purification sequence described above). Chemical modification of polysaccharide; linker if required; chemical processing of carrier if required; conjugation; separation of conjugated from un-conjugated species by chromatography; concentration of bulk conjugate, sterile filtration and stabilization;

		formulation; filling.
<u>Live attenuated viruses</u>	Growth of cells (from cell banks of continuous cells or isolation of primary cells), infection with attenuated virus, isolation and purification of virus.	Cell culturing (risk free medium) in bioreactors, roller bottles, hollow fiber, cell cubes, flasks, or microcarrier culture with various types of feeding; virus infection; cell controls; removal of cell or cell debris by centrifugation or ultrafiltration methodology; purification of virus if required, concentration; stabilization, formulation; filling.
<u>Multiple antigen peptide vaccines</u>	Linking of synthetic peptide antigens to a synthetic backbone (eg polylysine).	Peptide synthesis and purification; backbone synthesis and purification; linking of antigens to backbone; purification of multiple antigen peptide product; sterile filtration; stabilization; formulation; filling.
<u>Virus-like particles</u>	Growth of cells, infection by virus or recombinant virus producing non-replicating, non-infectious, particles with intact immunogenic antigens, isolation and purification of the virus-like particles.	Cell culturing (risk free medium) in bioreactors, roller bottles, hollow fiber, cell cubes, flasks, or microcarrier culture with various types of feeding; virus infection; cell controls; removal of cell or cell debris by centrifugation or ultrafiltration methodology; differential separation of virus-like particle from virus if required, purification and concentration; stabilization; formulation; filling.
<u>Live viral vectors</u>	Growth of cells, infection with genetically engineered replicating non-pathogenic viruses containing added gene of interest, isolation and purification of virus.	Cell culturing (risk free medium) in bioreactors, roller bottles, hollow fiber, cell cubes, flasks, or microcarrier culture with various types of feeding; virus infection; cell controls; removal of cell or cell debris by centrifugation or ultrafiltration methodology; purification of virus if required, concentration; formulation; filling.

Source: reproduced directly from WHO, Initiative for Vaccine Research (IVR), 2003

## 5. The Indian evidence: Technology and institution development<sup>7</sup>

Historically, Indian public-sector companies and research institutes have spearheaded the production of vaccines. In the last 10 years, however, a small but growing number of private Indian firms have developed process capabilities in vaccine development. There has been an increase in both the number of Indian firms supplying nationally as well as those that have developed export capability. This transition, from developing capability under national procurement, to further upgrading and expanding product lines under international procurement, marks an important turning point for private firms. In particular, Extended Programs of Immunisation have created a special incentive for Indian suppliers. These programs procure a larger range of vaccines as well as provide a broader potential geographic export base for approved suppliers. Various estimates put the Indian vaccine market at approximately ~\$150 million. In 2002-2003, vaccines accounted for 57% of the total Indian biopharmaceutical market, with an estimated growth rate of 27% in 2004 (Biospectrum-able, 2003). The country currently exports over 60% of current vaccine output to other developing countries where significant populations are at risk and need vaccine coverage.

<sup>7</sup> Details for this section can be found in Srinivas (2004).

The table below shows the list of Inactivated polio vaccine (IPV) and Oral Polio Vaccine (OPV) Manufacturers to the WHO vaccines and biologicals unit as of October 2002. The number of Indian manufacturers in this category is the highest from any single country. A newer organization, the Developing Country Vaccine Manufacturers Network (DCVMN), helps companies upgrade and meet procurement requirements. Public-sector companies like Haffkine Bio-pharmaceuticals have also become active suppliers again. In 1999, that company received WHO-GMP certification for oral polio vaccine blending facilities and subsequently obtained a UNICEF procurement order for supply of oral polio vaccine in India.

To underscore the geographic distribution of vaccine capabilities, the Table below shows suppliers worldwide for one example, the WHO Inactivated Polio Vaccine program. The shaded rows highlight that India has the largest number of suppliers, of which two are private firms for polio vaccines. While the domestic market need for polio vaccine is undoubtedly a cause of the large supply from India, in meeting WHO standards these companies compare favourably with multinationals such as GSK. In the case of other vaccines such as Hepatitis B, the majority of qualified suppliers are private firms. It is debatable whether the market will eventually be able to support them all through procurement.

Table 3 Worldwide Inactivated Polio Vaccine suppliers to WHO

COMPANY	COUNTRY
Glaxo Smithkline Biologicals	Belgium
Scientific Institute of Public Health Louis Pasteur	Belgium
Bio-Manguinhos	Brazil
National Vaccine and Serum Institute	China
Kunming Institute of Medical Biology	China
Statens Serum Institut	Denmark
Egyptian Organisation for Biological Products and Vaccines	Egypt
Aventis Pasteur	France
Agence Francaise de Securite Sanitaire de Produits de Sante (AFSSAPS)	France
Chiron Behring	Germany
Bharat Immunologicals and Biologicals Corp. Ltd/	India
Haffkine Bio-Pharmaceutical Corp. Ltd.	India
Panacea Biotec Lt.	India
Serum Institute of India Ltd.	India
P.T. BioFarma (Persero)	Indonesia
National Agency of Food and Drug Control	Indonesia
RAZI Institute	Iran
Institute Superiore di Sanita	Italy
Japan Poliomyelitis Research Institute	Japan
Birmex	Mexico
National Institute of Health	Pakistan
Institute of Poliomyelitis and Viral Encephalitides	Russia
Dong Shin Pharmaceutical Co.	S. Korea
Green Cross Corporation	S. Korea
Korea Vaccines Co. Ltd.	S. Korea
SBL Vaccine AB	Sweden
SVM	The Netherlands

Evans Vaccines	UK
Poliovac	VietNam
Institute of Immunology and Virology Torlak	Yugoslavia

Source: Adapted from “Vaccines and Biologicals, Access to technologies”, II WHO/UNICEF Consultation with IPV/OPV Manufacturers, Bharat Biotech April 2003, Geneva.

In addition to the Inactivated Polio Vaccine, other Indian vaccine companies are Biological E (TT, DTwP and working on DTP-Hep B), Panacea Biotec (Hep B, DTP-Hep B, OPV), Serum Institute of India (Measles, mumps, rubella, TT, DT, DTP, Hep B), Shantha (Hep B, working on Hepatitis E, Typhoid, Tuberculosis, Combination vaccine against Hep-B + DPT), and Bharat Biotech (Hep B, single-shot typhoid, working on malaria and rotavirus).

The following table lists some of the leading vaccine providers to the Government of India with their annual dosage capacity. The Indian government's Immunization Programme Department requires six different vaccines for infants and for pregnant women.

Table 4 National procurement and suppliers of vaccines

Vaccine	Name of manufacturing unit <sup>8</sup>	Annual Capacity (In million doses)
Tetanus Toxoid	Biological E	120
	Serum Institute	96
	Haffkine Bio-Pharmaceuticals	71.2
	Central Research Institute	30
	Pasteur Institute of India	30
DT Vaccine	State Vaccine Institute	10
	Biological E	24
	Central Research Institute	20
	Pasteur Institute of India	15
	Haffkine Bio-Pharmaceuticals	10
DPT Vaccine	Serum Institute of India	97.5
	Biological E	80
	Haffkine Bio-Pharmaceuticals	44.8
	Pasteur Institute of India	40
	Central Research Institute	25
Measles Vaccine	Serum Institute of India	100
BCG Vaccine	Unit of MOH (FW), Tamil Nadu.	35
Oral Polio Vaccine	Radicura Pharma	540
	BIBCOL	300
	Haffkine Bio Pharmaceutical	240
	Biomed	156

Source: Ministry of Health and Human Welfare, Government of India, also at <http://health.nic.in/vaccines.htm>

In other vaccine production as well, the number of private firms is rising and dominating the market. The Serum Institute, for example, is also the country's largest manufacturer of MMR (100% of local measles vaccine needs) and DPT vaccines (60% of local needs). Their quality

<sup>8</sup> Some are public sector units at national level, others run by State governments.

assurance and regulatory compliance profile highlights the challenges in scale, with DTP vaccine batches ranging between 2-4 million doses. The company was one of the first to seek export markets via institutional buyers.

Data compiled from WHO's also shows that six Indian companies are compliant with WHO requirements for vaccine production, and some have specific specialties for process development varying with the biological under consideration.

Table 5 Quality and capacity of WHO Vaccine Manufacturers from India

Company	Approved by Functional National Regulatory Authority	GMP compliance certificate obtained	GMP clinical batches capacity
<b><i>Private</i></b>			
Bharat Biotech International	Yes	Yes	Yes
Biological E	Yes	Yes	----
Panacea Biotec	Yes	Yes	Yes
Serum Institute of India	Yes	Yes	Yes
Shantha Biotechnics	Yes	Yes	Yes
<b><i>Public sector</i></b>			
Bharat Immunologicals and Biologicals	Yes	Yes	Yes

(Source: Adapted by the author from the WHO, Initiative for Vaccine Research (IVR), Vaccines, Immunisation and Biologicals, Database on Contract Manufacturers.

<http://www.who.int/vaccines-access/quality/contractmanufdb/index.htm>)

The interviews suggest that both national and international procurement resulted in large revenues for companies. In national procurement for antibiotics, they provided steady demand for otherwise sluggish growth segments where older antibiotics faced technological obsolescence. More importantly, they reduced the risk for Indian companies investing in greater anti-infective production, and assured their sales to the government.

The persuasive influence of international procurement goes beyond demand alone, in two additional ways: in its role as a voluntary upgrading mechanism for interested suppliers and in its ability to work in conjunction with National Regulatory Authorities (NRAs) to help streamline existing national procurement policies. For example, many companies which work through NRAs and national procurement programs act as suppliers to international procurers. Specifically, coordination exists for the characterization of starting materials, regulations concerning production consistency at the firm level, and varied tests and testing points for lot releases. The WHO requires functional NRAs to be able to produce guidelines, systems and enforcement to ensure six critical functions: 1) a published set of requirements for licensing, 2) surveillance of vaccine field performance, 3) system of lot release, 4) use of laboratory when needed, 5) regular inspections for GMP, and 6) evaluation of clinical performance.

One interviewee, reflecting on the importance of these agencies in opening market opportunities overseas, said,

*"In particular, the Serum Institute of India showed all companies the potential importance of institutional buyers in vaccines."*

Here, vaccine suppliers from developing countries have a potentially immense market, when linked to high quality standards, which also encourages some level of innovation on the part of these firms. This is because the procurer has an incentive to assist current suppliers to adapt to new public health concerns and increase production to supply to lesser-developed countries. Another interviewee stated:

*“These programs have played a huge role in sustainability and supply of vaccines because they do not have large commercial markets. At the same time, GMP requirements keep changing, so companies need procurement to really make the process viable. This is a guarantee to us and to others to have markets available. It also recognizes companies and thus makes new collaborations possible, while also helping with the standardization of platforms.”*

Firms thus have access to collaborations with other private firms and to public research infrastructure, often in their home countries.

The case of Hepatitis B deserves special attention. There are three hundred million carriers of hepatitis B worldwide, twenty million new annual infections. The disease is a significant Indian problem, with Hepatitis B surface antigen (HBsAg) prevalence at 2 to 10% among populations studied, with the number of HBsAg carriers estimated to be over 40 million (WHO India Hepatitis B Fact Sheet). In general, no particular therapy exists for the disease, so vaccine development and administration continue to be important. While the first vaccines were prepared from plasma of infected patients, they were effective at their task, but standardisation was low and samples were occasionally impure. More recently, companies such as Merck Sharp and Dohme and SmithKline Beecham created genetically engineered vaccines where the Hepatitis B virus gene or gene fraction is introduced into yeast cells. The then recombinant strain of yeast is used to develop the vaccine.

Hepatitis B now comprises a routine part of pediatric immunizations in India and the projected future annual growth rate is expected to be 10-20% for Hep B markets in India as universal immunization programs reach their full potential. (IMS health, company estimates). Current manufacturers of Hep B vaccines show the large increase in private manufacturers, mostly Indian with some foreign companies: Biovac B of Wockhardt, GlaxoSmithkline's Engerix B, Shanta Biotechnic's Shanvac, Pfizer's Hepashield, Zydus Cadila's HB Vac. Other suppliers are the Serum Institute, Bharat Biotech and Panacea Biotech.

The fact that Indian companies have moved into a position of some strength in vaccine markets is a combination of their capabilities, government preference for Indian companies and increasing demand from international agencies such as the WHO and UNICEF for developing country suppliers. The move into this position of advantage has been a long one, with various stages and selection environments (Srinivas, 2004). The table below shows a few of the vaccine “firsts” for Indian industry. Although many of the segments are entirely mature vaccines, their worldwide market share in these segments is significant and allows them room to experiment with newer R&D.



Table 6 Indian vaccine “firsts”

VACCINE	INDIAN “FIRST”	COMPANY
Measles	~90% world supply	Various
DPT	World’s largest supplier (1 out of every 2 children worldwide is vaccinated by a Serum Institute vaccine)	Serum Institute (private)
Veterinary vaccines	World’s 2 <sup>nd</sup> largest plant (largest worldwide supplier of vaccines for Foot and Mouth disease) 2 <sup>nd</sup> company worldwide to launch vero cell rabies vaccines	Indian Immunologicals (Publicly instituted company)
Hepatitis B (global capacity: all DC mfrs 21.5%, AIC mfrs 78.5%, WHO estimates). Combination Hep B capacity is almost all in developed countries.	Largest number of private companies in any one country developing recombinant Hep B for global market	Wockhardt, Shantha Biotechnics, Bharat Biotech, Panacea, etc.

In addition, within the country, the r-DNA based Hepatitis B vaccine, “Shanvac-B”, was indigenously developed by Shanta Biotechnics as its first product and became the largest selling Hepatitis B vaccine (by volume) in the country. Shanvac-B commanded an approximately 40% market share in the hepatitis B vaccine market in 2003 and Shanta Biotechnics also became the first Indian company to pre-qualify for WHO Hep B procurement. The first introduction of domestic Hepatitis B with a clear eye on both domestic and international procurement, had significant reverberations on the Indian market and supply. For example, Shanvac’s entry brought the price for imported vaccines down from Rs. 780 to Rs. 50 in 1997 alone, and to Rs. 25 in 2003 and its vaccine business accounted for more than 86% of total sales in 2003, with an expected 65 percent growth in 2004-2005 (Biospectrum, August 10<sup>th</sup>, 2004 and various news accounts). Domestic process development and manufacturing capabilities were linked directly to procurement aspirations for large markets and with stringent safety, efficacy and quality pressures. The fact that the public eye was on these features and particularly on the implicit social contract for the new companies, is clear from how market jockeying occurred. Bharat Biotech, a competitor and a very important Indian vaccine manufacturer today manufactured its Hepatitis B vaccine using a different means with the *pichia pastoris* vector. A controversy erupted in the news media over the safety of such vaccines in trials, and Bharat biotech was adversely affected, losing significant Indian market share and paving the way for a third company, Wockhardt to reap the benefits of the competition between Shantha Biotechnics and Bharat Biotech. After considerable industry efforts and that of the scientific and public health community, an initial program of national immunization of Hepatitis B was introduced in a phased manner in 2003. Today, all three companies, and others, supply Hepatitis B vaccines to immunization programs and/or to the WHO as qualified suppliers.

The fact that mature vaccines continue to be the mainstay of developing country industries does not preclude significant technological learning from occurring industry-wide. Although Hepatitis B had been on the market for many years, even in recombinant form, the ability of Indian manufacturers, through a combination of technology transfer, indigenous development and collaborative work, to develop multiple Indian strains shows that some advance has been occurring. Indeed, the existing of publicly available and off-patent Hep B nevertheless continues to propagate a search and experimentation routine for a domestic manufacture of significant value to Indian companies. When detailing the process development and R&D challenges, despite the existence of a known end product, one vaccine supplier, one interviewee said:

*“Hepatitis B being a known technology is like saying missile technology is known or the atom bomb is public domain. We still need ways to construct it and to take it to market and compete.”* (cited in Srinivas, 2004).

## **6. Gaps in Capabilities: Fine-tuning procurement programs**

There are newer trends and newer vaccines in the pipeline worldwide. These require specific laboratory and process capabilities, to take individual proteins from virus/bacterium, introduce these into other cells/organisms and produce these proteins, or synthesize them. They might also use transgenic plants as vaccine source. (E.G. Hep B antigens expressed through bananas). Another dynamic area, less concerned with public health but potentially important is where non-infectious diseases can be prevented through vaccines (I.e. those vaccines containing T-cells for autoimmune diseases). Overall, the capabilities of suppliers will be hard pressed to adapt to newer techniques, process technologies and products. In 1997 alone, there were 88 vaccine candidates in development, of which the combination vaccines also increased with six for 3+ combinations.

Furthermore, in the case of combination vaccines, only the multinational company Chiron internationally combines the Hib vaccine with other vaccines. Indian firms (shaded) such as Serum Institute combine DTwP with Hep B, as does Shantha Biotechnics and two other yet-to-be pre-qualified suppliers as the table below shows. The closing gap between various developing country manufacturers (India and Brazil are very similar) indicates increased process development capacity and the diversification of product lines partly in response to increased (procured) demand. However, it also highlights the need to shape procurement in such a way as to ensure that no over-supply occurs in some segments while large supply gaps in other segments continue to exist.

Table 7 Planned introduction of vaccines and combination vaccines

YEAR	COMPANY	VACCINE TYPE
2002	Chiron	DTwP - hep B
2003	Serum Institute	DTwP - hep B
	Shantha Biotechnics	DtwP - hep B
	Bio Farma	DTwP - hep B
	BioManguinhos with Butantan	DTwP - hep B
	2 Indian manufacturers (not PQ)	DTwP - hep B
	1 Chinese manufacturer (not PQ) and in clinical trials	DTwP - hep B
2004	CIGB	DTwP - hep B
2005	Chiron with KGC	DTwP- hep B - Hib
	Cheil Jedang	DTwP - hep B
2006	Aventis	Hep B monovalent
	CIGB	DTwP - hep B - Hib
2008	Aventis	DTwP combinations
not given	Serum Institute	DTwP - hep B - Hib
not given	Bio Farma	DTwP - hep B - Hib
not given	BioManguinhos with Butantan	DTwP - hep B - Hib

Source: Adapted by the author from McKinney, Jarrett, 2002 SAGE/UNICEF/WHO

Clearly, international procurement has succeeded in opening export markets for Indian vaccine producers and resulted in standardization and upgrading. Yet, some gaps in capabilities clearly remain. Some of these gaps are due to the geographic specificity of needs for some types of process capabilities and infrastructure. The segment “process development” in the WHO table refers to early process development for manufacture and is not to be confused with process development capabilities referred to in this paper which run the gamut from early to late (loosely, laboratory to factory) development. Nevertheless, as the table below shows, some comparison across listed suppliers and specific biologicals/vaccines is still possible. The first table indicates the advantages Indian firms have in two sub-areas (a) first by vaccine/biologicals type: Indian companies are concentrated in a few segments in the first half of the table, focusing on attenuated microbial cells, DNA vaccines, live microbial vectors and purified protein. Still, notable gaps in qualified supply exist for all Indian companies even for DNA vaccines in process development, analytical development, and downstream processing. (b) Secondly, by process capabilities: they have clear concentrations in analytical development and formulation and filling. They are not qualified WHO suppliers for any Indian firms have the advantage over other Asian suppliers. If we analyse the distribution of qualified supply by geography, (the second table) we see that nationally, specialisations are clear. No Indian suppliers have come forth for any stage of conjugated vaccines, live attenuated viruses, multiple antigen peptide vaccines, virus-like particles or live viral vectors, except for formulation and filling and the provision of animal test facilities. For the last two, there are no Indian suppliers whatsoever, at any type of capability. For the Asia region, for example, the second table indicates that for DNA vaccines alone, some specific Indian capabilities are available, but the gaps in capabilities (or the time lag in registering for these capabilities) are evident. Indian companies are the only qualified Asian suppliers of all segments of attenuated microbial cells, and the only suppliers of product development and end stage formulation and filling, and animal test facilities for DNA vaccines. However, their gaps in both tables indicate skills not offered relative to other Asian (predominantly public sector Iranian and Indonesian institutes) and European and US private suppliers. Some gains are yet to be made. While Indian vaccine suppliers are rapidly upgrading facilities and capabilities, private Indian firms will have to face some competition against public institutes in Iran and Indonesia, which

have consolidated positions in the last four biologicals to the right of the table and at most capabilities along the process chain. Furthermore, although WHO markets are geographically segmented and seeking developing country firms as suppliers, the reality is that even for attenuated microbial cells where Indian firms appear to have some advantage over other Asian suppliers, a large number of European and American suppliers exist with capabilities along the process chain. This contrast is meaningless by itself, of course, unless these Western suppliers take over Indian supply positions. What is more important, is that for newer vaccines and biologicals, the absence of these capabilities will mean continued dependence of Indian firms on western technologies, and/or the inability to advance in markets other than those for developing countries. Certainly, there are plenty of existing opportunities in the latter to explore. Nevertheless, current and future Indian suppliers will have to pay heed to the geographic distribution of process capabilities before they can realistically plan their expansion. From a policy standpoint, the process capabilities can be fine-tuned to some extent by designers of vaccine procurement policies. From an industrial standpoint, there are questions to be answered about excessive concentration of firms in some segments while others are thin, patchiness of firms in numbers for specific process capabilities and infrastructure and the absence of firms in some areas of analytical and process development altogether. Vaccine development and biopharmaceutical development need increasingly expensive infrastructure. Some of India's private firms managed their early growth by using facilities of public research institutes and have now developed in-house facilities. To date, this process of industrial development has been somewhat *ad hoc*, with

Table 8 Concentration of Indian contract vaccine manufacturers for vaccines and biologicals showing number of firms in each segment.

Source: Adapted by the author from the WHO, Initiative for Vaccine Research (IVR), Vaccines, Immunisation and Biologicals, Database on

Services	Attenuated microbial cells	DNA vaccines	Live microbial vectors	Purified protein	Conjugated vaccines	Live attenuated viruses	Multiple antigen peptide vaccines	Virus-like particles	Live viral vectors
Product development	2	1	2	3					
Process development	2		2	3					
Cell Banking GMP	2		2	2					
Analytical Development	5		5	5					
Fermentation	3		3	5					
Downstream processing	3		3	1					
Final Bulk (clinical grade)	2		2	2					
Formulation and filling	5	5	5	6	6	2	6		
Animal test facilities	4	4	4	4	4		4		

Contract

Manufacturers.

<http://www.who.int/vaccines-access/quality/contractmanufdb/index.htm>

**Table 9** Comparison of Asian WHO-qualified vaccine contract manufacturing capabilities<sup>910</sup>

<b>Services Offered</b>	<b>Attenuated microbial cells</b>	<b>DNA vaccines</b>	<b>Live microbial vector</b>	<b>Purified protein</b>	<b>Conjugated vaccines</b>	<b>Live attenuated viruses</b>	<b>Multiple antigen peptide vaccines</b>	<b>Virus-like Particles</b>	<b>Live viral vectors</b>
Product Development	INDIAN	INDIAN	INDIAN, IRANIAN, INDONESIA	INDIAN, IRANIAN, INDONESIA, HONG KONG		IRANIAN, INDONESIA		IRANIAN, INDONESIA	IRANIAN, INDONESIA
Process Development	INDIAN	-	INDIAN, IRANIAN, INDONESIA, HONG KONG	INDIAN, IRANIAN, INDONESIA, HONG KONG		IRANIAN, INDONESIA		IRANIAN, INDONESIA	IRANIAN, INDONESIA
Cell Banking GMP	INDIAN	-	INDIAN, IRANIAN, INDONESIA, HONG KONG	INDIAN, INDONESIA, HONG KONG		INDONESIA		INDONESIA	INDONESIA
Analytical Development	INDIAN	-	INDIAN, INDONESIA, HONG KONG	INDIAN, INDONESIA, HONG KONG		INDONESIA		INDONESIA	INDONESIA
Fermentation	INDIAN	-	INDIAN, IRANIAN, HONG KONG	INDIAN, INDONESIA, HONG KONG		IRANIAN, INDONESIA		IRANIAN, INDONESIA	IRANIAN, INDONESIA
Downstream Processing	INDIAN	-	INDIAN, IRANIAN, INDONESIA, HONG KONG	INDIAN, INDONESIA		INDONESIA		INDONESIA	INDONESIA
Final Bulk (clinical grade)	INDIAN	-	INDIAN, IRANIAN, INDONESIA, HONG KONG	INDIAN, INDONESIA, HONG KONG		INDONESIA		INDONESIA	INDONESIA
Formulation & Filling	INDIAN	INDIAN	INDIAN, IRANIAN, INDONESIA	INDIAN, IRANIAN, INDONESIA	INDIAN, IRANIAN, INDONESIA	INDIAN, IRANIAN, INDONESIA	INDIAN, IRANIAN, INDONESIA	IRANIAN, INDONESIA	IRANIAN, INDONESIA
Animal Test Facilities	INDIAN	INDIAN	INDIAN, IRANIAN, INDONESIA	INDIAN, IRANIAN, INDONESIA	INDIAN, IRANIAN, INDONESIA	IRANIAN, INDONESIA	INDIAN, IRANIAN, INDONESIA	IRANIAN, INDONESIA	IRANIAN, INDONESIA

Source: Adapted by the author from the WHO, Initiative for Vaccine Research (IVR), Vaccines, Immunisation and Biologicals, Database on Contract Manufacturers. Also, <http://www.who.int/vaccines-access/quality/contractmanufdb/index.htm>)

<sup>9</sup> The table is to be understood as showing comparative Asian capabilities. Thus, European and American companies also exist with capabilities in these segments, as discussed in the text.

<sup>10</sup> Although Hong Kong is a part of China, it is named here to distinguish it from other major mainland Chinese pharmaceutical and biotechnology suppliers, none of which are WHO pre-qualified suppliers.

There is the troubling fact that as vaccine become tightly tailored for distinct geographic markets, developing country firms may be hard-pressed to divide their efforts to serve both developing and developed countries alike. They may then opt to serve foreign populations in advanced industrialised countries with better-paying markets rather than their domestic ones. Measles, DTwP and OPV are well tailored today for developing country use, while MMR, DtaP, IPV and others are increasingly tailored to developed country needs. Newer vaccine such as DTwP-HepB or Hib and Pneumococcal vaccines thus face similar questions for appropriate geographically-based standards, production outputs, profits and whether developing country firms will produce these for their own populations.

Furthermore, some domestic institutional barriers for bidding and procurement still exist. Despite many manufacturers of vaccines, India still imported some polio vaccines in 1995. However, the future looks brighter for newer vaccines such as Hepatitis B since many companies now indigenously manufacture it. Additionally, the New Drug Policy of 1994 lifted price restrictions on genetically engineered vaccines produced by recombinant DNA technology and specific cell/tissue culture targeted drug formulations for five years from date of manufacturing to provide an impetus to the private sector to ensure adequate national supply.

The clear demand signals (although not assured) from the national and international procurement program combined with some competition, appear to have played the appropriate market role for Hepatitis B. Nevertheless, the institution context for technological development appears less clear. Many companies did this in parallel, at different rates, and with varying degrees of success. Not all have pre-qualified for the procurement programs to the same extent. Indeed, there may be too many Hep B vaccine suppliers and a shake-out from over-supply may not occur easily for reasons of delayed certifications, discussions with the national regulatory authorities and the relative lack of integrated forums where vaccine manufacturers can interact with both health policy and industrial policy at once. National Ministries overseeing Health are distant in more ways than one from Ministries for Industry or Departments of Science and Technology, as in many other countries. In interviews, many suppliers spoke of considerable secrecy, antagonism with competitors and distrust of the procurement policies and decisions. Certainly, in the case of Indian diagnostic kits, for example, procurement has been a mixed blessing. Domestic suppliers appear to have been ignored and India continued to import diagnostic kits for various diseases despite the presence of domestic suppliers. Moreover, only recently have international organisations such as the Developing Country Vaccine Manufacturers Network and national efforts-through links with public research-provided vaccine suppliers to come together for discussions. The absence of clear guidelines and national regulatory processes which oversee all such supply becomes increasingly important when domestic suppliers exist but who may still need some process upgrading certification from a third party of experts.

In the Indian case, there were clearly certain capabilities within pharmaceutical and biopharmaceutical sectors before international public procurement became a significant demand-side advantage. National procurement did occur earlier and was influential, but capabilities were built up in a variety of different ways (Srinivas, 2004). We would be ill-served to extend the findings here to countries with little or no technical infrastructure, or those meeting technical elements of standards for the first time. For such countries, the attainment of the standard is less a technical issue (important though that aspect is) than an enormous institutional challenge.

## **7. National realignment of innovation institutions**

As new vaccine quests emerge and as newer, more complicated processes are used, the obstacles facing specific firms and regulatory agencies become translated into a re-alignment of institutions dealing with

innovation. India is currently engaged with vaccine quests for Rotavirus, Meningococcus and Neurococcus, Japanese encephalitis, Malaria and various combination vaccines for more the mature DPT, DT, MMR, Hep B, and BCG for specific market segments such as newborns, children and teens and geriatric populations. Sixty percent of Indian exports are to other developing countries, and South-South technical assistance programs will take on greater importance as Indian firms expand their capabilities.

There have been two noteworthy changes at the national level that have arisen because of international participation. While firms have been upgrading their vaccine process capabilities, they have been forced to work more closely with the NRA. In turn, the NRA has been pressured for change to some degree by attempts by national and state governments and professional associations to build up hubs of vaccine suppliers. Secondly, firms that engage in international procurement have found new collaborations with both national and international institutes for R&D, diffusion and grant support.

More collaborative partnerships have opened up between Shantha Biotechnics and Bharat Biotech, two leading Hepatitis B suppliers. While India has always had some level of interaction between private companies and the government in vaccine production, the voluntary participation in an international procurement program allows for further streamlining and coordination of efforts for both parties. In addition, the firm, while clearly influenced by NRA guidelines as a conduit to export markets via the WHO or UNICEF, in turn influences the future form of the NRA through its own professional association representation. Thus, the learning process for both institutions, firm and regulatory body alike, are ongoing, driven by their participation in an international effort synchronous with national goals for public goods delivery. In a sense, because the vision and goals of the national and international policy are aligned (unlike in the case of international participation in the WTO where national policy efforts are often stymied), internal learning and adaptation can occur.

From a technical standpoint, the advantages of Indian companies are now evident in their lower costs for R&D and manufacture, and their ability to conduct clinical trials. In particular, Indian contract service providers now exist for various elements of vaccine development and manufacture, such as molecular cloning, fermentation, gene expression, development of cell lines for vaccines and clinical trials. These latter skills are augmented by India's vast domestic demographics for various diseases and the large, yet unmet local demand for many sub-segments.

However, as a group, Indian firms have had some notable teething pains in both technological advance as well as in facing regulations and standards. First, no degree of well-designed technology transfer can overcome many in-house process challenges and there has been much re-inventing of the wheel. Some of this is inevitable for any search and experimentation routine in-house; it remains to be seen how industrial measures either from industry associations or other organisations, could assist in this process of information-sharing despite the conditions of secrecy and competition. Second, there is the continued, murky regulatory area of the use of non-approved yeast or other media in laboratory research, despite higher yields. Some laboratories have had to discontinue the use of a promising strain because the regulatory environment is unclear. Third, from a world standpoint, Indian firms have continued until relatively recently to manufacture products discontinued elsewhere (e.g. nerve-tissue vaccines). Four, shortened product development lifecycles for newer vaccines and combination vaccines are proving difficult. Nevertheless, this last point is possibly the least of their difficulties.

There are broader institutional problems such as fragmented foreign markets, although procurement by international agencies has mitigated this somewhat. Nevertheless, the strategies for companies seeking to enter advanced industrialised markets for vaccines, is still not clearly mapped out. At home, there is a perception in many sub-segments of the vaccine market that foreign products are better. This is a longer-term challenge for both Indian vaccines and other Indian drugs. The approvals process within India at various stages has been patchy and has faced challenges from Indian companies eager to meet demand.



Finally, there are significant product liability concerns for vaccine trials and vaccine immunization programs that remain unresolved. Indian firms have been following the outcomes of legal cases in the West, but little corresponding institutional development and technical expertise has been developed within the country to date.

## **8. Discussion**

### **8.1. Demand-necessary, but not sufficient**

The WHO estimates that approximately three million lives are lost worldwide each year to diseases for which vaccines already exist. To reduce this number, vaccine procurement, supply and immunisation programs are all important. At the same time, trends indicate that many firms in advanced industrialised countries are ceasing to manufacture mature vaccines for their own populations, and for those in developing countries. Therefore, there continue to be technical and institutional issues to ensure that high-quality, safe vaccines be developed and manufactured by firms in developing countries. However, the Indian case of vaccine process development and manufacture suggest some technical institutional bounds to the discussion of procurement as a demand-policy instrument. Well-designed procurement policies linked to strict standards are important. The persuasive influence of international procurement policies in particular is embedded in its ability to assure large, if not always steady, demand to firms in developing countries. Nevertheless, this research suggests that its utility lies in three components which go beyond demand alone: (a) Its role as a *voluntary* technical upgrading mechanism for interested suppliers (b) Its ability to work *in conjunction with* National Regulatory Authorities (NRAs) and national procurement (c) Its premise that both supplier and procurer have a set of compatible technical and regulatory in-house skills, or at least the procurer having more than the supplier. In the first case, it behaves more generously than do institutions with mandatory regulations for all manufacturers of a product. Inclusion in the WHO or UNICEF list of suppliers is therefore a voluntary exercise. Thus, programs via the WHO to assist developing country firms meet such standards is a welcome part of industrial streamlining and advance. However, unless the second mechanism works robustly i.e. the procurement program works in conjunction with the national regulatory authority, policies such as these that intend to provide good health outcomes, will continue to be at odds with the broader regulatory environment of industrial development. Thus public procurement alone i.e. the signalling of demand and subsequent procurement, is insufficient in itself.

Secondly, procurement is not simply about ensuring efficient and timely supply. The link to the NRAs requires well-designed national and international procurement to shape the supply of products with local relevance channelled into better immunization programs. It is up to national industrial measures to ensure that vaccine manufacturers are suitably linked to both health and industrial ministries. Globally, the improvements of NRAs in developing countries has been steady, with the WHO classifying eleven country NRAs in developing and transition countries as being fully functional, of which eight countries have manufacturers with various UN pre-qualified products. Details of specific regulatory pathways for vaccines in developing countries can be found in Milstien and Belgharbi (2004).

### **8.2. Beyond process-induced cost reductions: Seeking broader technological advance**

As the table on comparisons of Indian and European or US vaccine providers demonstrated, there are some technological gaps for Indian vaccine suppliers. Not all vaccines with local relevance are being pursued with equal alacrity, nor are all capabilities for local vaccine needs completely indigenous, which partly explains why international collaborations continue to be attractive. Furthermore, a tiered path for vaccine development using recombinant technology is less than straightforward as biological substances have different standards and monitoring guidelines relative to synthetic drugs. The segmented markets and suppliers established through WHO guidelines also place some limits on market expansion in the long run. Nevertheless, international procurement continues to play an important demand-side role to promoting upgrading and some gradual innovation, and also increases export reach for indigenous

vaccine suppliers. Such programs provide a promising variant on traditional technology procurement at the national level.

The primary data collected for this research also suggests the following ways for specific technological improvements by firms and government (as procurer and regulator). The incentives for better process capabilities in firms are necessary because they go beyond process-induced cost reductions. Besides the generalized goals of safety, quality and speed that result from process upgrading, firms can also develop capabilities in newer vaccine challenges, such as developing tests for distinguishing between effective and non-effective lots, and between content specificity of the same vaccine from different producers (which may have different carrier proteins and in varying amounts). Furthermore, biological specificity at various stages raises the bar for firms to distinguish at higher levels of certainty, various process characteristics of vaccines at every stage.

In the case of international procurement with explicit social goals for health, the basis for upgrading and process development can be characterized as quality and speed competition, as opposed to that based on price alone. Furthermore, upgrading is also not only limited to process development in terms of “doing things better,” but also to infrastructure upgrading, which is a closely related issue.

From a research policy standpoint, demand instruments such as public procurement can have specific technological goals. Beyond the setting of clear guidelines for meeting certain standards and regulations for safety, quality and speed, they can add to a specific sub-set of process capabilities that are becoming invaluable worldwide for both the vaccine and broader pharmaceutical industries. These are the abilities to move into newer vaccine development, the capability to develop efficacy tests for separating effective and non-effective lots (this is not just a criterion to be used, but an industrial capability of its own an a potential sub-sector for assays) and the capability to develop tests for distinguishing between supplier-specificity, by studying content variation through different carrier proteins, or for different concentrations of sub-contents). Finally, firms that are able to separate out specifics of processes and their characteristics manifested in the vaccines, will be better able to demarcate the biological specificity of a specific vaccine at each stage of its development. As biological specificity becomes an increasingly important criterion of standards and regulations for the biopharmaceutical and vaccine industry, this skill will rapidly distinguish firms with some manufacturing capabilities from more advanced firms both R&D and manufacturing capabilities.

A key feature of international institutional buyers is that they are able to combine risk mitigation with open bidding and segmented markets. Thus, while offering developing country firms with significant export reach, they offer an element of protection to newer, less experienced firms, in allowing them to upgrade and sell away from multinational western firms. A range of procurement best practices is available from various international agencies. (See, for example, the WHO guidelines on procurement, WHO/VSQ/98.05, and WHO/V&B/99.12, I.D.1) An R&D policy question is whether vaccine delivery times linked to procurement needs can be correlated with measurable elements of technological advance, such as upgrading of specific process development capabilities. A proposed hypothesis, requiring further testing, is that technological advance is best when delivery times available to the supplier are long *and* the number of competing suppliers is large. Thus, emergency items or small volumes procured through national or international programs, where the delivery time is short, are unlikely to be good candidates for procurement. By this gauge, bulk-buying of single-source drugs or vaccines is also likely to be a poor correlate with technological advance. More research is needed to examine under what conditions technological advance is most likely for developing country firms.

Finally, international procurement offers perhaps its strongest impact--it actively seeks to disseminate standards information and meet with suppliers. Thus, while this shares characteristics with private global buyers, suppliers in this case have significant domestic markets they can target with the same innovations

and can utilize various national programs and public domain research collaborators to help them upgrade. Importantly, the buyer here is not at competition in any way with suppliers and thus faces no disincentive from suppliers that may upgrade rapidly into the specialization areas of the buyer (highlighted in Schmitz, 2000 in the case of the shoe industry).

However, public procurement can be more targeted for upgrading and even innovation. In addition, some suppliers face uncertain product liability issues in new markets, which could be more directly addressed by procurers through broader information campaigns and insurance mechanisms that lower the risk to suppliers, while still protecting patients, particularly for pediatric vaccines. Thus far, most health debates are primarily concentrated on access to medicines and tend to under-research the utility of demand-led technological upgrading, which, in principle, can also positively affect access to medicines in developing countries.

The early selection environment, which governmental policies certainly influenced, has been discussed most often in the developing country literature in terms of biased weighting in favour of indigenous firms and infant industry protections that were undeserved. While the record of state protections to young industries is mixed, the Indian pharmaceutical history suggests that variants of traditional protections such as procurement, may be helpful in understanding how government policies can assist technological advance. The demand that the state--and international agencies--can generate through technology procurement programs, particularly those linked to public health in this industry, may be a powerful stabilizing factor that diminishes uncertainty and provides legitimacy to firm-level search efforts and helps build an entire industry to maturity or for specific product lines deemed to be in the national interest. These, however, can only assist long-term learning if they are closely linked to technical and institutional requirements. However, in such demand-driven procurement policies, the extent of innovation as an outcome is not dependent on the capabilities of the firm alone. It is affected by the technological capacity of the public sector procurer as well as the size of the initiated demand that mitigates risk in undertaking new innovations (Dalper, 1994). There is some evidence to indicate that procurement programs do stimulate innovation in a range of countries (Rothwell, 1994 for Japan and Europe), but little recent data is available for developing countries. Furthermore, in many cases of procurement, the public procurer is not necessarily a first-user of the innovation, which makes procurement to stimulate innovation through a non-using procuring agency even more complicated. From a domestic standpoint, while the Indian regulatory experience is considerable, there is the question of how to assist other developing country procurers and suppliers alike, especially those in countries with lesser scientific or technological capabilities. Efforts by the Developing Country Vaccine Manufacturers Network and other organisations promoting cooperation between developing countries hold some promise. Certainly, on vaccine process development and manufacture, very little has been written from an industrial viewpoint for even existing vaccine suppliers.

## **9. Conclusions**

Fewer companies worldwide are taking on vaccine supply for a variety of economic and technical reasons. Clearly, the vaccine industry affords opportunities for technological learning beyond discovery alone. Indeed, the process development and manufacture challenges are considerable. The fact that some process can be accomplished in the laboratory is by no means an indication that it can be replicated at factory scale. Considerable tweaking of national regulatory mechanisms is still necessary both to specify the standards and regulations in a clear way, to speed up review and feedback, to provide forums for discussion between suppliers and between suppliers and government, but also to explicitly link health policy to industrial policy in this sector. Low quality and supply in some vaccine sub-segments is not a mystery if it is treated as an integral part of industrial and health policy alike and demand policy instruments, especially procurement programs, must be integrated accordingly.

However, the international environment in which developing countries can simply continue to assist their own firms, has changed. The World Trade Organisation's various Agreements, preclude entirely open-ended support by developing country governments for industrial or technological advance. Public health has some limited flexibility in the current multilateral regime as an issue of national interest. It therefore becomes even more imperative for governments to work with groups concerned with supply of affordable medicines, as well as industry representatives, to closely tie instruments of public health policy to more finely tuned industrial development through the technological opportunities they present.

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