

32040

Vaccines and Drugs: Characteristics of Their Use to Meet Public Health Goals

Julie B. Milstien, Amie Batson and Albert I. Wertheimer

March 2005



Public Disclosure Authorized

**VACCINES AND DRUGS: CHARACTERISTICS OF THEIR USE
TO MEET PUBLIC HEALTH GOALS**

Julie B. Milstien, Amie Batson and Albert I. Wertheimer

March 2005

Health, Nutrition and Population (HNP) Discussion Paper

This series is produced by the Health, Nutrition, and Population Family (HNP) of the World Bank's Human Development Network ([HNP Discussion Paper](#)). The papers in this series aim to provide a vehicle for publishing preliminary and unpolished results on HNP topics to encourage discussion and debate. The findings, interpretations, and conclusions expressed in this paper are entirely those of the author(s) and should not be attributed in any manner to the World Bank, to its affiliated organizations or to members of its Board of Executive Directors or the countries they represent. Citation and the use of material presented in this series should take into account this provisional character. For free copies of papers in this series please contact the individual authors whose name appears on the paper.

Enquiries about the series and submissions should be made directly to the Managing Editor. Submissions should have been previously reviewed and cleared by the sponsoring department, which will bear the cost of publication. No additional reviews will be undertaken after submission. The sponsoring department and authors bear full responsibility for the quality of the technical contents and presentation of material in the series.

Since the material will be published as presented, authors should submit an electronic copy in the predefined format. Rough drafts that do not meet minimum presentational standards may be returned to authors for more work before being accepted.

The Managing Editor of the series is Joy de Beyer (jdebeyer@worldbank.org). The Editor in Chief of the series is Alexander S. Preker (apreker@worldbank.org). For information regarding this and other World Bank publications, please contact the [HNP Advisory Services](#) (healthpop@worldbank.org) at: Tel (202) 473-2256; and Fax (202) 522-3234.

© 2005 The International Bank for Reconstruction and Development / The World Bank
1818 H Street, NW
Washington, DC 20433

All rights reserved.

Health, Nutrition and Population (HNP) Discussion Paper

Vaccines and Drugs: Characteristics of their Use to Meet Public Health Goals

Julie B. Milstien,^a Amie Batson^b and Albert I. Wertheimer^c

^a Adjunct Assoc. Professor, Center for Vaccine Development, Division of Geographic Medicine, University of Maryland School of Medicine, Baltimore, Maryland, USA

^b Sr. Health Specialist, Human Development Network, The World Bank, Washington, DC, USA

^c Director, Center for Pharmaceutical Health Services Research, Temple Univ., Philadelphia, PA, USA

Paper commissioned as part of a World Bank review of pharmaceutical policy in low- and middle-income countries. Draft finalized June 2004

Abstract: The major characteristics of vaccines and drugs are reviewed and contrasted in seven key areas: research and development, the market, supply sources, regulation, procurement, financing, and access. The comparison helps to identify areas where access could be enhanced. These conclusions are drawn: (1) While public investment in R&D has been more frequent for vaccines than for drugs, it has normally covered only a fraction of R&D costs. Concerted action is needed to stimulate development of innovative public health products, with public-private partnerships being a way to stimulate work towards a specific goal. (2) Drugs and vaccines face different market conditions that affect the ability to forecast demand. While for drugs, use depends on individual willingness to pay; the vaccine market depends on government willingness to pay, based on epidemiological justification for use of a product. (3) The supply landscape differs for drugs and vaccines, with fewer vaccine manufacturers. This limits competition, compared to the case of generic drug products. Strict control of the supply chain for vaccines minimizes leakage, and makes differential pricing easier to implement. (4) A joint approach to the regulatory process for drugs and vaccines will have benefits, especially as their regulation is normally controlled by a single agency within a country. Risk-benefit assessments by the US FDA do not consider global implications, creating a need for capacity to do risk-benefit assessments in developing countries. (5) Similar procurement principles could be applied to the prequalification process for drugs and vaccines. (6) Societies often undervalue prevention in health care, which impacts vaccine prices and financing. (7) Activities that enhance access to drugs will also enhance vaccine access, although the relative importance of different factors inhibiting access may differ. Both differential pricing as well as compulsory licensing may be considered.

Keywords: vaccines, access, regulation, immunizations, health financing, pharmaceuticals, private sector, research and development

Disclaimer: The findings, interpretations and conclusions expressed in the paper are entirely those of the authors, and do not represent the views of the World Bank, its Executive Directors, or the countries they represent.

Correspondence Details: Julie Milstien, 3 bis rue des Coronilles, 34070 Montpellier, France, Tel: 334-6706-5779, Email: milstien@medicine.umaryland.edu

Table of Contents

FOREWORD.....	VII
ACKNOWLEDGEMENTS	IX
INTRODUCTION.....	1
RESEARCH AND DEVELOPMENT	3
FUNDING SUPPORT	3
PATENTS	4
ORPHAN DRUG LEGISLATION.....	4
OTHER APPROACHES	5
MARKET: CHARACTERISTICS AND FORECASTING OF DEMAND.....	5
MARKET CHARACTERISTICS	5
FORECASTING DEMAND	6
<i>Forecasting routine vaccine demand</i>	<i>6</i>
<i>Forecasting uptake of new vaccines.....</i>	<i>6</i>
<i>Forecasting drug demand.....</i>	<i>7</i>
SUPPLY: SOURCES, CONSIDERATIONS FOR PRODUCTION AND THE SUPPLY CHAIN	7
SOURCES OF SUPPLY	7
GENERIC PRODUCTS	8
PRODUCTION CONSIDERATIONS	9
SUPPLY CHAIN	10
REGULATION	10
NATIONAL REGULATORY AUTHORITIES.....	10
REGULATORY RISK-BENEFIT	11
PROCUREMENT.....	11
LARGE PUBLIC SECTOR PROCUREMENT AGENCIES.....	11
THE TENDERING PROCESS	12
PREQUALIFICATION	12
TENDER SPECIFICATIONS AND RECEIPT OF PRODUCTS	13
NEW PRODUCTS	13
FINANCING: PRICING AND FUNDING	13
PRICING	13
FACTORS INFLUENCING PRICES	15
FUNDING.....	16
ACCESS: PATENTS, DIFFERENTIAL PRICING, ALLOCATION, DELIVERY INFRASTRUCTURE	16

LIMITATIONS DUE TO PATENTS	16
DIFFERENTIAL PRICING STRATEGIES	17
ALLOCATION	17
DELIVERY INFRASTRUCTURE	18
DISCUSSION	18
RESEARCH AND DEVELOPMENT.....	18
MARKET: CHARACTERISTICS AND FORECASTING OF DEMAND	18
SUPPLY: SOURCES, CONSIDERATIONS FOR PRODUCTION AND THE SUPPLY CHAIN.....	19
REGULATION	19
PROCUREMENT	19
FINANCING: PRICING AND FUNDING	20
ACCESS: PATENTS, DIFFERENTIAL PRICING, ALLOCATION, DELIVERY INFRASTRUCTURE	20
ANNEX 1: SUMMARY CHARACTERISTICS OF DRUGS AND VACCINES.....	21
REFERENCES.....	23

List of Tables

Table 1: Vaccine-preventable diseases, by year of vaccine development or licensure United States, 1798-1998*.....	3
Table 2. Price comparisons for common medicines	14
Table 3. Price comparisons for HIV therapies.....	14
Table 4. Comparison of treatment prices for amoxicillin 250 mg tab, US\$.....	15

FOREWORD

Several inputs are indispensable in ensuring health services function properly. These include pharmaceuticals, equipment, other consumables, capital, human resources, and knowledge. This publication – *Vaccines and Drugs: Characteristics of Their Use to Meet Public Health Goals* — by Julie B. Milstien, Amie Batson and Albert I. Wertheimer, reviews and compares the major characteristics of vaccines and drugs in terms of research and development, the market, supply sources, regulation, procurement, financing, and access. It is part of a series of publications on the role of pharmaceuticals as critical inputs to health services in low- and middle-income countries.

Drugs are often the most important cost driver of health care expenditure on hospitals and ambulatory care. Patients that have access to adequate and effective drugs at the time of need are more likely to be happy with the treatment they receive. When such drugs are not available or ineffective after use, patients will go elsewhere, even if they have to pay high prices to private providers, to get the care they think they need.

The availability of affordable and effective drugs is, therefore, one of the most visible indicators of the quality of health services. Satisfaction with the drugs received is a key determinant of utilization of health services and return visits in the public sector. And the cost of out-of-pocket spending on drugs is a major contributor to the impoverishing effects of illness.

Despite significant progress in increasing access to essential medicines in low- and middle-income countries during the past decades, many of the health services used by the poor still lack adequate supplies of basic medicines. Drug shortages and quality problems continue to undermine the performance of health systems throughout the developing world.

Many factors influence whether poor people can obtain affordable drugs of good quality. This includes issues related to pricing and procurement of existing drugs, new product development, patenting/intellectual property rights, manufacturing or import of drugs, macroeconomic constraints, and foreign exchange fluctuations. Without addressing these issues, many countries will fail to reach their poverty and Millennium Development Goal targets.

This paper reviews some of the key similarities and differences of vaccines and drugs in terms of: research and development, supply, demand, pricing, markets, regulation, and procurement. The authors conclude that activities that enhance access to drugs will also enhance vaccine access, although the relative importance of different factors may vary.

Alexander S. Preker

Lead Economist
Editor of the HNP Publications

ACKNOWLEDGEMENTS

The authors of this Report are grateful to the World Bank for having published the Report as an HNP Discussion Paper.

INTRODUCTION

Drugs and vaccines are both classified as pharmaceutical products. In some ways this classification is useful, as they share many similar characteristics. However, the classification ignores some facets related to availability, accessibility and economic impact. This paper will consider their differences and similarities in the following seven general areas:

- Research and development
- Market: characteristics and forecasting of demand
- Supply: sources, considerations for production, supply chain
- Regulation
- Procurement
- Financing: pricing and funding
- Access: patents, differential pricing, allocation, delivery infrastructure

At the outset it is useful to define the terms “drug” and “vaccine”:

A **drug**, or chemical medicine, is a pharmaceutical product composed of a chemically defined amount of pharmaceutically active ingredients (plus excipients), normally given for treatment of illness, although there are preventive uses (antimalarials, for example).

A **vaccine** is pharmaceutical product that is a biological medicine, made in, composed of, and/or tested through living systems, and thus difficult to standardize. It functions by eliciting an immune response and is generally for preventive use, although therapeutic vaccines (for example, for treatment of some forms of cancer) are now being developed.

The characteristics included in these definitions give rise to some of the major differences. The discussion below will highlight others, such as the role of the public *vs.* the private sectors in their use.

The major conclusions from these considerations are that chemical and biological medicines have many areas of similarity but several important differences that impact their development and availability. Vaccines differ from drugs in that they are generally provided free or at low cost to a healthy population by national governments, have traditionally commanded fairly low prices in comparison to production and quality control costs, and many vaccine products are about 50 years old with mature markets and off-patent technologies. This has meant that profit margins in the vaccine industry have been low. During the last 25 years, many vaccine companies in the industrialized world have been acquired by large pharmaceutical firms or have left the business. Today there are only 12 licensed vaccine manufacturers in the US, down from 26 in 1967, with only four producing most of the products.¹

Given the overall objective to facilitate access to and rational use of drugs and vaccines, there are lessons from each of the two kinds of product that could usefully be applied to the other. Some questions to consider while reading this paper include:

1. **Research & development.** Should public sector support for vaccine R&D be replicated for priority drugs? Do the characteristics of the disease against which an intervention is targeted determine public sector support for R&D? Are public-private partnerships such as the Medicines for Malaria Venture a good model for this? Are there other mechanisms the public sector could use that would stimulate more private sector R&D for interventions against diseases of public health importance both for drugs and vaccines?
2. **Market: characteristics and forecasting of demand.** What are the major characteristics of the markets for vaccines and for drugs? Are stockpiles a reasonable strategy to smooth out variations in demand? How can market estimation be made more robust, and what impact would this have?
3. **Supply: sources, considerations for production and the supply chain.** The strict control imposed by the cold chain for vaccines has been important in limiting leakage and facilitating market segmentation, thus enabling differential pricing strategies. Would greater attention to the drug supply chain facilitate implementation of differential pricing?
4. **Regulation.** Are efforts to strengthen a single regulatory authority for functions controlling both drugs and vaccines appropriate and will they facilitate access to products? How can different valuations of risk-benefit of products be addressed given the important global role of the US and European regulatory authorities?
5. **Procurement.** Prequalification is a tool used to limit the procurement process. The prequalification process for drugs is in its early stages and is currently a global process, independent of any functions of a national Regulatory Authority of the producing country. This is in contrast to that for vaccines, which relies on prior assessment of the producing country Regulatory Authority as a prerequisite to prequalification. Should assessment of national Regulatory Authorities be an integral part of the prequalification process for drugs as well as for vaccines?
6. **Financing: pricing and funding.** Competition has been important in lowering prices of both drugs and vaccines, but in the drug industry it is a much more important factor. Would enhanced competition in production of innovative vaccines, for example, from nontraditional sources (emerging suppliers, biotechnology firms, or the public sector), be useful in lowering prices for these vaccines? There is a higher willingness to pay for curative drugs. As willingness to pay could be an individual as well as a government characteristic, how do drugs and vaccines differ? Prevention is undervalued, and advocacy efforts have not yet succeeded in changing this perception.
7. **Access: patents, differential pricing, allocation, delivery infrastructure.** Can differential pricing strategies be augmented for both drugs and vaccines to enhance access?

A summary of characteristics in each of these areas is found in Annex I.

RESEARCH AND DEVELOPMENT

At its inception, the vaccine industry was developed mostly through public sector institutions with a mandate to develop new products for the public good. This is likely due to the fact that use of vaccines lead to a global public good, the prevention of communicable disease, and because governments distribute vaccines free of charge through their public health programs. Table 1 illustrates a partial history of vaccine development in the United States. The vast majority of these were developed, and many were manufactured, in the public sector. It can clearly be seen that most of these vaccines are over 45-50 years old.

Table 1: Vaccine-preventable diseases, by year of vaccine development or licensure United States, 1798-1998*

Disease	Year	Disease	Year
Smallpox	1798	Rubella	1969
Rabies	1885	Anthrax	1970
Typhoid	1896	Meningitis	1975
Cholera	1896	Pneumonia	1977
Plague	1897	Adenovirus	1980
Diphtheria	1923	Hepatitis B	1981
Pertussis	1926	<i>Haemophilus</i>	
Tetanus	1927	<i>influenzae</i> type b	1985
Tuberculosis	1927	Japanese	
Influenza	1945	encephalitis	1992
Yellow Fever	1953	Hepatitis A	1995
Poliomyelitis	1955	Varicella	1995
Measles	1963	Lyme disease	1998
Mumps	1967	Rotavirus	1998

*Note: this summary does not include enhancements of specific products such as cell culture rabies vaccine or conjugated polysaccharide vaccines nor does it include combination vaccines. For smallpox, routine vaccination was ended in 1971. Recommendations for universal use of rotavirus vaccine were rescinded in 1999 after cases of intussusception were noted in connection with its use.

FUNDING SUPPORT

Recently, there has been an increasing move for consolidation in the pharmaceuticals world, with the result that most multinational vaccine producers are part of large pharmaceutical firms. Internal resource allocations now pit R&D investment requests for vaccines against drugs. Given that vaccines account for less than 2% of the total pharmaceutical market (\$6.9 billion² vs. \$380 billion), and usually have lower profit margins, and longer production lead times, they have historically competed poorly in terms of R&D allocation. Innovation in the vaccine industry has been limited compared to that for chemical medicines. In terms of investment in R&D, for 1999-2000, yearly expenditure figures are illustrative (the vast majority of which are private sector, and include in addition to basic research, process development and clinical trials): \$26 billion for pharmaceuticals, \$9.9 billion for biotechnology, and \$1.5 billion for vaccines.³ Traditionally funding for basic vaccine R&D has been largely from public sources, contributing to collaboration between public and private partners. Clinical trials and process development are extremely expensive for vaccines, and for the most part have been financed by the private sector.

Two exceptions to this are special cases. One example is the yearly public-private decision on the composition of influenza vaccine. WHO collaborating centers coordinate this effort and provide public and private manufacturers with the vaccine seed. Another example is the US government's recent decision to contract for the development and production of vaccines against potential bioterrorism agents, such as smallpox and anthrax, and now against severe acute respiratory syndrome (SARS). Thus, for vaccines, infectious disease burden, or its threat, has been a major driver of R&D allocations, albeit with more attention paid to infectious diseases in the industrialized world.

On the other hand, drug manufacturers, with generally higher prices, higher profit margins, and shorter time frames for returns on investment tend to compete for products serving wealthy market segments. For example, the drug market in the US now has 15 ACE inhibitors and 12 beta-blockers and invests tremendous amounts in "lifestyle" drugs.

PATENTS

One aspect of R&D that both drugs and vaccines potentially share is the need to patent new technologies. In the case of drugs, patents and the role of generics are contentious issues, dominating discussions in the World Trade Organization and its TRIPS provisions (Agreement on Trade Related Aspects of Intellectual Property Rights).⁴ In the case of vaccines, where production processes are more difficult to standardize, know-how rather than patents becomes a much more important factor. A case in point is the 69k protein of *Bordetella pertussis*, an essential component of acellular pertussis vaccines. In a final non-appealable decision in March 1998, this patent was revoked by the European Patent Office Technical Board of Appeal,⁵ thus removing intellectual property protection barriers to its use. Similarly restrictive patents that referred to all methods of making a particular product such as the Biogen patent for recombinant hepatitis B, have been revoked.^{6,7} Know-how, the ability to run a synthetic process consistently to produce the desired product, is possibly difficult to acquire in the case of production of chemical medicines, although many examples of reverse engineering of patented products are known. In the case of vaccines, it may be an insurmountable barrier, effectively removing the threat of reverse engineering for many products.

ORPHAN DRUG LEGISLATION

An area where both drug and vaccine development for public sector interests can be promoted is in the orphan drug legislation, now in force in both the US and Europe.^{8,9,10} The US Orphan Drug Act of 1983 proposed financial and regulatory incentives for the R&D of drugs to treat rare diseases. Incentives included a 50% deduction tax credit for clinical trial expenses, market exclusivity of seven years, and flexibility in registration requirements designed to accelerate the approval process, particularly in cases where the target market was so small that clinical testing was of necessity limited. Similar legislation has passed in Europe. The proposed European criteria for classification included disease prevalence of 5 per 10,000 Europeans, and specified incentives in terms of R&D assistance, possible fast-track approval, fee waiver, tax credits, and market exclusivity for 10 years.

As of 1997, in the US, 837 products had been designated orphan drugs and 152 had obtained authorization compared to the previous 14 years when only 34 orphan products were authorized.⁸ Five years later those numbers were 1186 designations, and 226 authorized.⁹ However, these

identified orphans included only eight vaccines, seven for therapeutic use. In Europe, where the legislation has been in effect since 2000, as of March 2002 165 applications for designation as orphan drugs had been received by the EMEA, and by January 2003, over 120 products had been so designated.¹⁰ Only seven of these had received marketing authorization and only one was a vaccine (but not one of interest to the developing market).

This information suggests that orphan drug legislation may have a role to play in stimulating R&D for pharmaceuticals, but to date has not been very effective for vaccines. An additional problem is that many of the diseases of public health importance for which vaccines would be desirable have the majority of the target population in the developing world. Furthermore, the characteristics of the disease organism, the target population, and/or the method of disease transmission may differ so that a vaccine product developed in the industrialized world might not be useful for disease prevention in the developing world, or vice versa.

OTHER APPROACHES

Other mechanisms have been discussed that will not be covered in detail here, including the so-called “push” and “pull” mechanisms for vaccine development. A discussion of these can be found on the website of the Global Alliance for Vaccines and Immunization.¹¹ They include investments in production facilities, tax breaks, patent extensions, support of clinical trials (all examples of push funding), as well as guaranteed purchase commitments (pull funding, of which the US government’s bioterror strategy is an example).

MARKET: CHARACTERISTICS AND FORECASTING OF DEMAND

In general the sizes and characteristics of the markets for drugs and vaccines differ, and these differences are illustrated by industry’s view of the perceived market risks.

MARKET CHARACTERISTICS

The total market for chemical medicines is far larger than that for vaccines. The estimated vaccine market in 2001 was \$6.9 billion, well below the annual sales of many pharmaceutical companies. In fact, annual sales of a single pharmaceutical product exceeded that figure in 2000.¹²

Because vaccines are preventive, the primary customer is the public sector, accounting for roughly 80% of the total production volume, but less than 20% of the revenue. Drug sales are primarily to private sector customers, even when distributed through public health sector channels. Thus willingness to pay depends on individuals in the case of drugs, and governments in the case of vaccines.

The size and characteristics of the market are undoubtedly the primary consideration in the decision of a manufacturer to produce a new product. In the case of vaccines, manufacturers will look at historical behavior in uptake of products to determine the robustness of the market.

FORECASTING DEMAND

One of the major difficulties in public and private sector forecasting of demand is the confusion that has arisen over the definition of demand. The public sector has frequently confused need with demand. Need is the number of doses that should be used in all populations to control the disease effectively. However, demand is the number of doses that are actually purchased, depending on access, willingness and ability to pay, and perception of need.

Vaccine demand can be divided into three general categories: routine, supplemental (e.g. campaigns, outbreak response immunization and response to an emerging threat such as bioterrorism), and new product introduction.

Forecasting routine vaccine demand

Forecasting demand is relatively easy for the routine category, which in the US comprises both public and private sector use, but globally is largely in the public sector. Demand depends on the number of doses in a series (usually one to three, typically given over a six month period), the target population, a factor for wastage (based on a multidose vial presentation), and a factor reflecting the likelihood of reaching the target population (usually based on coverage figures for previous years).

Forecasting for the other categories is generally more difficult. Outbreaks cannot be predicted, but stockpiling may be a useful strategy in smoothing out demand for supplementary vaccine needs. Stockpiling is not useful when the infectious agent is unknown, as for an influenza pandemic.¹³ Criteria for establishing a stockpile should be followed, such as those outlined by Milstien and Lambert¹⁴ and by the US General Accounting Office.¹⁵ Following are some of the factors to be considered when it is critical to develop a comprehensive strategy to plan and manage a stockpile:

- Sufficient size with vaccine of sufficient efficacy to protect at-risk populations;
- No other viable treatment options available;
- Vaccines can be mobilized within the required time;
- Real/potential demand and market size can be estimated;
- Inventory of current/potential manufacturers meeting standards exists;
- Identification completed of production and regulatory bottlenecks, total capacity, lead times, and where and how stockpile will be stored;
- Sustainable financing is available;
- Fair distribution mechanisms are agreed;
- Consequences of stockpiling on supply of other vaccines are addressed.

Forecasting uptake of new vaccines

The uptake of new products for universal use will depend on programmatic readiness (related to infrastructure and perception of need), available financing and available supply. To better link supply, demand and financing, the Global Alliance for Vaccines and Immunization (GAVI) is experimenting with an innovative team¹⁶ from WHO, UNICEF and the Vaccine Fund designed to collaboratively manage uncertainties arising from operational, financial and supply decisions to new product introduction.

Forecasting for elective use of vaccines is similar to forecasting drug demand and is based on market analysis and willingness to pay surveys. This type of forecasting is not always easy nor accurate. An illustrative case is the experience with Lyme disease vaccine, which was developed and introduced in the United States in January 1999 by GlaxoSmithKline. It was a relatively expensive vaccine, targeted at a specific market segment, both regionally and economically. It was recommended for use by persons aged 15-70 who resided, worked, or recreated in areas of high or moderate risk, and not for the general population.¹⁷ In February 2002, citing diminishing sales, GlaxoSmithKline pulled the vaccine off the market. Factors involved in lower than expected use included the small eligible market, some unforeseen adverse events, and perception of low efficacy.

Forecasting drug demand

Forecasting drug use is complicated by the need for multiple-dose treatment and the inability to project how many people will need treatment for a particular disease, unless it is endemic or chronic.

Compliance and price per dose will impact the annual demand, especially for products for which treatment continues indefinitely, such as antiretrovirals for AIDS treatment. An example of the problem of compliance is the patient behavior that impelled the World Health Organization to put in place the DOTS (Directly Observed Treatment, Short-course) strategy for anti-tuberculosis medications.¹⁸

In some countries, the use of Essential Drug Lists and projecting utilization based on previous years' use can give an idea for use of older products (like the routine vaccine category),¹⁹ but for new products, especially when prices are high, demand will be difficult to predict. For expensive new products, available funding is often less than the actual clinical need. Therefore, demand may equal the budget amount available for pharmaceuticals.

SUPPLY: SOURCES, CONSIDERATIONS FOR PRODUCTION AND THE SUPPLY CHAIN

There are three defining characteristics of supply for both drugs and vaccines: characteristics of producers, characteristics of production, and the supply chain.

SOURCES OF SUPPLY

Many countries produce pharmaceutical products. In fact, many governments seek self-sufficiency in pharmaceutical production as a strategy to reduce prices and optimize supply, to conserve foreign exchange, and, ideally, to export excess volume. Large-scale pharmaceutical production has economies of scale that can lower production costs and raise profit margins. It is estimated that there are about 2,500 different pharmaceutical products, many of which have different presentations and dosage forms, and may be produced by several manufacturers. However, many of these products are either obsolete or have higher toxic effects than other, more widely used agents. There are an estimated 4,000 manufacturers of chemical medicines in the world. It is estimated though that more than 3,000 of these are local or regional repackagers -

- firms that fill capsules from purchased bulk ingredients. Still others may produce finished dosage forms, but do so for only a few products.

The number of producers and products is much lower for vaccines with roughly 200 vaccine products, including all presentations, and vaccine production in only about 45 countries. The vaccine industry is dominated by a small number of multinational firms: GlaxoSmithKline, Aventis Pasteur, Wyeth and Merck. These firms have seen their share of the vaccine market (measured by revenues) rise from approximately 50% in 1988 to about 70% today. Small to medium-sized companies, notably Chiron and emerging companies in Korea, India, and Indonesia, comprise an additional 10%, with the remaining revenues attributable to local industrialized and developing country producers.

What are the reasons for this drastic fall in number of vaccine suppliers? There appear to be two major reasons: the difficulty of producing vaccines to acceptable quality standards, and the low profit margins, especially on some of the older vaccines. At the moment the global community is in a situation of vaccine supply crisis. This situation has also occurred recently in the United States, although for slightly different reasons. The major factors have been the low profit margins on vaccines, forcing some manufacturers to either go out of business or shift their resources to products with higher profit margins; spiraling regulatory costs which demand even more investment in facilities and process development as regulatory authorities become stronger, and the diseases the vaccines are directed against disappear, making perceived safety considerations essential; the prohibition of thimerosal in some products, which resulted in a lowered effective filling capacity for manufacturers, as they had to shift from multidose to single dose vial presentations; product divergence across markets (both the thimerosal issue and product divergence will be addressed more fully below); demand forecasting that was poorly reflective of the market; and lack of uptake of some products already on the market. One response to this crisis has been the resolve in the United States to develop and use stockpiles more effectively. Criteria for stockpile allocation and the need for good stockpile management have already been mentioned above. The Centers for Disease Control and Prevention (CDC) have already developed and maintained stockpiles for vaccines for which there was only one licensed source in the United States, and will be extending this to other products. In addition, the CDC maintain stockpiles for vaccines and drugs as needed for emergency situations.²⁰ In some situations, the use of stockpiles can thus promote access.

The implications of the change in supply sources for vaccine manufacturers are several: on the one hand, it means a larger likelihood of a monopoly supplier, a greater sensitivity to threats of supply shortages, and the probability of higher prices. On the other hand, it means that the supply issue is logistically easier to consider, with fewer involved parties. The difficulty of making vaccines and the need to meet high quality and consistency standards mean that there are far fewer local manufacturers. In fact, most of the surviving domestic manufacturers in developing countries have large export markets, and very few of them are still in the public sector.

GENERIC PRODUCTS

The international pharmaceutical market is driven by research-based multinational companies that develop new, expensive proprietary products for which profit margins are usually high.

Manufacturers with new products will seek to limit the market entry of competitive generic products once patents expire. By contrast, for biological products, the term generic is not relevant. Because of the variabilities in biological product production, each lot of product is unique, and products produced by the same manufacturer but in different facilities may have different characteristics. The same product with the same biological actions may be produced using different technologies, and thus patent protection may not limit its manufacture.

Although generics are not an issue, the vaccine market is increasingly split by the divergence between traditional and new products across markets. The high-end private sector market may introduce newer products that are safer (inactivated poliovaccine *vs* oral poliovaccine (OPV)), more effective (conjugate meningitis C *vs* polysaccharide meningitis C vaccine), or purer (acellular *vs* whole cell pertussis vaccine) in single dose presentations free of thimerosal and produced by the multinational companies. The developing world public sector market may continue use of multidose presentations (with thimerosal in most cases) of the traditional vaccines, including OPV and diphtheria-tetanus-whole cell pertussis (DTwP) vaccine, made with decades-old technologies, often by emerging manufacturers. Product divergence in the vaccine market has the capacity to impact access through its effects on the possibility of price tiering (if a product for the developing market has no high-end market, price tiering is not an option); economies of scale (the market will be split among users of the divergent products, lowering the possibility of economies of scale); regulatory aspects (products formerly licensed in the country/region of manufacturer but no longer actually used in that area may no longer be eligible for marketing authorization). While product divergence also exists in the world of chemical medicines, its impact on distribution and prices is far less than that of generic *vs* proprietary products. More information on product divergence is available from WHO.²¹

PRODUCTION CONSIDERATIONS

For chemical medicines, the production process consists of compounding or formulating raw materials, including active ingredients, excipients, and stabilizers, into stable oral or injectable dosage forms. Control of the process is focused mainly on control of the raw material and the consistency of the procedure used, and final product testing to ensure bioavailability and shelf life. For vaccines, the process is inherently more complex. Because of the biological nature of the active ingredients and the production process, all parameters affecting viability of living organisms, especially pH and temperature, as well as concentrations of buffers and other chemical components, will affect the yield of product. As a result, process development and production of vaccines require long lead times, with every step and variable in the process standardized, controlled, validated, and tested.

Both types of processes require sterile products and full GMP compliance entailing significant investment, personnel hiring and training, and documentation. However, the constraints on pyrogenicity for an oral tablet are not as rigorous as for an injectable liquid.

The additional investments required for consistent GMP-compliance production of vaccines necessitates extensive fixed costs. As a result, biological production is highly scale intensive, generally more than for chemical medicines. In addition, the standards that vaccine producers must meet are stricter and more difficult to achieve. This not only raises barriers to entry in this market (because startup costs and expertise required are high), but also increases the pressure on

pricing (because with high fixed costs, economies of scale are more important, and there is less flexibility for pricing). In the US, several vaccine manufacturers have thus chosen to exit the vaccine market, including the only US-licensed producer of OPV and DTwP vaccines. Factors that facilitate large volume production have a significant impact in lowering costs, which can help to enable affordable pricing. This can further increase demand and thus assure use of these volumes.

SUPPLY CHAIN

Chemical medicines can generally be stored within a wide range of temperatures, a characteristic that is further enhanced by protective packaging. Exposure to excessive heat and humidity for limited time periods usually does not compromise potency or effectiveness; it may however decrease shelf life. Vaccines, on the other hand, are much more sensitive to fluctuations in temperature and must be stored, transported and used within a tightly managed cold chain – a system of temperature and stock control that assures that vaccines are potent and safe to use. The cold chain, in fact, necessitates a strict stock management system requiring excellent documentation, tracking vaccine (and diluent) flows at each level, adherence to strict temperature requirements, and intensive maintenance of the refrigerators, freezers, and transport vehicles that comprise the “chain”.²² This public sector managed system has limited leakage of product into other sectors, including the informal sector. By contrast, chemical medicines do not have strict stock management controls. Chemical drugs tend to have higher prices and far higher demand, thus creating incentives for leakage. While the supply chain needs could have the effect of lowering access to vaccines because of infrastructure constraints, in practice well over 80% of the world’s children are reachable by the routine vaccine delivery infrastructure, with an even higher percentage accessed during special immunization activities. On the other hand, the supply chain may, along with the generally low market value of vaccines, protect against counterfeits and parallel imports.

REGULATION

NATIONAL REGULATORY AUTHORITIES

The World Health Organization²³ has defined the major functions that a national Regulatory Authority should fulfill for producers and distributors of drugs and vaccines within their jurisdictions. These functions include granting marketing authorization, surveillance of product safety and efficacy both pre- and post-marketing, lot release (in the case of vaccines), testing in an accredited laboratory (for which the use of biological standards is critical in the case of vaccines as absolute potency measures are difficult if not impossible to perform), inspections of manufacturers for compliance with GMP (and of distributors in the case of drugs), evaluation of clinical performance through valid clinical trials, and regulation of promotional materials (for drugs). Since vaccines are generally distributed through public sector channels, the last function and that pertaining to distributor inspection are not major issues.

This catalog of regulatory functions has been used as a basis to assess how well each national Regulatory Authority is meeting performance criteria and areas requiring strengthening. As adopted by WHO,^{24,25} a focus on regulatory functions facilitates strengthening one national

organization to regulate both drugs and vaccines. This approach has also been used for blood products and diagnostic kits, and to some extent for medical devices.

The regulatory component that is unique to vaccines, lot release, is indicative of the difficulties of maintaining a controlled production procedure given the variable nature of biological processes. As vaccines become more biologically defined, composed of purified or synthesized components rather than cell extracts, some of the differences between vaccines and drugs may disappear. Already, manufacturers that can demonstrate a completely controlled manufacturing process may have the lot release requirement waived by the Regulatory Authority.

The stricter regulatory control of distributors and of promotional materials for drugs is probably a response to the more fragmented private sector distribution system for drugs.

REGULATORY RISK-BENEFIT

Risk-benefit considerations are becoming an increasingly important issue for vaccines. Decisions by the US FDA on products that do not pass the US risk-benefit assessment may impact trials, licensing and production of products not only in the US market but globally.²⁶ An example of the far-reaching impact of US regulatory decisions is the use of thimerosal as a preservative in multi-dose vials of vaccines. Authorities in the US have requested that manufacturers lower thimerosal content immediately in vaccines for use in children²⁷ because of an extremely small, perhaps theoretical, risk associated with the miniscule amounts of mercury in the preservative. The problem is that global supply of the standard vaccines is dependent on production lines built for multidose vials. Not only will there be tremendous vaccine shortages if there is a global shift to single dose vials, but the cost and price per vial will increase significantly. The risk-benefit assessment by the US, which does not take into account any of the global implications, could undermine immunization around the world. More information on the thiomerosal issue is available.²⁸ Similar situations have arisen with drugs where the FDA has removed products, such as Cisapride and Troban, from the market once an effective alternative was available in the USA. There are two approaches to this issue: change the risk-benefit assessment in the leading regulatory agencies to take into account global issues, or strengthen the capacity of developing country agencies to make their own risk-benefit assessments. Undoubtedly the second approach will yield more long-term benefits.

PROCUREMENT

The different characteristics of vaccines and drugs and their primary purchase by the public or private sector also influence the procurement process. Key considerations are the use of procurement agencies, type of tendering process, prequalification of sources, development of tender specifications, characteristics of the receipt process, and special considerations for new products. Pricing will be considered in the next section.

LARGE PUBLIC SECTOR PROCUREMENT AGENCIES

UNICEF provides procurement services for countries for both drugs and vaccines and also acts as a procurement agent for other partners, including governments, non-governmental organizations, other United Nations agencies, and international funding agencies. UNICEF does

not procure for individuals or for profit-making entities. The procurement arm of the World Health Organization will act as an agent and purchase non-standard pharmaceutical products including vaccines, for governments on a case-by-case basis. Each purchase is made following the issue of a specific bid established for the purpose.

Other regional entities such as the Pan American Health Organization (PAHO) procure vaccines for governments via defined procurement arrangements between vaccine suppliers and purchasers. PAHO established a revolving fund in 1977 to centralize and support its regional procurement of vaccines. The Gulf Cooperation Council (GCC) unites 25 million people in six countries - Saudi Arabia, Kuwait, Oman, United Arab Emirates, Bahrain and Qatar - and procures safe and effective pharmaceutical products and vaccines for their member countries, among other functions. In the United States vaccine procurement for the Vaccines for Children Program and for public health emergency situations is handled by a part of the Centers for Disease Control and Prevention specifically set up to do this.²⁹

THE TENDERING PROCESS

A competitive tendering process is widely used both for drugs and vaccines, in the public and private sectors, for national and global use. An exception, sole-source procurement, is used primarily for small volume purchases, proprietary products (only one supply source), or emergency needs.³⁰

One objective of International Competitive Bidding or open tender is to provide all eligible prospective bidders with an equal opportunity to participate in the tender. In most cases, awards are based on the most attractive offer from suppliers who can meet the terms of the tender. There may be some room for negotiation within the context of the tendering process, depending on how the procedure is set up.

Because the potential number of bidders is so large for drugs and the quality standards so strict for vaccines some sort of prequalification process is used. The use of an open tender combined with a prequalification process is known as Limited International Bidding.

PREQUALIFICATION

For a national tender, prequalification could mean that the product is licensed within the country. For the purpose of United Nations agency vaccine tenders (such as UNICEF, PAHO or WHO) WHO performs prequalification services for the procurement entity. The process reviews the national Regulatory Authority of the producing country to assess its performance on six essential regulatory functions, ensuring that the product complies with the specifications, and ensuring that there is likely consistency of production through GMP compliance, with reassessments every two years.³¹ WHO also participates in resolution of reported problems. A complete description³² and a current list of prequalified products³³ are available.

For drugs, WHO is piloting a prequalification system for HIV/AIDS, tuberculosis and malaria drugs,³⁴ such as those being bought for implementation of the Global TB Drug Facility, Roll Back Malaria, and WHO's 3x5 initiative for drugs against HIV/AIDS. Product dossiers received in response to an Expression of Interest are reviewed for compliance with WHO recommendations and guidelines on multi-source products³⁵ and bioequivalence data, and then

GMP inspections are commissioned. The lists of prequalified products is reviewed and updated at regular intervals. The procedure and a list of products already prequalified are available.³⁶

For other drugs purchased by the pharmaceutical purchasing and storage arm of UNICEF located in Copenhagen, UNICEF Supply Division uses a prequalification process that includes the following considerations:³⁷ purchasing only from manufacturers with a proven record of competence, knowledge and experience (traders are not accepted), conformity with the *WHO Guidelines on Good Manufacturing Practices (GMP)*,³⁸ a GMP assessment either by UNICEF Supply Division or by an independent third party, as well as reports on file of regular GMP inspections by the national Regulatory Authority, a Marketing Authorisation for the product in the market of the country of origin, a Certificate of Analysis for each batch supplied. In addition, the Quality Assurance Centre in UNICEF Supply Division checks and approves the suitability of the packing and labeling prior to purchasing.

TENDER SPECIFICATIONS AND RECEIPT OF PRODUCTS

Tender specifications are developed in consultation with user groups (local physicians, the national immunization program, etc) as well as the national Regulatory Authority. In the case of products on the Essential Drugs List and vaccine products prequalified by WHO, these specifications have been developed through an international consultative process and are available to countries. On arrival at their destination, all products are checked to ensure that they comply with the specifications of the tender.

Drugs may then undergo a review of Certificates of Analysis as well as some testing. In the case of vaccines, each lot of product procured by international tender has been subjected to lot release, at minimum by the national Regulatory Authority of the producing country. This requires extensive document review and may also involve testing. If the receiving country has the expertise to do so, they may also perform lot release review of these products.

NEW PRODUCTS

Tendering for new products with unknown demand poses challenges in demand forecasting and negotiating the tender. Transparent and frequent consultation between the public financing, procurement and demand creation groups and the product manufacturer is essential for both drugs and vaccines.

FINANCING: PRICING AND FUNDING

The most critical aspects of financing are factors influencing product costs and prices and factors influencing the funding for the purchase of the products.

PRICING

Vaccines are used, at most, four to five times during a lifetime; however, every child is targeted to receive these doses. In contrast, drugs are given to a limited population but with an extended dosing schedule.

In the recent past, vaccines procured by UNICEF for use in developing country public health programs cost no more than \$0.10-0.20 per dose. In the most recent 2003 tender, a shift in the product mix resulted in considerably higher prices: hepatitis B vaccine for roughly \$0.50 per dose, measles-rubella for over \$1.50, and DTwP-*Haemophilus influenzae* type b (Hib) at over \$2.25.³⁹ These prices are still considerably lower than those published by the Centers for Disease Control and Prevention for US public sector products: measles-mumps-rubella \$15.99, hepatitis B \$9.00, Hib \$7.79, whereas private sector US prices are even higher: measles-mumps-rubella \$34.73, hepatitis B \$23.20, Hib \$15.88.⁴⁰

Price comparisons have been made available for a number of selected pharmaceutical products through the International Drug Price Indicator Guide,⁴¹ and some partial price ranges are given in Table 2. These include prices on the international market available to poorer countries.

Table 2. Price comparisons for common medicines

Generic name	Therapeutic class	Range of supplier prices US\$	Range of agency prices US\$
Captopril	Antihypertensive	0.0071-0.04/tab-cap	0.0065-0.0268/tab-cap
Carbamazepine	Anticonvulsive	--	0.0451-0.0933/tab-cap
Clindamycin	Antibacterial	--	0.0705-0.2229/tab-cap

A tabulation of prices for products for HIV therapy and diagnosis is also available.⁴² Some representative price ranges are provided in Table 3, which compares potential access prices to those available in Europe. The variation in price across markets is very clear.

Table 3. Price comparisons for HIV therapies

Product	Class	Dose	# Mfrs	# Countries	Individual price range US\$	List prices US\$	
						UK	Spain
Cefoxime	Antibacterial beta-lactam	200 mg tab	4	2	0.21-1.31/tab	2.45	0.66
Zidovidine	Antiviral	100 mg cap	8	7	0.08-0.81/cap	1.70	0.58
ZDV/3TC	Antiretroviral combination	300 mg/ 150 mg tab	3	3	0.36-4.26/tab	8.15	4.53

Both vaccines and drugs have significant price differences in different markets. But the prices themselves do not tell the whole story. A compilation of treatment costs in an available guide⁴³ has an analysis of treatment affordability. Thus, for amoxicillin at the 250 mg tablet strength, for which a treatment course is seven days, three times per day, the treatment price can range widely depending on the product used and the type of access to drugs the patient has. Table 4 is illustrative. Again, price tiering across markets can be seen.

Table 4. Comparison of treatment prices for amoxicillin 250 mg tab, US\$

Product type	Public procurement	Public patient	Private retail	Other patient
Brand	50.69	69.85	69.84	69.43
Most sold	24.65	33.83	33.74	33.74
Lowest price	22.49	30.83	31.88	--

FACTORS INFLUENCING PRICES

Prices are generally somewhere between the cost of production and the absolute amount the “market will bear”. For the lowest tier markets, “cost plus” pricing, the cost of producing one dose plus an added factor for profit, may be used. The full market price will include production costs, overheads, amortized R&D investments, marketing costs, and profits, and thus may no longer bear any relation to the cost of production. The factors influencing price often evolve as the product moves through its lifecycle. Some of these factors include the degree of competition, the elasticity of demand, the balance of demand and available supply, the future pipeline of products and willingness to employ strategies such as differential pricing.

The traditional vaccines (measles, Bacille Calmette Guerin (against some forms of childhood tuberculosis), DTwP, tetanus toxoid, OPV) are “mature” and off-patent products, having been on the market for decades. They are widely used around the world and reach on average 50-80% of infants each year. Due in part to increasingly efficient production resulting from both learning over time and economies of scale (i.e. costs per dose decline as volume increases because of more efficient use of fixed costs), as well as the impact of competition, these vaccines are sold at very low prices and provide low marginal rates of return to producers. These low prices have allowed the public health sector to buy many more vaccines for immunization programs around the world. But they have also led to the feeling that vaccines are –and should be– cheap compared to drugs, a perception that makes introduction of more expensive innovative products a more difficult decision for governments. Drugs generally have much higher prices than vaccines, especially if calculated over the lifetime of the individual. For example, a course of diphtheria vaccine to protect for a lifetime will cost about \$0.50, while one course of antibiotic treatment will cost in excess of \$50 for just the drug. With several new vaccines becoming available, the vaccine market is going from the older products to innovative ones. It is in a state of transition, and a reflection of that will be increased prices.

Pooled procurement has helped lower prices. UNICEF and PAHO purchase large quantities of vaccines at very low prices. The ability of the international procurement agencies to demand vaccine at low prices, and the willingness of various suppliers to produce vaccine at these prices, has been an important factor in the success of national immunization programs. However, it has also had some less desirable consequences. In comparison to other products and markets, the UNICEF and PAHO market generates little revenue and even less profit for manufacturers—two key factors driving a company’s decision to maintain production lines and invest in new R&D and new capacity. Companies must internally justify their continued involvement in this “marginal” market. The result is low levels of investment in vaccine R&D and production capacity for the products needed by the poorest countries. As vaccines used by the industrial and developing markets diverge, this gap between the markets is becoming increasingly problematic.

For drugs, the introduction of generic products has a major impact on prices. Prices of patented products are higher, not only because of lack of competition but also because of the need to pay royalties. In contrast, even when patents are in force for vaccines, the royalties have had little impact on price, being about 5-13% of the selling price.⁴⁴

FUNDING

Because of their contribution to population immunity and the potential for actually eliminating or eradicating infectious diseases, vaccines have tremendous externalities, reducing transmission of communicable diseases. Because vaccines have these positive externalities, their societal value is not always captured and paid for. Thus vaccines are economically undervalued. However, it is these positive externalities that make them attractive to donors.

In contrast, most drugs primarily benefit the individual being treated. Willingness to pay is higher as the user is seeking to alleviate symptoms and pain and avoid disability or death. User fees are thus successful for drug purchase even in the poorest countries, as the experience with the Bamako Initiative has shown in some,⁴⁵ but not all⁴⁶ cases. However, user fees have been documented to create a barrier to uptake of vaccines.⁴⁷ Thus for vaccines financing, options are limited to governments, through government budget lines, and donors.

A major difference between curative and preventive strategies is that in the case of the former, it is the willingness to pay of the individual that is important, whereas for preventive strategies (and for curative strategies to the extent that they are made available by the public sector), one must look at the government's willingness to pay. This means that financing strategies will necessarily be different in most cases.

ACCESS: PATENTS, DIFFERENTIAL PRICING, ALLOCATION, DELIVERY INFRASTRUCTURE

LIMITATIONS DUE TO PATENTS

There is a significant body of work exploring the impact that patents and TRIPs^{4,48,49} may have on access to chemical medicines. As noted earlier, vaccines are more protected by process know-how than by patents, because know-how is essential for use of biological technologies, whether patented or not.

The World Trade Organization (WTO) meeting held in Doha, Qatar, in November 2001 considered the public health impact of TRIPS. A clarification was issued emphasizing that countries were free to use the flexibility allowed in the original TRIPs agreement when faced with public health emergencies, including the compulsory licensing of a patent to ensure supply of a desired product at a reasonable price. For countries with limited or no domestic manufacturing capacity, there was a dispute whether this allowed them to import products from low-cost manufacturers under compulsory licensing provisions. The Doha Declaration called for the WTO to develop a scheme to facilitate access to necessary pharmaceutical products for poorer countries. With the decision of the General Council of 20 August 2003,⁵⁰ products of

production under compulsory licensing can be supplied to countries with no pharmaceutical production.

DIFFERENTIAL PRICING STRATEGIES

For vaccines, a primary limitation to access especially for new products has been financing. Long “trickle down” times have been seen even for products as cost-effective as hepatitis B or Hib vaccines. These products were available in the US in the 1980s, but are just now becoming available to the poorest countries. In recognition of differing willingness and capacity to pay, the public health sector has promoted the use of differential pricing, also called equity pricing. Tables 2-4 and the section on financing show that a wide range of prices exists already for similar drug products across markets.

Differential pricing of pharmaceuticals has been proposed to ensure adequate revenues to manufacturers while also helping increase equitable access to life saving products. While differential pricing between industrial and developing country markets has existed for vaccines for some years, it has been difficult to implement for drugs. This is partially because pricing of pharmaceuticals is subject to legal controls in almost every industrialized country, with the exception of the US, and partially due to increased incentives for leakage. A recent paper showed that prices for AIDS drugs in 15 countries were essentially independent of national wealth.⁵¹ However, these figures date from prior to the time when compulsory licensing and bulk procurement strategies had brought down the price of these products to the public sector in developing countries.

Important considerations in implementing a differential pricing strategy include:

- Agreement by high-end purchasers that prices offered to poorest countries will not be used as a reference point to secure lower prices;
- Effective means to limit re-importation or onward exportation of differentially priced products;
- Strategies to ensure appropriate communication of the differential pricing policy and protect pharmaceutical companies from negative publicity, especially in wealthier countries;
- Increased investment in training and infrastructure to ensure compliance with drug and vaccine regimens and to ensure target populations can be reached with safe and potent products.

ALLOCATION

Another barrier to access occurs when insufficient product is available and it must be allocated according to specific criteria. An example of allocation strategies is the criteria used for access to smallpox and anthrax vaccines in the US.⁵² A further example is that applied by the Interagency Coordinating Group for yellow fever and meningitis, which allocates stockpiles of meningitis and yellow fever vaccines for outbreaks in Africa on the basis of country-supplied surveillance data to demonstrate the existence of an outbreak, a plan for the use of vaccines, and a commitment to repay funds advanced as criteria that are reviewed to allocate stockpiled vaccines. When these criteria are not in place, or have not been set and disseminated in a

transparent manner, a supply shortage situation becomes exacerbated as countries or individuals seek to obtain the product in short supply by any means possible.

DELIVERY INFRASTRUCTURE

Any consideration of access would be incomplete without a consideration of the capacity of programs to absorb the products provided. It has been increasingly clear that lack of financing or inability to access a particular product may not be the only problems inhibiting its use. This applies to both drugs and vaccines to the extent that drugs are delivered in the public sector.

DISCUSSION

RESEARCH AND DEVELOPMENT

Public support of vaccine R&D has happened historically, probably because of the global public good aspect of vaccines. Nevertheless, this investment brings in only a fraction of the costs for developing a vaccine, which includes not only basic research costs, but also process development and clinical trials costs – which may be major compared to the original research investment. Historically, investment in drugs tended to result in a higher return than investment in vaccines. However, recent investments in vaccine R&D have resulted in “blockbusters” equal to pharmaceutical products, such as the conjugate vaccine against *Streptococcus pneumoniae*. Public sector “pull” funding can be a means to influence R&D, as recent experience of contracting for bioterrorism vaccines in the US has shown. Public-private partnerships, in which representatives of both groups work together for a narrowly defined goal, for example, the Medicines for Malaria Venture, may be one way to stimulate research for specific products. Other mechanisms include “pull” type mechanisms, such as tax credits, government contracting for guaranteed purchase (as for bioterrorism products), or “push” mechanisms such as investment by government in production facilities or clinical trials.

Conclusion: While public investment in R&D has been more frequent for vaccines than for drugs, probably because of the nature of the diseases and global public good aspect of prevention, this investment has covered normally only a fraction of R&D costs. To truly stimulate development of innovative products for public health, more concerted action will be needed, with public-private partnerships being an example of a way to stimulate work towards a specific goal.

MARKET: CHARACTERISTICS AND FORECASTING OF DEMAND

The differing markets for drugs and vaccines impact the relative importance of critical variables in forecasting demand. For both, forecasting demand for mature products is easier, while for new proprietary products it is quite difficult. The extent to which a market exists will influence the ease with which manufacturers can be found to develop products against certain diseases.

Conclusion: Drugs and vaccines have different markets. For the curative sector, the market will depend on individual willingness to pay. For vaccines, market assessment for innovative products, especially in the developing world, will depend on government willingness to pay, based on the epidemiological justification for the use of a product. In some ways, willingness to pay can be predicted using historical evidence about other products that have been taken into

national immunization programs. Products that are just being introduced or those used to respond to outbreaks pose difficult problems in forecasting demand. In such cases stockpiles may be considered to smooth out variations in demand.

SUPPLY: SOURCES, CONSIDERATIONS FOR PRODUCTION AND THE SUPPLY CHAIN

The basic characteristics of drugs and vaccines have a large impact on their supply structure. Drugs and vaccines differ greatly in the number of products on offer, the number of manufacturers of those products, the complexity of the manufacturing process, and the importance of generics. In the case of vaccines, the number of manufacturers has dwindled, due to low vaccine prices that give low profit margins, as well as the increasing need to invest in infrastructure to meet regulatory needs, since as disease incidence dwindles, the public sets higher standards of safety. The difference in the inherent stability of the products has dictated a strictly controlled stock management system for vaccines compared to the drug distribution chain.

Conclusion: The supply landscape differs for drugs and vaccines, with relatively few vaccine manufacturers. This limits possibilities for competition, leading to monopoly suppliers. In the case of drugs, generic products play a greater role in competition. The strict control of the supply chain for vaccines could minimize leakage from the supply chain, which could make differential pricing easier to implement, although this need for strict controls could have a negative impact on delivery of the product.

REGULATION

There are many similarities in the regulatory process for drugs and vaccines, and it is expected that the same agency will perform these functions for both types of products. However, because of the biological nature of vaccines, and the difficulty of completely controlling the production process, there are some differences in the way functions are applied. Lot by lot release of the product is required for vaccines to ensure product consistency, an important issue for biologicals. Differences in the distribution pathways of drugs and vaccines have also resulted in some variability in regulatory oversight. Both drugs and vaccines are susceptible to a varying interpretation of risks vs. benefits that might impede licensing and access to new products.

Conclusion: A joint approach to the regulatory process for both drugs and vaccines will have benefits as it is normally controlled within the same agency within a country. The differing risk-benefit assessment across countries can best be addressed by capacity building within developing country regulatory authorities.

PROCUREMENT

The different characteristics of drugs and vaccines, especially the biological nature and primarily public sector use of vaccines, affects the procurement process, but the principles of procurement are the same for both drugs and vaccines.

Conclusion: Similar procurement principles could also be applied to the prequalification process.

FINANCING: PRICING AND FUNDING

Pricing of vaccines has generally been low compared to that of drugs. A large part of this relates to the use of vaccines in prevention, which is generally not regarded as an emergency, compared to the use of drugs in the case of disease or accident. Prevention has generally been undervalued. Another issue is that willingness to pay for vaccines is based on the will of governments to invest in them, whereas willingness to pay for drugs generally rests with the individual user, making user fees an attractive option. Competition has been important in lowering prices of both drugs and vaccines, but is a much more important factor in the drug industry. Nontraditional sources, such as emerging developing country manufacturers, are enhancing competition and driving down prices for both drugs and vaccines.

Conclusion: The undervaluing of prevention by society is a major difference between drugs and vaccines that impacts vaccine prices and financing.

ACCESS: PATENTS, DIFFERENTIAL PRICING, ALLOCATION, DELIVERY INFRASTRUCTURE

Factors impacting access to drugs and vaccines are similar, although their relative importance may differ. For drugs, patents are much more important in limiting access to innovative products than for vaccines, although voluntary and compulsory licensing have now been used to enhance access. However, financing and price are major barriers to access for both. For vaccines, the delivery infrastructure needed may negatively impact access, but does minimize leakage, which could facilitate imposition of differential pricing. For both drugs and vaccines, differential pricing is already in force. However, there has been more resistance to its implementation for drugs than for vaccines, which may have to do with the other differences mentioned above, such as the global public good aspects of vaccines, and their already low prices.

Conclusion: In general, activities that enhance access to drugs will also enhance vaccine access, and vice versa, although the relative importance of different factors inhibiting access may differ. Both differential pricing as well as activities allowed under the TRIPS agreement, such as compulsory licensing, may be useful to consider.

ANNEX 1: SUMMARY CHARACTERISTICS OF DRUGS AND VACCINES

Area	Specific attributes	Drugs	Vaccines
R&D	Public sector financing and response	x	XX
	IPR issues	XX	x
	Orphan drug legislation	X	X
Market	Public sector volume	x	XX
	Simplified public sector forecasting	X	X
	Complex prediction of new product uptake	X	X
Supply	Large number of producers	X	
	Many developing country producers	X	X
	Divergence of products across markets		X
	Existence of generics	X	
	Complexity of standardizing and scaling up production		X
	Leakage from supply chain an issue	X	x
Regulation	National Regulatory Authority controls:		
	• marketing authorization	X	X
	• surveillance for safety and efficacy	X	X
	• lot release		X
	• laboratory testing	X	X
	• GMP compliance for manufacturers	X	X
	• GMP compliance for distributors	X	
	• clinical evaluation	X	X
	• regulation of promotional materials	X	
• Risk-benefit differences across populations	X	X	
Procurement	Public sector: use of large procurement agencies	X	X
	Limited IB tender process with prequalification	x	X
	Receipt and release includes lot release		X
Financing	Range of prices	X	X
	Price impact of royalties	X	x
	User fees for purchase	X	
Access	Role of patents in limiting access	X	x
	Use of tiered pricing to enhance access	x	X
	Use of stockpiles	x	X

Note: XX is highly significant, X is significant, x is minor and blank is not an issue.

REFERENCES

- ¹ Mark Elengold, presentation at the 10th ICDRA, Hong Kong, June 26, 2002
- ² Michel Greco, Development and Supply of Vaccines: an industry perspective, Levine M, Kaper J, Rappouli R, Liu M, Good M eds, New Generation Vaccine, 3rd Edition, New York: Marcel Dekker Inc. chapter 7, 2004
- ³ Rappuoli Rino, Miller HI, Falkow Stanley. The intangible value of vaccination. Science 2002; 297: 939-939
- ⁴ World Trade Agreement and Public Health 2002. World Trade Organization/World Health Organization. Printed by the WTO Secretariat, Geneva.
- ⁵ At legal.european-patent-office.org/dg3/pdf/t950780eu1.pdf, accessed 21 May, 2004
- ⁶ European & UK Case Law Review in the area of Biotechnology, World Biotech Supplement ,4 October 1999
- ⁷ Toshika Takenaka, Highly Anticipated UK Decision of Biogen v. Medeva about Validity of Biotechnology Patents, 1997 University of Washington, School of Law
- ⁸ Lang Jean, Wood Susan C. Development of orphan vaccines: an industry perspective. Emerging Infectious Diseases 2000; 5 (No 6): 1-13
- ⁹ <http://www.fda.gov/orphan/index.htm>, accessed 6 March, 2003
- ¹⁰ <http://pharmacos.eudra.org/F2/register/orphreg.htm>, accessed 9 May, 2003
- ¹¹ <http://www.vaccinealliance.org> accessed 20 May, 2004
- ¹² IMS HEALTH, Douglas Long, personal communication
- ¹³ WORLD HEALTH ORGANIZATION. Influenza pandemic plan. The role of WHO and guidelines for national and regional planning. (1999)
http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_EDC_99_1/en/, accessed 19 April, 2003
- ¹⁴ Julie Milstien, Scott Lambert: Emergency response vaccines – a challenge for the public sector and the vaccine industry. *Vaccine* (2002) **21**: 146-154
- ¹⁵ United States Government Accounting Office: Childhood vaccines. Ensuring an adequate supply poses continuing challenges. GAO-02-987 (2002)
- ¹⁶ See <http://www.vaccinealliance.org> for more information (under Board Documents), accessed 5 March, 2003
- ¹⁷ MMWR June 04, 1999 / 48(RR07);1-17. Recommendations for the Use of Lyme Disease Vaccine Recommendations of the Advisory Committee on Immunization Practices (ACIP)
- ¹⁸ <http://www.who.int/gtb/dots/whatisdots.htm>, accessed 25 May, 2003
- ¹⁹ <http://www.who.int/medicines/organization/ood/ood6paggers.shtml>, accessed 24 May, 2003
- ²⁰ <http://www.bt.cdc.gov/stockpile/index.asp>, accessed 25 May, 2003

- ²¹ <http://www.who.int/vaccines-access/supply>, accessed 20 May, 2004
- ²² Ensuring the quality of vaccines at country level. Guidelines for health staff *Ordering code: WHO/V&B/02.16*
- ²³ Informal consultation of experts on national regulation of vaccines *Ordering code: WHO/V&B/99.08*
- ²⁴ Regulation of vaccines: building on existing drug regulatory authorities *Ordering code: WHO/V&B/99.10*
- ²⁵ World Health Organization, Essential Drugs and Medicines Policy, Review of national regulatory capacity: a strategy to strengthen national authorities, at http://www.who.int/medicines/organization/qsm/activities/drugregul/assessment_tool.doc accessed 24 May, 2003
- ²⁶ Julie Milstien, Nora Dellepiane, Scott Lambert, Lahouari Belgharbi, Chris Rolls, Ivana Knezevic, Jacqueline Fournier-Caruana, David Wood, Elwyn Griffiths. Vaccine quality - can a single standard be defined? *Vaccine*, 2001. **2956**, pp 1-4
- ²⁷ Center for Biologics Evaluation and Review, FDA, <http://www.fda.gov/cber/vaccine/thimerosal.htm>, accessed 25 May, 2003
- ²⁸ At <http://www.who.int/vaccines-safety/topics/thiomersal/en>, accessed 19 May 2004.
- ²⁹ <http://www.cdc.gov/nip/vacman/contr.htm>, accessed 24 May, 2003
- ³⁰ Guidelines for the international procurement of vaccines and sera, *Ordering code: WHO/VSQ/98.05*, at http://www.who.int/vaccines-access/procurement/PDF_Proc_Manual/, accessed 24 May, 2003
- ³¹ WHO, Vaccines and Biologicals, A system for the prequalification of vaccines for UN supply, at http://www.who.int/vaccines-access/quality/un_prequalified/prequalification_system.htm, accessed 24 May, 2003
- ³² Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies (WHO/V&B/02.08) (replaces WHO/VSQ/97.06)
- ³³ http://www.who.int/prequalifiednt/vaccines-access/quality/un_prequalvaccinesproducers.html, accessed 24 May, 2003
- ³⁴ <http://www.who.int/medicines/organization/qsm/activities/pilotproc/ppdoc2.doc>, accessed 24 May, 2003
- ³⁵ Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for a Drug Regulatory Authority. WHO/DMP/RGS/98.5
- ³⁶ <http://mednet3.who.int/prequal/>, accessed 20 May, 2004
- ³⁷ <http://www.supply.unicef.dk/health/essentdrugs.htm>, accessed 25 May, 2003
- ³⁸ World Health Organization, Technical Report Series, 823, WHO guidelines on Good Manufacturing Practices (GMP)

- ³⁹ http://www.supply.unicef.dk/health/GAVI_HEP_HIB.pdf;
http://www.supply.unicef.dk/health/2003_Vaccine_Projection%20.pdf, accessed 25 May, 2003
- ⁴⁰ http://www.cdc.gov/nip/vfc/cdc_vac_price_list.htm, accessed 25 May, 2003
- ⁴¹ http://erc.msh.org/dmpguide/index.cfm?search_cat=yes&display=yes&module=dmp, accessed 25 May, 2003
- ⁴² <http://www.who.int/medicines/library/par/hivrelateddocs/prices-eng.pdf>, accessed 25 May, 2003
- ⁴³ <http://www.who.int/medicines/library/prices/medicineprices.pdf> accessed 25 May, 2003
- ⁴⁴ Children's Vaccine Initiative, Intellectual property protection: Its role and benefits 1999. Children's Vaccine Initiative. CVI/99.04. World Health Organization, Geneva.
- ⁴⁵ <http://www.unicef.org/exspeches/99esp3.htm>, accessed 25 May, 2003
- ⁴⁶ Riddle, Valery. Fees-for-service, cost recovery, and equity in a district of Burkina Faso operating the Bamako Initiative. WHO Bulletin 2003. 81: 532-538.
- ⁴⁷ Practice and policies on user fees for immunization in developing countries (*Ordering code: WHO/V&B/01.07*)
- ⁴⁸ Globalization and Access to Drugs: Perspectives on the WTO/TRIPS Agreement. 1999. WHO/DAP/98.9 Revised. World Health Organization, Geneva.
- ⁴⁹ Attaran, A. and Gillespie-White, L. Do patents for anti retroviral drugs constrain access to AIDS treatment in Africa? JAMA 2001. 286:1886-1892.
- ⁵⁰ WTO, Implementation of paragraph 6 of the Doha Declaration on the TRIPS Agreement and public health. Decision of the General Council of 30 August, 2003. WT/L/540, at http://www.wto.org/english/tratop_e/trips_e/implemen_para6/e.htm, accessed 19 May 2004
- ⁵¹ Scherer, FM and Watal, J. Post-Trips options for access to patented medicines in developing countries. CMH Working Paper Series, Paper no WG4:1. WHO Commission on Macroeconomics and Health, 2001.
- ⁵² See <http://www.bt.cdc.gov/>, accessed 25 May, 2003



HEALTH, NUTRITION,
AND POPULATION



HUMAN DEVELOPMENT NETWORK

THE WORLD BANK

About this series...

This series is produced by the Health, Nutrition, and Population Family (HNP) of the World Bank's Human Development Network. The papers in this series aim to provide a vehicle for publishing preliminary and unpolished results on HNP topics to encourage discussion and debate. The findings, interpretations, and conclusions expressed in this paper are entirely those of the author(s) and should not be attributed in any manner to the World Bank, to its affiliated organizations or to members of its Board of Executive Directors or the countries they represent. Citation and the use of material presented in this series should take into account this provisional character. For free copies of papers in this series please contact the individual authors whose name appears on the paper.

Enquiries about the series and submissions should be made directly to the Managing Editor Joy de Beyer (jdebeyer@worldbank.org) or HNP Advisory Service (healthpop@worldbank.org, tel 202 473-2256, fax 202 522-3234). For more information, see also www.worldbank.org/hnppublications.



THE WORLD BANK

1818 H Street, NW
Washington, DC USA 20433
Telephone: 202 473 1000
Facsimile: 202 477 6391
Internet: www.worldbank.org
E-mail: feedback@worldbank.org