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# Improving Access to Medicines in Developing Countries

## Application of New Institutional Economics to the Analysis of Manufacturing and Distribution Issues

C. James Attridge and Alexander S. Preker

March 2005





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## Health, Nutrition and Population (HNP) Discussion Paper

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## Improving Access to Medicines in Developing Countries

### *Application of New Institutional Economics to the Analysis of Manufacturing and Distribution Issues*

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**Abstract:** The debate on improving access to medicines in developing countries has focused attention on the macroeconomic context and defining the demand side needs, based upon disease categories and purchasing power in a range of middle-income and Least Developed Countries. Far less attention has been given to understanding the diversity of supply side processes and their likely future evolution. This paper examines alternative frameworks for empirical analysis of supply side activities, namely, the manufacture and distribution of medicine, through the application of New Institutional Economics (NIE) concepts. Attention is focused particularly upon the potential utility of ideas from agency theory, transaction cost analysis and contemporary ideas from strategy theory. The major purpose of this paper is to use these theoretical frameworks to provide insight for policy makers, when faced with specific situations, whether in an international agency, or a private company, or in defining a national strategy. The analysis attempts to show the importance of distinctions between ideas of ‘make’ or ‘buy’, between ‘national self sufficiency’ and ‘international purchasing’ strategies, the limitations of contractual agreements under market governance and the crucial linkages between strategy formulation, strategy implementation and the necessary capabilities to achieve successful performance in practice. The current international situation on the investment, location and capacity of pharmaceutical manufacturing is reviewed and likely future scenarios suggested. Correspondingly current patterns of trade in medicines and their likely development within the context of the WTO and bilateral trade agreements are discussed. Against this background the promise and the pitfalls for new forms of public-private partnerships, which may offer attractive alternatives to conventional structures are evaluated. The implications of alternative future strategic options for national governments in setting the balance between health and industrial policies are examined and in particular the extent to which a national manufacturing capability should be developed or sustained. Similarly the scope for improving low cost distribution systems for medicines, based upon a mix of public and private sector channels, is assessed. We conclude with suggestions for further development of a transaction-based framework.

**Keywords:** medicines, access, developing countries, new institutional economics, pharmaceuticals, private sector

**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.

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## PREFACE

Several inputs are indispensable in ensuring that health services function properly. This includes pharmaceuticals, equipment, other consumables, capital, human resources, and knowledge. This publication – *Improving Access to Medicines in Developing Countries: Application of New Institutional Economics to the Analysis of Manufacturing and Distribution Issues* – by C. James Attridge and Alexander S. Preker reviews key issues related to the industrial organization of the pharmaceutical industry in low- and middle-income countries. 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 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, patents/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 reduction and Millennium Development Goal targets.

This paper provides a framework for empirical analysis of the supply side of the manufacture and distribution of medicine. Attention is focused particularly on the potential application of ideas from institutional economics – agency theory, transaction cost analysis and theories on organization of the contemporary firm.

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# INTRODUCTION

## **The Access to Medicines Debate**

The public debate on improving access to medicines in developing countries has been conducted in the context of the complex interplay between macroeconomic development, disease patterns and healthcare needs and provision. Many countries are in what appears to be an inescapable 'Catch 22' situation, in which improved macroeconomic status can only be achieved by improved health status and vice versa.<sup>1,2</sup> This assessment appears to be undeniably correct for the poorest 60-70 poorest least developed countries (LDCs), as does the conclusion that this impasse will only be overcome by a large scale injection of international funding and other resources over many years.

The validity of this diagnosis and remedy is less clear, as we progress upwards through the macroeconomic hierarchy of countries, such as China, India, Brazil to the countries of Central and Eastern Europe (CEE), some of which are entering the European Union.

In terms of international policy formulation there are now two strands of thinking - two quite different 'mind sets' - which are inextricably intertwined. These are the domains of the macroeconomics of globalization and international trade, as pursued in the context of the WTO, and global health policy, as pursued in the context of the WHO. The origin of the tension that exists between these two increasingly influential groupings is not difficult to see. The WTO is primarily concerned with the orderly evolution of a capitalist, free market global economy based upon the principles of market competition and free trade. In contrast, the WHO is preoccupied with improving health status, which following the models and thinking of most developed countries, is an objective that many see as self evidently best pursued within institutional, or public sector frameworks.

The new Global Health Fund, proposed by Sachs et al.<sup>1</sup> is now operational and supporting a range of initiatives primarily in HIV/AIDS, Malaria and TB.

## **Supply Side Processes - Manufacture and Distribution**

Within this context, this paper is concerned with the specific issue of improving access to medicines, through developing more efficient and cost-effective approaches to the manufacture and distribution of medicines.

Through the application of contemporary ideas from industrial economics and strategy theory, it addresses the question 'How, over the next decade, might the maximum global improvement in access to the medicines which are available today, be achieved?' Note therefore it is not, for the most part, concerned with the vital related issue of incentives for innovation and R&D investment.

The aim is not to argue a particular ideological point of view, or to advocate specific solutions, but to develop a deeper understanding of the realities of manufacturing and distribution activities, within sound conceptual frameworks.

The paper begins with a brief overview of theoretical concepts, the macro or global environment and essential features of the economics and technological basis of the pharmaceutical sector.

The core of the paper then examines likely future scenarios for global manufacturing and trade in medicines over the coming decade and their implication for alternative approaches in terms of new incentives for the private sector, public-private partnerships and selective extension of international procurement and distribution by public and/or other ‘not for profit’ organizations. This emphasizes the need to recognize the realities of where supply processes are likely to go under their own momentum, rather than adopting the more idealistic approach of focusing on ‘the way things ought to be’.

In the final section of the paper, we address the implications of the foregoing analysis for those responsible for devising national strategies, in terms of trading-off health and industrial policy objectives, in effect, making national ‘make or buy’ decisions and setting the balance between manufacturing or supplying, through public or private sector entities.

## **RELEVANT THEORIES AND MODELS**

New institutional economics (NIE) encompasses a range of theoretical approaches, which might usefully be deployed. However, the primary aim will be to utilize basic ideas from Agency theory and Transaction Cost Analysis but to supplement the latter with current concepts from business strategy theory. Despite the technical nature of the terminology, many of these models have an obvious ‘common-sense’ appeal and hopefully will not make the analysis inaccessible to non-specialist readers. We offer the following short explanation of these concepts for the benefit of those who may not be familiar with them.

### **Agency Theory**

Agency theory is based on the idea that there are principals, or people who wish to do things, and agents, who have the necessary expertise and experience to do them in practice. The grander the objectives, the more it is necessary to contract with various agents to contribute to organizing and putting into place activities to achieve them. Thus politicians must delegate to or contract with administrators in government and investors, or shareholders must contract with chief executives and directors in the private sector. Agency theory is particularly concerned with how, in the face of human behavior, it is possible to establish contracts, or agreements, between principals and agents that are effective.<sup>3</sup>

### **Transaction Cost Analysis**

This theory, attributable to Coase and Williamson,<sup>4,5</sup> flows naturally from agency theory, in that it elaborates principles of human behavior and organization that need to be taken into consideration when considering how best to undertake a particular enterprise. However, it also introduces another key distinction that is particularly relevant to this paper, namely doing things under market governance or hierarchical (or organizational) governance. Regardless of whether we are part of a government or business organization, we may choose to undertake a particular

activity necessary for achieving our overall aims, either within the boundary of the organization itself or by going out into the market place and contracting with an independent third party to do so on our behalf.

The latter option raises the agency theory issue of how well is it possible to write a contract with a third party to ensure that they will deliver to an agreed set of terms and conditions. A naïve approach, commonly adopted in real life, is to treat this choice as a simple matter of accountancy by comparing the market price versus internal cost.

Williamson elaborates five principles to provide a sophisticated socio-economic ‘trade off’ model for making such choices.

**Bounded Rationality** - Decision makers’ ability to make rational decisions is limited by the availability of information and their capacity to process it. In a transaction context, there is the additional important issue of ‘information asymmetry’, in which one party has a great deal more information than the other.

**Opportunism** - Individual decision makers may make choices based upon motives of self-interest, which are not optimal in meeting organization aims.

**Asset Specificity** - The assets (human or physical) needed to undertake an activity may be widely available in the market place or exceedingly rare. Increasing specialization in equipment and human skills, coupled with cumulative experience generally lead to high levels of asset specificity.

**Externality** - In this context, externalities refer to third party agents or organizations, who may pursue their own private goals whilst contracting to carry out activities, which may detract from fulfilling their contractual obligations.

**Hierarchical Decomposition** - This archaic term was originally used by Williamson to specify the extent to which business organizations had evolved delegated processes of decision making, which were more efficient and hence made doing things under corporate governance a more attractive option. A further elaboration of this idea is given below in terms of modern business strategy models.

In summary, Transaction Cost Analysis (TCA), in the form of these principles, represents a considerable advance towards a general theory of microeconomics and organizations. However, applying it in a coherent manner to specific situations still constitutes a formidable challenge. Its value lies, not so much in providing a formulaic approach to optimizing performance but as a timely *aide mémoire* to practitioners, that important decisions are invariably judgmental in nature and must be taken cognizant of the real world limitations on information, rationality and the vagaries of human behavior.

### **Resource and Capability Based Strategy Models - A General Strategy Model**

Over the past decade, much thinking in business strategy model development has evolved from the more fundamental work of economists such as Williamson. The capabilities based model is

particularly relevant here. The essential idea is that organizations consist of sets of resources (human, physical, intangible), which are bundled together into capabilities (or competencies) to do things. In a market context, the key to successful or superior performance lies in having better capabilities than competitors to deliver strategies that add value to customers. However, all organizations exist in dynamic macro and sectoral (in this case healthcare) environments, which continually throw up new opportunities and threats.

There is a substantial literature analyzing the capabilities, or competencies<sup>1</sup> necessary to perform successfully in the pharmaceutical sector.<sup>6,7</sup>

## Resources and Capabilities in the Pharmaceutical Sector

Yeoh and Roth,<sup>8</sup> in analyzing the capabilities necessary for successful, efficient performance in the pharmaceutical sector, drew a distinction between component and integrative capabilities. Component capabilities are defined as economies of experience, the knowledge and skills embedded within the firm and organizational routines, which are regular patterns of activity achieved through coordination by individuals in a company over time. Often these routines require highly complex interactions. Integrative capabilities reflect the ability of the organization to adapt and to deploy resources and capabilities in new or flexible ways, in order to renew it, in response to environmental shocks and new strategy imperatives.

Haanes and Fjeldstad<sup>9</sup> suggest that in the pharmaceutical sector, key competences are necessary to support three types of competitive behavior: **Entrepreneurial, Contractual and Operational**. The first of these is essential in innovation, for managing network relations in biotechnology for example. The other two are more pertinent to this paper.

Important **Contractual** competencies are defined as:

- Understanding of markets, actors and resources
- Ability to see opportunities, where they do not already exist
- Ability to organize commercial contracts,
- Ability to mobilize new resources.

Important **Operational** competencies are:

- Efficiency in production and transformation
- Quality management
- Efficient management of complex flows of goods and information
- Negotiating Skills.

The authors note that for superior performance within the generic drug sector, operational competences are clearly dominant. However, as is currently apparent for the Indian generic sector, contractual competences that allow generic producers successfully to access market outlets on a global basis, are also vital to sustain growth and build efficiency, through economies of scope and scale.

<sup>1</sup> For the purposes of this discussion, we will regard the terms 'capabilities' and 'competencies' as interchangeable



### *'Stretch and Fit'*

The key to sustainable superior performance lies in matching - or 'the fit' - between opportunities in the environment to pursue worthwhile objectives and the capabilities of the organization to synthesize strategies, which are both relevant in delivering value and can be implemented with those capabilities.<sup>10</sup>

Successful organizations are also dynamic and engage in an element of 'stretch' in taking on new strategy challenges, which require the evolution of the organization by growing new capability-resource sets, or radically re-modeling existing ones.

This model is equally applicable to public or private sector organizations when formulating future strategies, in focusing attention on the question: 'Do we have the necessary capabilities to implement the strategies better than other alternative organizations and, if not, if we are determined to pursue these strategies, how do we acquire these capabilities?'

## **THE MACRO-ENVIRONMENT**

Whilst it is clearly beyond the aim of this paper to elaborate the components and drivers for change in social, technological, economic and political (STEP) factors which will shape future global and national environments, it is appropriate to remind ourselves at the outset that there are many uncertainties in this regard, and hence, many alternative scenarios may be painted with some degree of credibility. In recent years there has been a flourishing literature on the possible collapse of capitalism, green environment discontinuities based upon global warming, and political ones based upon global religious conflicts.

This paper broadly presumes that, over the next decade or so, currently discernible trends towards an open, democratic capitalist based world economy will continue. Whilst recognizing that there is the low chance of major political and economic discontinuities, this implies slow, but uneven progress in improving per capita GNP and health status in many emerging or middle-income countries. We recognize that, for the 60%-70% poorest least developed countries (LDCs), the lack of the necessary political and economic stability and international aid and trade packages suggests a far less optimistic prognosis.<sup>11</sup> The critical significance of the spread of HIV/AIDS as a determinant is well known and much may hinge upon when, or if, an effective HIV/AIDS vaccine is developed, manufactured and distributed.

For the purposes of this analysis, we will use the conventional distinction between the OECD, middle-income countries and LDCs.<sup>12</sup> We will on occasion, highlight the further distinction between the middle-income countries of Asia, Latin America and Eastern Europe, which have quite different environmental and historical backgrounds.

# THE TECHNOLOGICAL ECONOMICS OF MEDICINES

## MANUFACTURING CAPABILITIES AND RESOURCES

### Key Components

This section provides the reader with sufficient background information to be able to follow the subsequent analysis and discussion of strategy options, but will not describe the economics of the pharmaceutical industry *per se*. For a more comprehensive historical account of the evolution of this sector, see Ballance et al.,<sup>13</sup> Schweitzer,<sup>14</sup> Landau et al.<sup>15</sup> and, more recently, Granville and Leonard.<sup>16</sup>

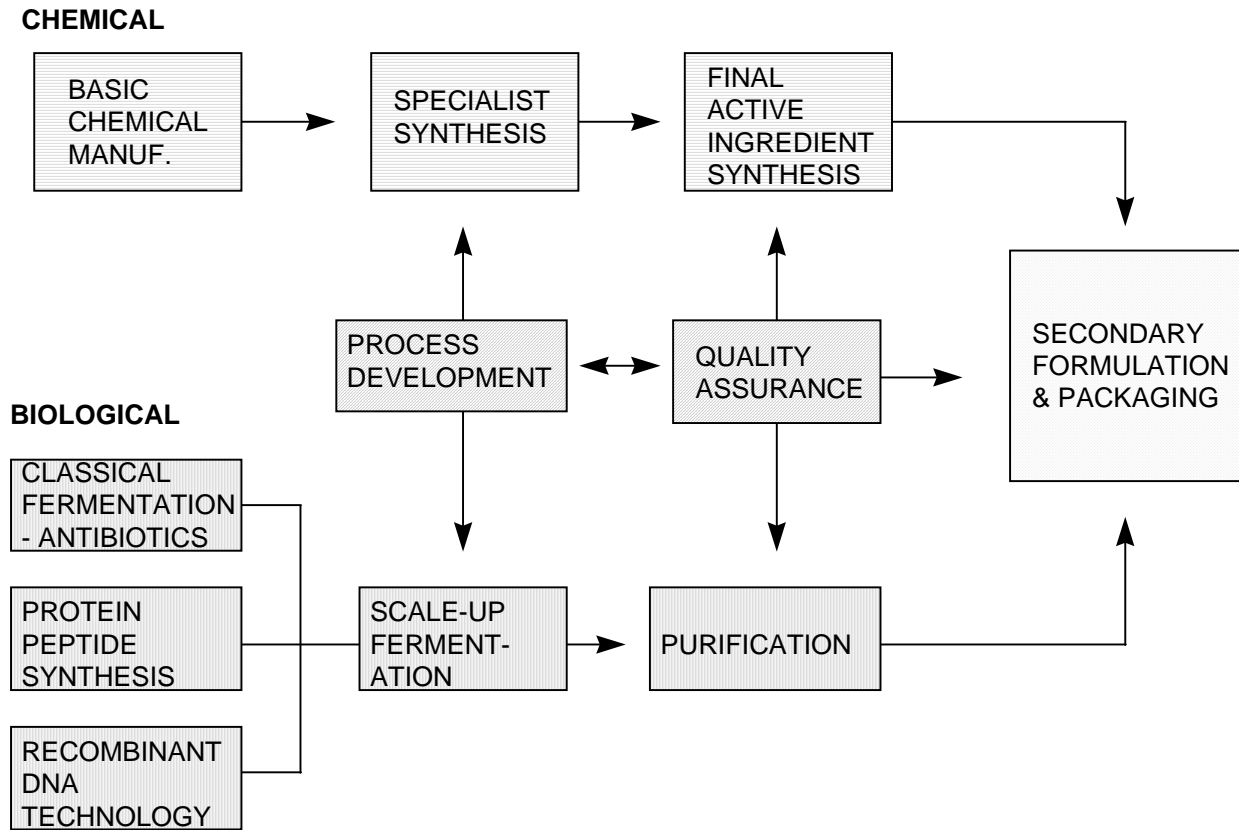
Figure 1 provides an outline of the main components of manufacturing processes. Primary, or active ingredient manufacture may be either chemical or biological in nature, involving quite different types of plant, technologies, skills and knowledge. Many contracting companies specialize in one or the other. The manufacture of active ingredients is by far the most expensive in terms of sunk cost investment in capital equipment and process development. Much chemical plant is 'multi-purpose', in that a range of different products can be manufactured in the same equipment, subject to extremely rigorous procedures to avoid cross-contamination.

The chemical and biological stages involved vary greatly from product to product in terms of their robustness, or reliability. The more modern or sophisticated the products, the greater is likely to be the need for a highly skilled capability to develop and maintain the processes. The human resources (skilled scientist and engineers), laboratory facilities and instruments are specific assets, which may be scarce in many middle-income countries and effectively non-existent in LDCs.

Some products require dedicated plant. In such cases capital investment is clearly a high-risk activity for a new product, because if the product does not achieve technical regulatory approval by government authorities, or fails to capture significant sales in competitive markets, then the plant will have to be written off.

Secondary manufacture, or formulation into tablets, capsules or injection, is routine for many products, involving long-established technologies. Similarly, packaging is a relatively low-cost activity. But in both cases there are important imperatives in terms of procedures and operational disciplines needed to ensure high quality standards. For both formulation and packaging in a developed world context, these processes are highly automated with low labor costs, whereas in developing world situations, with low labor costs, it may be more efficient to make lower investments in automated computer-based equipment and rely upon manual processes. However the latest highly automated investment offers a higher guarantee of quality in substantially eliminating the scope for human error.

**Figure 1: The Main Elements of the Pharmaceutical Manufacturing Process**



## Quality Assurance

The imperative for all major international suppliers is to build, staff and operate plants that are approved by leading national regulatory authorities. There is an increasing drive across the world to establish and enforce common high standards. The requirements of regulators take two discrete forms. The first consists of a highly specific Master File for each product, which defines scientific data on input materials, processes and the quality specification of the final product. The second, which is much less well understood, is operational, or procedural and is based upon the cumulative experience over many years of how to organize manufacturing systems, procedures and documentation to avoid mistakes or errors at all stages.

The enforcement of these standards is through regular inspection of plants by experts from the authorities. On a routine basis, the guardian of these standards, effectively on behalf of the agencies, performs the Quality Assurance function. This group, which organizationally stands apart from the normal manufacturing function, is responsible for approving the release of product batches from the site for distribution and sale.

The most important capabilities in secondary manufacture are constant vigilance to ensure adherence to standards and procedures, through rigorous training of staff and quality checks.

## Capital Investment and Capacity Planning

Normally, unlike much routine chemical manufacture, pharmaceutical companies do not strive to operate plants close to their maximum output capacity. This is because demand fluctuates across many markets, and, under the terms of their licenses, companies have a legal obligation to keep markets supplied.

Periodically, decisions must be taken to invest in new plant. This cost can vary considerably. Basic routine chemical plant extensions might cost no more than US\$20-100M, but there is currently a shortage of modern 'state of the art;' biologics manufacturing capacity, where it has been estimated a new plant might cost of the order of US\$300M.<sup>17,18</sup>

The economics of capacity planning is an important issue in the context of improving access to medicines, because the unit cost of increasing volume output on a modest incremental basis in an existing plant may be very low but, at the point at which new or extended plant is required, a quite different computation must be done to account for the capital and operating costs of additional capacity and services.

As this last point illustrates, simple generalizations regarding costs can be misleading. At the present time, rough estimates suggest that, for a leading R&D based company with considerable economies of scale and scope, aggregate manufacturing costs are of the order of 20%-25% of revenues. For a small generic company, with no R&D and much lower marketing costs, this figure might be of the order of 50%-60% of revenues.<sup>19</sup> However, it is likely that, in order to sustain a high reputation with regulators in core markets such as the USA and Europe, leading multinational companies (MNCs) will make much higher investments in strong capabilities in process development and maintenance and quality assurance, which will offset their economy of scale and scope advantages.

A final consideration, looking to the future, is that, even if effective patent protection begins now in middle-income countries, it will not affect products actually in the market for maybe five to ten years. Thus, all current products now in the market, patented or otherwise, will be available from low cost generic manufacturers in middle-income countries.

The share of volume sales held by generic, or branded generic products in OECD countries outside of the USA is likely to rise considerably higher than at present. The net effect of this is likely to be that 70%-80% of global consumption in volume terms, which will be the prime determinant of health outcomes, should be available as cheap generics, through increasingly efficient international trade.

## Asset Specificity

It is useful at this point, for the purposes of later discussion in terms of TCA, to evaluate the assets (human, physical and financial) deployed here. Table 1 offers a simple taxonomy. The designation of low, high or very high, whilst somewhat arbitrary, seeks to portray the realities of the current situation. Thus, whereas at one end of the spectrum for most of the products on the WHO Essential Drug list, asset specificity is low and it is possible to go to the market and obtain

multiple competitive offerings which ensure keen price competition, at the other end, for some newer biological products, asset specificities are high, market competition low and prices will be accordingly high.

We would particularly draw attention to assets, particularly experienced, skilled staff in quality assurance, process maintenance and regulatory compliance, which are the key to ensuring that the highest quality standards are maintained. Even in China and India, which have strong and rapidly growing generic sectors, it is widely recognized that these resources are scarce relative to the potential demand.

**Table 1: Asset Specificity and Pharmaceutical Manufacturing**

<b>LOW</b>	-	Routine Manufacture of Organic Intermediates
	-	Basic Antibiotic Manufacture
<b>HIGH</b>	-	Quality Assurance
	-	Process Maintenance
	-	Regulatory Compliance
<b>VERY HIGH</b>	-	Specialized Organic Synthesis
	-	Modern Biologics Syntheses and Purification
	-	Recombinant DNA Technologies

## **DISTRIBUTION CAPABILITIES AND RESOURCES**

### **International Manufacturers**

As Haanes and Fjeldstad observed above, successful efficient international manufacturers require highly specific resources in terms of skilled staff and modern information and communication technologies to be integrated into operational capabilities to manage the flow of goods and information in global distribution chains. Furthermore, they must invest in, or contract for high security storage facilities in many countries. These requirements apply equally to R&D based MNCs and International Generic Manufacturers.

Particularly for generic manufacturers, where global margins are lower, it is critically important in seeking to extend low price access for patients, that systems for matching stock holdings with demand across many different national environments are well organized and low cost.

Figure 2 illustrates this general pattern of distribution across the three main country categories. Basically, in OECD markets and the upper echelons of the middle-income countries, revenues will support wholly owned affiliates, where direct control of distribution makes for efficient integrated systems - in TCA terms, hierarchical or corporate governance is preferable. In smaller and less affluent middle-income countries and some LDCs, transaction costs are such that it is more efficient to operate by contracting with local third party national distributors. Whilst this leads to a greater exposure to externalities and scope for opportunistic behavior, that are beyond

the principals' control, often local distributors have advantages in terms of local knowledge and negotiating skills and lower direct costs structures, which make this a more attractive option.

Finally, for many LDCs, the paucity of any effective local distribution infrastructure for medicines results in only the most limited supplies of essential medicines through tenders funded by national governments and international agencies.

**Figure 2: Alternative Supply Mechanisms for Medicines in Different National Situations**

Mechanism Country Groups	Affiliate	Third Party Distributors	National/ International Tender
OECD			
EMERGING			
LDC			

This pattern currently represents the type of cascade through which R&D based MNCs have globalized operations. Leading generic MNCs are rapidly advancing to develop a similar distribution infrastructure, based upon the same patterns of incentives.

**International Wholesaling and Trading Companies**

The development of regional, much less global wholesaling companies remains at present very much in its infancy. The reasons for this are not hard to find. Medicines clearly cannot be treated like most other goods. Failures of quality, not to mention deliberate counterfeiting and a failure to guarantee continuity of supply to a given patient population can have catastrophic consequences. National regulatory authorities cognizant of this and their statutory obligations in this regard therefore constitute a serious impediment to widespread trading in finished pharmaceutical generic products.

In Europe, over the past decade there has been a dramatic concentration of wholesaling down into the hands of just a few leading companies. These companies and their counterparts in North and South America and parts of Asia are also forming alliances, which will result in even larger

groups. Both the nature and timescale of this phenomenon remains very uncertain at present but it could contribute significantly to opening up new and more efficient patterns of international trade in both active ingredient and packed products.

If the necessary conditions of quality and continuity of supply can be fulfilled, *prima facie* this would appear to be a desirable evolution for generic products. However, this would not be the case for innovative patented products where a reasonable return to R&D based companies is critically dependent upon maintaining price differentials between market categories.

## **A GLOBAL PERSPECTIVE ON DEMAND-SUPPLY INTERACTIONS**

### **DEMAND PATTERNS IN OECD, MIDDLE-INCOME & LDCs**

#### **Innovative, Generic and Traditional Medicines**

Numerous analyses<sup>1,8,20</sup> have drawn attention to the obvious imbalance between the fundamental human need in LDCs and the rural and urban poor in countries such as India, China and Brazil for even the most basic medicines on the WHO Essential Drugs List (EDL) and the effective supply, which is constrained by a combination of lack of funds, infrastructure and, in some cases, the cost of the products.

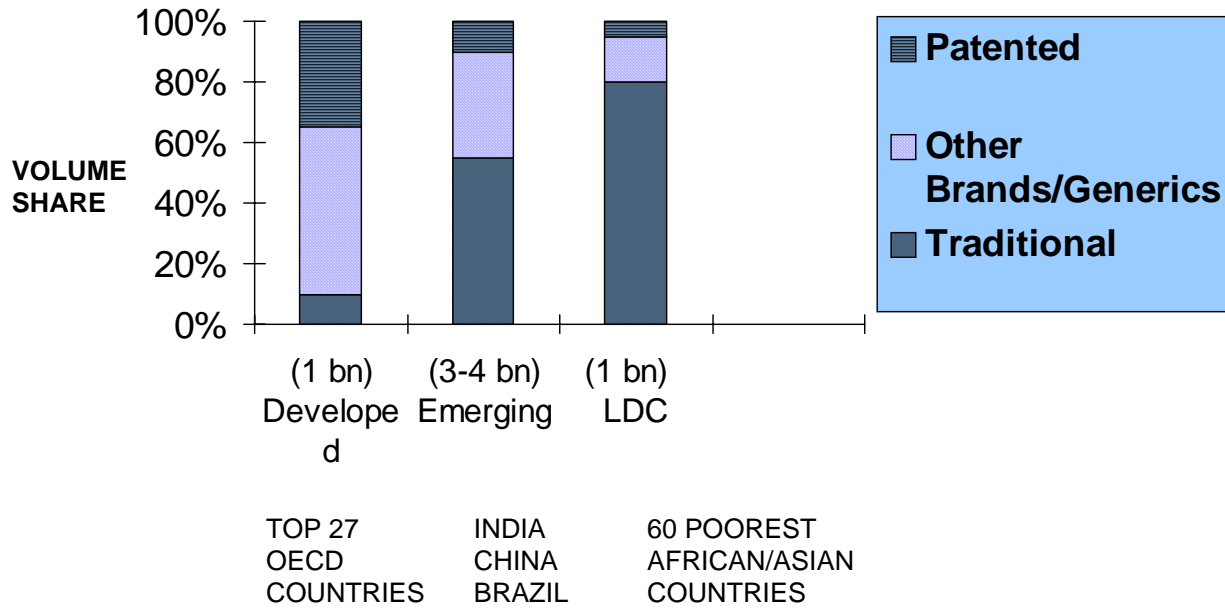
Much has been made of the lack of incentives for innovation through investment in R&D in diseases endemic in developing countries, an issue that is substantially beyond the scope of this paper. For a fuller discussion, see Sachs et al..<sup>1</sup>

Figure 3 shows a schematic global view of access to medicines. This does not purport to be an accurate quantitative assessment, but serves to illustrate the nature of the challenge. It suggests that across the world sick people receive one of the following four possibilities:

- 1) Assured quality brand name (often patented) medicine, regardless of cost
- 2) Assured quality low cost generic medicine
- 3) Local traditional medicines of variable effectiveness and quality
- 4) No treatment at all.

Their chances of moving up the evolutionary scale from 4) to 1) depends primarily upon the country in which they live, as shown by the three categories of countries: OECD, middle-income (Emerging) and LDC. The evidence from WHO and national studies would appear to support the view that vast populations, of the order of several billion, have little or no access to any modern medicines and, at best, are treated with inferior traditional remedies.

**Figure 3: World Volume Consumption of Medicines by Region**



Source: Various Industry Estimates

### Structural Barriers to Diffusion of Modern Medicines

Achieving some access to modern diagnosis and treatment for these groups would appear more likely to yield an overall improvement in health outcomes and status for the limited funds available, than from either upgrading the minority already receiving them to the latest modern expensive medicines from the R&D based industry, or improving traditional remedies.

Obviously, in an ideal world, the aim should be for all to obtain the best possible treatment. However even in the affluent OECD countries there are still serious doubts regarding the benefits and feasibility of this aim. The editor of the Lancet, in a recent article, has emphasized what he regards as the unacceptably high risk of ‘side effect’ damage from innovative medicines.<sup>21</sup> In a recent European analysis, Schoeffski<sup>22</sup> reviewed numerous studies, illustrating how slow can be the diffusion into general practice of many modern medicines, even in developed countries.

In examining strategies for manufacturing and distribution, we are concerned primarily with obtaining more widespread use of essential, generically available medicines. In consequence, we will not address the current contentious debate regarding intellectual property protection, but will comment later upon the likely consequence of compulsory licensing for manufacturing investment location and supply patterns in international markets.



## INTERNATIONAL SUPPLY SIDE DYNAMICS

### Location Investment Incentives

In this section we will elaborate more fully the nature and dynamic of international supply outlined above. Patterns of manufacturing location and trade have changed dramatically over the past decade and are likely to undergo further substantial change in the next decade.

Pre-1990, the vast majority of active ingredient manufacture was in USA and Europe, much of it under the control of twenty to thirty leading multinational companies, but with a substantial grouping also of medium-sized companies operating on a regional basis. The sizeable Japanese market was supplied almost exclusively by its own local industry, which had successfully copied Western technology. Within the Soviet bloc, under the Comecon ten year planning systems, Hungary and Yugoslavia were the designated specialists in pharmaceutical production, which was concentrated in five or six locations. Beyond this, most other countries imported active ingredients or finish products.

During the late 1980s and 1990s, several significant changes occurred:

Leading EU and US companies began to internationalize operations and, rather than just build more plants on existing 'home' market sites, began to take a more pragmatic global view about where best to locate active ingredient manufacture. As already explained above, secondary formulation and packaging activities continued to be more widely distributed across countries, due to *force majeure* pressure by governments and because of relatively low costs. Broadly speaking, the following factors emerged in making decisions as to where best to locate manufacture:<sup>14</sup>

- a) **Local Cost and Infrastructure** - availability of sites, utilities, skilled labor and government incentives at low costs
- b) **Fiscal Incentives** - many smaller countries have adopted low, or no, corporate tax policies or long periods without tax post-investment as a means of attracting inward investment from modern industries
- c) **Good Citizenship** - major countries with large current or potential markets exert considerable pressure on MNCs to invest locally in manufacture once they have established a successful business in the country.

During this period, notable investment 'winners' in terms of attracting inward investment were small countries that offered mainly tax-led packages. Hence Puerto Rico, Singapore and Ireland are all important centers for active ingredient manufacture.

Some major countries--France, Italy, Spain and Japan--have been moderately successful in attracting inward investment. Also, uniformly now, the mainstream pharmaceutical industry has been inclined to internationalize investment. Leading US, Swiss and UK companies have led this process, with German and Japanese companies preferring to expand their home base.<sup>15</sup>

The second phenomenon that emerged in the 1990s, fits within the classical application of 'make or buy' decisions of TCA, in that many leading companies assessed that, for long

chemical synthesis, asset specificity was low and they could contract with specialist chemical manufacturers in the market to do this less expensively with guaranteed quality and continuity of supply, more cheaply than doing it 'in-house'. Increasingly, therefore, only the final stages that required FDA/regulatory authority plant approval were done internally. For older products, the entire manufacturing of the active ingredient may be contracted out.

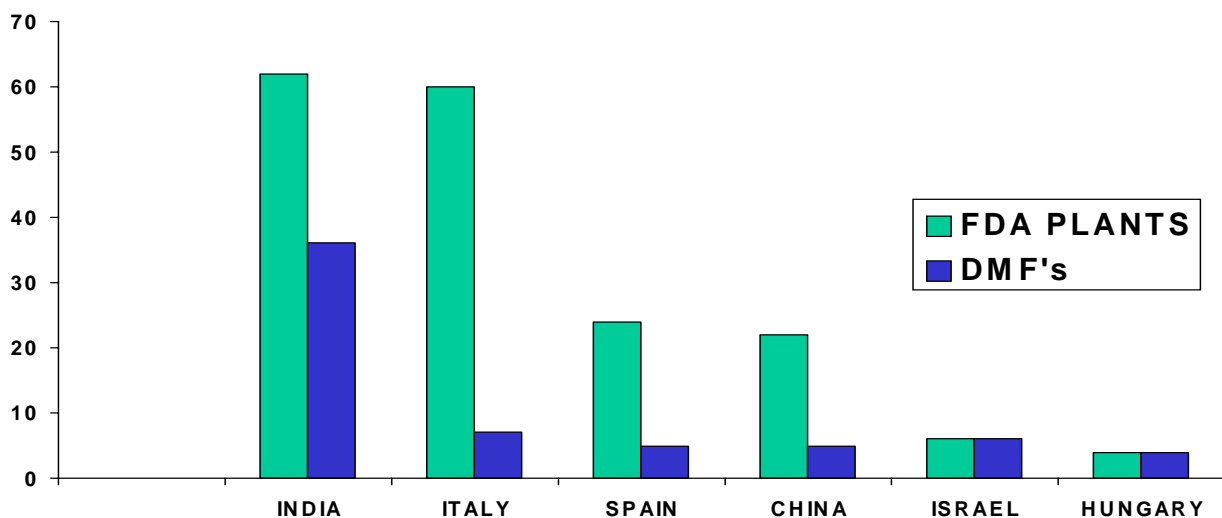
The third significant phenomenon, particularly in the mid-late 1990s, was a process of merger and acquisition amongst major companies, leading to further pressure to achieve economies of scope and scale, by reducing the number of manufacturing plants and sites.<sup>23, 24</sup> Whilst no authoritative study of the impact of this factor on manufacturing exists, anecdotal evidence suggests that progress in this respect has been modest thus far.

### The Emergence of India and China as Generic Manufacturers

The most important global phenomenon, however, has been the rapid growth of active ingredient companies in India and China. Particularly in India, unfettered by constraints of patent laws, the local fine chemicals industry has been able to develop highly specialized manufacturing capabilities, covering almost the entire range of modern medicines from basic antibiotics to HIV/AIDS drugs and Viagra.

Leading companies, such as Ranbaxy, Dr Reddy's, Sun Pharmaceuticals and Lupin have patiently invested in manufacturing facilities that meet the exacting EU and US Good Manufacturing Practice (GMP) and built strategic alliances with US and EU generic marketing companies. Figure 4 shows the current strong position of Indian manufacturing compared to other nations in terms of US FDA approved plants and US Drug Master Files held. They are now achieving dramatic growth in export sales of active ingredients to the USA and Europe.<sup>25,26</sup>

**Figure 4: Comparison of National Assets in terms of US FDA Approved Plants and Drug Master Files for the US**



India exports to the USA and Europe were \$1.5 bn in 2000, were estimated to be around \$3bn in 2004 and predicted to grow to \$4bn in 2005.<sup>27</sup> Ranbaxy, which expected to achieve export sales of \$1 bn by 2004, has established a presence in major EU markets to distribute generic products.<sup>28</sup> A small core of Indian companies has emerged operating plants to FDA standards, that have achieved dramatic growth in sales and profits, primarily as suppliers of active ingredients into the rapidly expanding generic/brand generic markets in the US and Europe. Table 2 shows the latest market capitalization, revenues and exports for the top ten Indian manufacturers and individual company data for the leaders Ranbaxy and Dr Reddy's.

**Table 2: Leading India Pharmaceutical Companies**

<b>Company</b>	<b>Market Capitalization (\$M)</b>	<b>2003 Revenues (\$M)</b>	<b>Exports (\$M)</b>
<b>Ran Baxy</b>	3,470	950	665
<b>Dr Reddy's</b>	1,770	430	301
<b>Aurobindo</b>	197	317	158
<b>Lupin</b>	339	275	137
<b>Other Top 10 Companies</b>	1,217	893	270
<b>Total Top 10</b>	<b>6,993</b>	<b>2,865</b>	<b>1,531</b>

*Source:* Financial Times, London, 22 January 2004, p.19.

Since the mid 1990s there has been much debate regarding the impact that the enactment of an Indian TRIPS compliant Product Patent Law might have upon the domestic industry. The Indian government might be said to have hastened slowly on this matter, with a clear view as to where its own long term industrial policy interests lie. Thus, almost a decade since the 1995 WTO TRIPS agreement, we are still only on the brink of the introduction of a form of product patent protection, whose effectiveness and 'even-handedness' remains doubtful.

Thus for example recent judicial opinions appear to have confirmed a policy position, whereby patents will only remain valid in India, if manufacture of the active material is undertaken within India, i.e. the patent holder will not in effect be allowed to import the active material and to exercise the patent rights through distribution and marketing, which is the norm in most other countries.

Experience suggests that we might well see another decade of dispute and complaints on this and many other issues of interpretation, before India finally has a patent system that closely approximates those in OECD countries. This should allow ample time for the Indian industry to concentrate and for the leading companies to establish viable R&D positions.

### **Manufacturing and Supply in Central and Eastern Europe**

The slow emergence from the communist regime and industrial and technological infrastructures have led to a slower evolution of the indigenous Chinese industry. But in more recent years, China has been noticeably more effective in attracting inward investment into joint ventures with Western companies and hence acquiring direct transfer of manufacturing technology and 'know-

how'.<sup>29, 30, 31, 32</sup> Even so, in 2001 China achieved exports of bulk pharmaceuticals valued at US\$2.1 bn compared to imports of only US\$0.7 bn.<sup>33</sup>

The fall of communism in Central and Eastern Europe (CEE), resulting in the abrupt exposure of local manufacturers to the shock of private sector disciplines, thus far has resulted in few success stories. A notable example would be Pliva in Croatia. The leading Hungarian, Czech and Polish plants mostly have been taken over by Western companies and many smaller companies have gone bankrupt.

Similarly, political and economic instability in Latin America has inhibited evolution of an internationally competitive manufacturing sector; most countries in this region are becoming increasingly reliant upon imports of active ingredients from leading MNCs and Indian suppliers.

### Trade Patterns, Tariffs and Non Tariff Barriers

Trade in medicines amongst OECD countries has been greatly facilitated by the 1995 GATT agreement to zero tariffs on specified lists of active ingredients for medicines (as opposed to general chemicals).<sup>34</sup>

However for many middle-income countries as shown in Table 2, there remain substantial tariff barriers. Many pharmaceuticals come within trade classification codes for chemicals, and these tariffs often reflect broader national industrial and trade policies, concerned with protecting and promoting a national chemical industry. Often, little consideration appears to be given to the access to medicines implications within the health policy domain.

**Table 3: Comparative Trade and Tariff Data (US\$ '000s)**

Country	Exports to		Imports from		% Tariff on Product Imports
	OECD	Middle-Income/LDCs	OECD	Middle-Income/LDCs	
<b>China*</b>	1,145	1,407	423	203	10
<b>India</b>	288	576	NA	NA	35
<b>Brazil</b>	64	183	1,325	263	12
<b>Singapore</b>	166	426	522	69	0
<b>Mexico</b>	304	410	955	109	12
<b>Argentina</b>	25	277	638	139	12

\* Including Hong Kong

Source: WTO, IFPMA data.

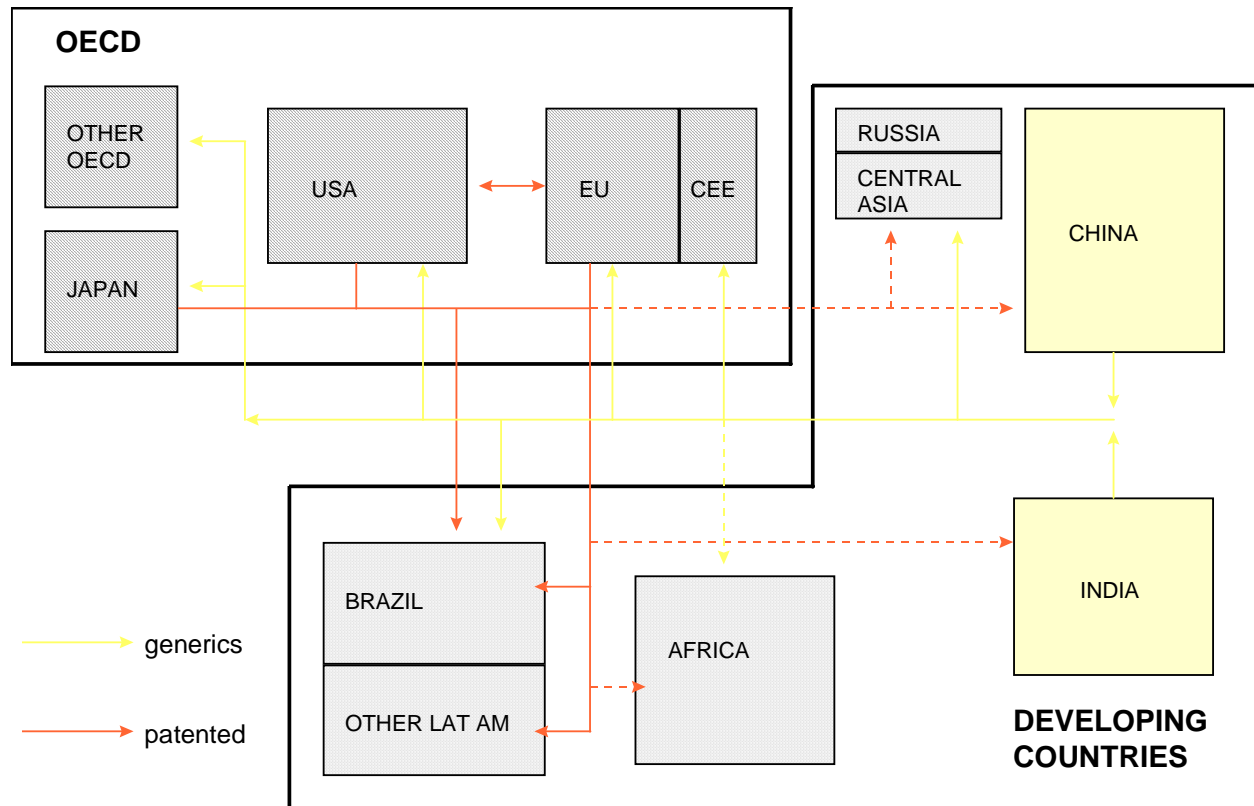
Efforts continue to extend the WTO 'zero for zero' agreement to a wider range of middle-income countries. Many countries, including China, on entry to the WTO have agreed to phase down import tariffs over a period of years.<sup>27</sup> Significantly, India has also recently reduced import tariffs on some imported active ingredients.

Often tariffs are addressed as a bargaining issue between OECD and developing countries in general, whereas from a health policy viewpoint, the biggest potential gain in achieving better access through more open trade would appear to lie in reducing tariffs on generics *within* the middle-income countries and LDCs.

Many countries, notably India, continue to deploy other non-tariff barriers to protect national industries from cheaper imports, potentially to the detriment of local consumers and health systems obtaining access to the cheapest products. Typically, ‘anti-dumping’ regulations, complex systems of certification of origin and quality, and pharmaceutical legislation requiring local manufacture are still relatively common.

Figure 5 shows schematically the current main pattern of trade flow for pharmaceuticals. The continuing predicted shift away from use of patented brands, or originators of patent brands towards cheapest generic or brand generics in OECD countries generally, suggests that there will be a considerable growth in demand for cheap active ingredient supplies from India and China.

**Figure 5: Regional Trade Flows for Medicines**



**Future Scenarios**

From the viewpoint of the technological economics of active ingredient manufacture as outlined above, leaving aside the more specialized fields of biologics manufacture, it is difficult to see

who might rival India and China as the key manufacturing locations in a future open global market.

At least for the foreseeable future, they would appear to have inescapable competitive advantage with regard to the three key criteria - skilled labor force, low input costs and very large and growing high volume domestic markets, which will underpin future cost savings based upon economies of scale.

Only a major breakdown in world trade agreements, leading to the re-erection of tariff and non-tariff import barriers for active ingredients, could reverse this trend. Although improbable, such a negative scenario might be predicated upon a growing trade imbalance between OECD countries and India and China, whereby the latter achieve dominant sales as exporters of intermediates and active ingredients for all categories of products into OECD markets, but failure to implement effective patent laws in India and China precludes effective access by Western MNCs to those markets. In the extreme, this could provoke the re-erection of tariff barriers against generic imports from India and China by OECD countries.

### **Collaboration versus Competition**

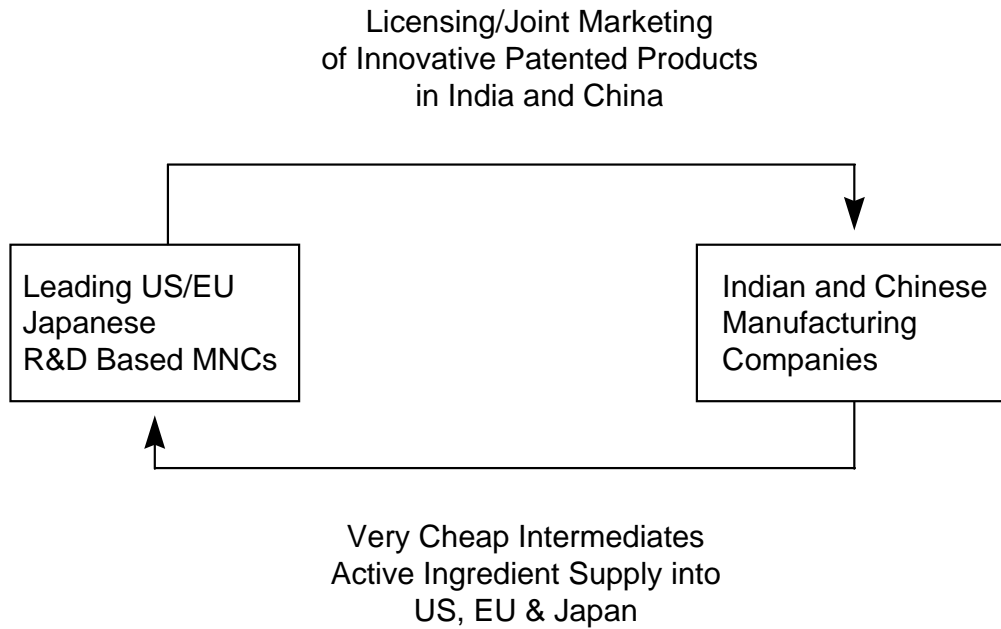
A common theme which has emerged from NIE thinking, from the discipline known as game theory has been the potential efficiency gains that can accrue from adopting a more rigorous analytical approach to determine when to compete in markets and when to collaborate. As markets such as pharmaceuticals steadily become more global from a customer demand perspective, suppliers can see increasing merit in forming alliances and partnerships to extend their capabilities to compete in it.

Hence a more positive scenario can be based upon signs of a growing commonality of interest between R&D based and Generic companies. There is a natural and, at first sight perhaps surprising, potential synergy, which is already fuelling collaborative joint ventures between the leading western MNCs and the Indian and Chinese industries in both manufacturing and R&D. This is also running in parallel with a growing confidence that, albeit very slowly, there will be a wider acceptance of the WTO-TRIPS agreement and patent protection in these countries.

Some major multinational R&D based companies have for many years operated quite independent generic arms that are based upon acquisitions in middle-income countries. A typical example would be Sandoz, which is the generic arm of Novartis. Lek, a relatively recently acquired Slovenian company accounted for 38% of the \$2.9bn turnover of Sandoz in 2003.

Figure 6 illustrates in general terms the considerable potential for further collaborative activity.

**Figure 6: Potential Synergy Between Innovative and Generic Manufacturers**



As western R&D based companies see their core markets being eroded by cheap generics, in the not too distant future, if only ten percent of the 2.7 bn combined populations of India and China can afford modern medicines at Western prices, this will be more or less equivalent to another EU or US market.

Empirical research<sup>35,36</sup> has shown the importance of ‘clusters’, which possess ‘state of the art’ technologies and human resource skills and experience, both in various facets of R&D and manufacturing. It appears highly likely that such ‘clusters’ will emerge in both India and China. This is not to suggest that a future world market would preclude manufacturers from a diverse range of other countries participating successfully in it. In order to do so, it appears likely that, as technologies continue to evolve, particularly in the diagnostics and biologics fields, this will only be possible based upon ‘niche’ ownership of highly specialized intellectual property or ‘know-how’ capabilities.

Also, many long-established national companies that market and manufacture products locally will continue to leverage their local reputation and specialist knowledge and experience of their environments to continue to thrive.

# INTERNATIONAL STRATEGIES FOR IMPROVING ACCESS TO MEDICINES

## STAKEHOLDERS AND RELATIONSHIPS

### International and National Stakeholders

Formulating a consensus on policies and strategies involves an increasingly complex network of international agencies, interacting with national governments. The HIV/AIDS crisis, and the Sachs Report and consequent establishment of the Global Health Fund have all served to intensify the debate as to how far better use of international funds and resources can improve the situation. Policy makers face the classic dilemma of whether to create yet more agencies and supporting international infrastructure and bureaucracy, or focus primarily upon exhorting and advising national health system politicians and administrators on appropriate reform paths, backed with carefully managed funding programs.

The aim of this section is to analyze the primary alternative funding and supply mechanisms, based upon the transactions involved and the capabilities and resources necessary for organizations to fulfill their roles under conditions of hierarchical governance.

### Relationships between Manufacturers, Distributors and Funders

We have included the funding options here because, in the final analysis, improving access inescapably depends upon the economics of supply, in terms of balancing costs and the flow of funds available. Self evidently from this picture, there are a multiplicity of combinations of funding, manufacture and distribution available. In NIE terms all of these offer different combinations of activities, some carried out under corporate governance and some contracted for under market or quasi market conditions. Clearly a rigorous application of TCA principles to compare transaction costs and evaluate their relative merits represents a formidable challenge.

For the purposes of this discussion, we focus attention on the following components:

- R&D based MNCs
- emerging International Generic Suppliers
- national manufacturer and distributors
- alternative public sector combinations
- new public-private partnerships (PPPs).

Figure 7 maps the main components involved in this process. A distinction is made between international and national entities and between public, or 'not-for-profit' agencies and private sector ones. This model has two obvious limitations. Firstly, it cannot reflect the wide range of national situations that exist. Secondly, by consigning the pharmacy/healthcare infrastructure systems to a single box, we are in danger of overlooking important differences, which might influence choices at an earlier stage in the supply-demand sequence. However, its primary function here is to display visually the alternative combinations of pathways that are possible, in order to discuss their utility in improving access. In the following section we will address in more detail issues of national government policies and strategies in a range of different settings.

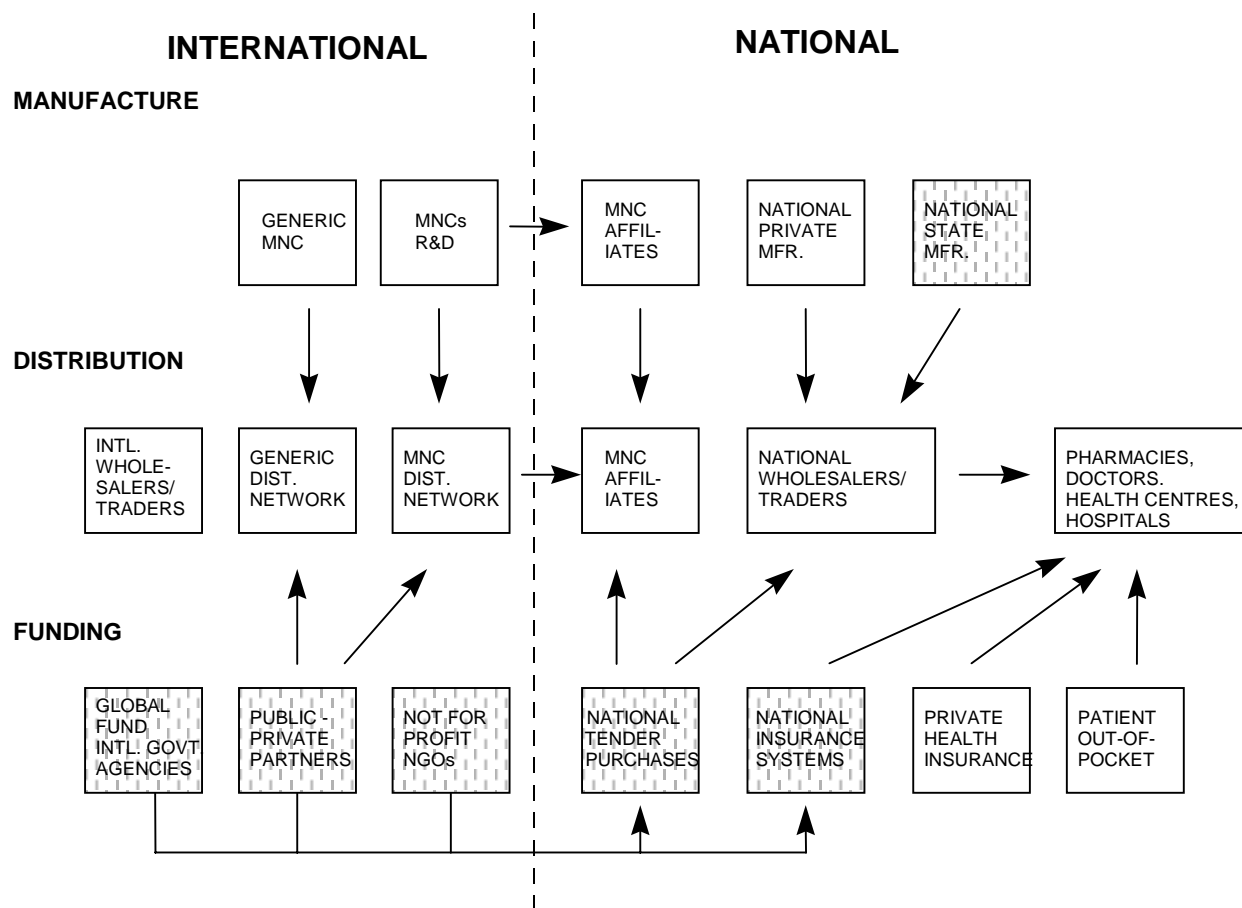


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**Figure 7: An Overview of Manufacture, Distribution and Funding Mechanisms**



## REDUCING TRANSACTION COSTS

### International Market-Based Competition

The first three components listed above--MNCs, emerging International Generic Suppliers and national manufacturer and distributors--constitute the normal private sector, profit driven, market competition basis through which the vast majority of medicines are provided world-wide. Notwithstanding the recognition that inadequacies in funding and demand side infrastructures are major impediments to improving access, the organization of the supply side of the market has been the subject of considerable criticism.

Over several decades, the capabilities of the major R&D based companies have evolved to fit the business opportunities in the core developed world markets. Their foremost strengths, therefore, are innovation through high levels of R&D expenditure and highly sophisticated networks of scientific and medical teams and 'safety first' manufacturing functions. These are strongly oriented to the demands of regulators and rapid international diffusion of new products through marketing. The penalties to the business of falling foul of the exacting standards of regulators, by squeezing manufacturing costs, can be severe.

Hence, the resources that make up the key capabilities of primary and secondary manufacture, process maintenance and development and quality assurance, tend to be of the highest order. The best up-to-date plant and equipment are used and large numbers of top-class scientists and engineers employed for the most part in 'state of the art' laboratories.

In TCA terms, because most of the products are innovative patented ones, generally, asset specificity is high. Thus, despite the trend to contracting out early stage processes to third parties in the fine chemicals market, such options are subject to extensive scrutiny for risk of externalities that might put at risk either product quality or continuity of supply.<sup>37</sup> TCA provides an appropriate framework for analyzing the market factors that determine whether manufacture and supply is under market or hierarchical governance. Governments, through health legislation and, to a degree, industrial legislation, play a major role but international companies have considerable choice in most cases. Truly international generic suppliers are still in their infancy and hence there is limited information on their behavior. Insofar that their margins are lower than R&D based MNCs and they do not have large profitable OECD business from which to cross-subsidize sales to low demand, low price countries, this may constrain their ability to invest speculatively or widely in such markets.

The scope for opportunism, whilst always present in large MNCs, is substantially constrained in R&D based pharma companies by strong organizational networks, team working and sophisticated information flows, leading to improved transparency, which limits information asymmetry.<sup>2</sup>

<sup>2</sup> In many other commercial and industrial fields, MNCs internationalize their business by adapting products to be less sophisticated and as a result cheaper to improve access to less affluent markets. The ethics of healthcare preclude this option for leading pharma companies.

## Low Cost Generic Suppliers

If we consider the relatively new generic suppliers from India and China, it is much more difficult to make such generalizations. In both countries, there are many thousands of pharmaceutical manufacturers, most of which are small and have quite a specialized technology base.

In China, there is now widespread recognition that the key to future international growth lies in developing capability to manufacture to global Good Manufacturing Practice (GMP) standards, in order to obtain registration for sale certificates in other countries. To quote the President of NCPC, the second largest pharmaceutical manufacturer in China, when explaining why joint ventures with Western companies were important: “It is not the technology we lack any more but the management techniques, which have already been implemented and followed by the Western pharma factories for years. For us to get up to speed will take years - co-operation will enable us to lessen the gap quickly”.<sup>17</sup>

Again we see here the coming together of NIE concepts, regarding competition versus collaboration and a pragmatic practical recognition of the need to acquire new capabilities to operate successfully in the emerging world market.

There is also a challenge for China to upgrade and broaden the range of products manufactured. Currently there is over-capacity in manufacturing of basic antibiotics, such as gentamycin, paracetamol and metronidazole but a need for more investment in modern medicines for cardiovascular disease and cancer.

An interesting example of growing rivalry between China and India is the international market for rifampicin, an essential drug for treating TB. In India, the cost of imported rifampicin from China at US\$40 per kg. is considerably lower than domestically manufactured material at US\$70 per kg. Indian manufacturers question the quality of the Chinese material and are demanding anti-dumping restrictions on these imports.<sup>38</sup> There is already domestic over-capacity for rifampicin manufacture in India. This represents a typical ‘health policy - industrial policy trade off’ for government, which is becoming increasingly common. India is estimated to have 25% of the world’s TB cases. Which is more important: getting the cheapest rifampicin (from China), which would presumably help improve patient access, or sustaining and developing national rifampicin manufacturers?

At present, the tone of the discussion on industrial policy, whilst positive and optimistic, is also clearly based upon the premise that the state is in a position to dictate to manufacturers plans for re-structuring, mergers, closures, joint ventures, etc. Whilst this may have considerable merit in the short term to enforce rapid change, as companies grow larger and more independent and build links with Western companies, policies will need to focus more on market incentives for profit led companies, rather than state directed objectives.

Leading Indian companies are undoubtedly more advanced in terms of their technical and managerial capabilities and in establishing international contracts, joint ventures and wholly owned businesses. Generally speaking, there are no major difficulties in India with the concept

of private ownership and profit. The main difficulties domestically lie in myriad layers of bureaucracy and associated corruption.

Therefore, taking these two groupings together, plus some other specialist generic players from around the world, over the next five to ten years there should be a major new potential high quality, cheap source of active ingredients and packed products to rival the leading R&D based companies. In principal, this should offer much greater scope for all would-be purchasers to buy at keen prices.

### **Rent Seeking Behavior**

However, on a cautionary note, it must be recognized that, even for these companies, rent seeking behaviors will dominate. They will give highest priority to competing in the lucrative OECD generics markets for recently patent-expired products, followed by the more affluent emerging country private insurance sectors.

National manufacturers and distributors, not surprisingly, vary enormously in the scope and scale of their activities. In larger emerging countries, they may have substantial capabilities in many aspects of primary and secondary manufacture and extensive national distribution networks. Smaller, less affluent emerging countries may be limited to a few major companies who only engage in traditional basic manufacture or secondary formulation and packing.

For the LDCs there will be maybe only one or two local importing distributors, who act on behalf of all the international manufacturers.

This pattern currently very much represents the cascade through which R&D based MNCs have globalized operations. In the future, it appears highly likely that generic MNCs will develop similar patterns of investment based upon the same patterns of incentives.

Another phenomenon to be considered will be the development of the global ‘wholesaling plus trading’ company.

In Europe, over the past decade there has been a dramatic concentration of wholesaling down into the hands of just a few leading companies. These companies and their counterparts in North and South America and parts of Asia are also forming alliances, which will result in even larger groups. Both the nature and timescale of this phenomenon remains very uncertain at present, but it could contribute significantly to opening up new and more efficient patterns of international trade in both active ingredient and packed products.

## **PUBLIC AND NOT-FOR-PROFIT SECTOR STRATEGIES**

### **Organizational Boundaries, Capabilities and Resources**

As already noted in Figure 6, there are many international agencies with diverse objectives. Broadly speaking, they engage in three types of activity, which are relevant to improving medicines access:

- expert resources in healthcare (WHO, dedicated Health NGOs)
- funding for economic and social development (World Bank, Oxfam)
- information on systems of healthcare.

The WHO has played a leading role in this area, producing a number of important publications over the years.<sup>39</sup> In its core advisory document ‘How to Develop and Implement a National Drug Policy’ the authors note:

“Barriers to a reliable source of affordable, quality drugs are complex and go beyond simple financial constraints. To understand them it is necessary to look at the characteristics of the drug market and to study the attitudes and behavior of the main actors involved.”

The main thrust of much WHO analysis is how to organize the demand side of a national market in the face of chronic lack of funds and resources.

In the context of

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Figure 7, the perennial challenge to international agencies is: ‘Should they extend their organizational boundaries to take on a more direct role in organizing and controlling international purchasing of medicines?’ This inevitably raises the question: ‘How far do they have the necessary capabilities and resources to do this, or a mandate and the funds necessary to acquire them?’

### **The Emergence of Public-Private Partnership Structures**

The considerable impetus generated by the Sachs study<sup>1</sup> and the establishment of the Global Health Fund specifically to improve access to medicines for HIV/AIDS, Malaria and TB, has brought this issue into sharper focus in recent years and, with it, a recognition that, when faced with such intractable challenges, the traditional view of an adversarial relationship between purchasers and suppliers might not be the best way forward. Similarly, from the perspective of the R&D based MNCs, a growing awareness of the need for a broader conception of social as

well as economic purpose has led to a similar willingness to engage positively in co-operative arrangements.

These changing perceptions clearly mirror contemporary thinking from game theory on the merits of co-operation versus competition.<sup>40</sup> Such ideas have led to a flurry of recent activity in establishing Public-Private Partnerships.<sup>41,42</sup> Much of the focus of these groups has been to improve R&D investment, which is not within the scope of this paper. However, many are also addressing current issues of manufacture and supply.

The Global Drug Facility (GDF), established by the ‘Stop TB Partnership’ and the WHO, have established an international direct procurement mechanism, whereby they negotiate low prices for products, such as, ethambutol, isoniazid, streptomycin and piperazinamide, through bulk buying. Sixty countries have applied to be recipients under this program and a ‘pre-qualifying’ list of manufacturers.<sup>43</sup>

The legal status, corporate governance and operational efficiency of such new entities raise many interesting questions. Most obviously in the context of this analysis, how best to audit performance, to determine whether they provide a more efficient, lower cost route to access than conventional market approaches? How far will it be possible for them to contract efficiently for manufacture as well as supply logistics, storage and documentation, as the scale and complexity of the operation grows - or will it be necessary to recruit, train and develop resources to undertake such functions internally?

If we look at private sector supply mechanisms for LDCs and smaller, less affluent emerging ones, there may be considerable merit, particularly if funding is also by international agencies, to interpose such a demand side intermediary as an actor in the international market with strict terms for audit and performance guarantees, at least for a transitional period. It might well provide a valuable conduit to establish contact between the lowest cost Chinese manufacturers and LDC markets, which otherwise might never be made.

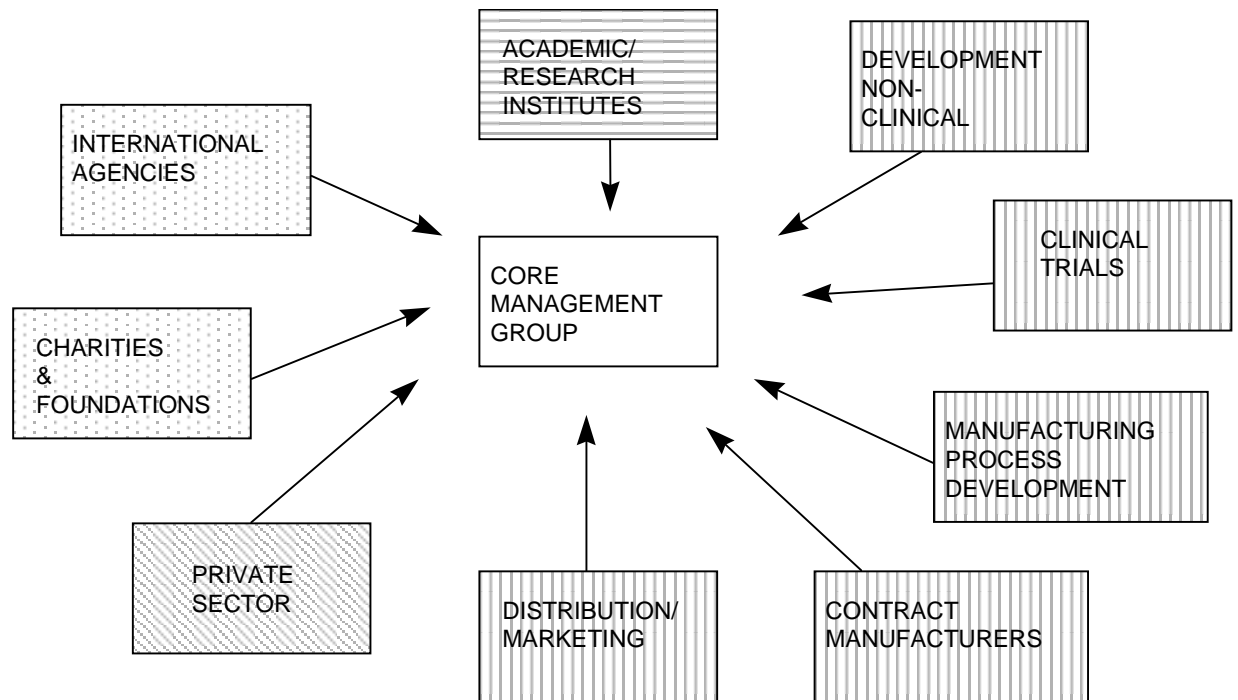
The arguments against such agencies are well rehearsed. Under ‘not for profit’ or public governance, they have a tendency to evolve into inefficient bureaucracies, where most of the potential ‘added value’ is dissipated in administrative costs and poor management and opportunism are unchecked by market discipline.

### **Negotiating and Managing Multiple Contracts**

A concept which has attracted some interest within this field is that of the ‘virtual company’, in which a very small but skilful and experienced set of agents (administrators or managers) in some form of properly constituted organization could effectively contract for all of the various component parts that make up an integrated pharmaceutical company, including R&D.

Figure 8 illustrates the wide range of capabilities that would need to be contracted for. Writing and implementing multiple contracts and managing these interfaces would require a core management staff with a good knowledge of all these areas of expertise and relationships across the boundaries.

**Figure 8: The International Virtual Company Model**



**PUBLIC-PRIVATE FUNDERS**

**CONTRACT PROVIDERS**

Clemons and Row<sup>44</sup> argue that the greatest impact of new information and communication technologies has been their ability to lower transaction costs, through reducing information asymmetry. This would support the view that over time PPP managers may be able to control these multi-interface organizations more effectively than would have been possible in the past. At first sight, however, limitations of bounded rationality would be unaffected by this.

As noted above, key resources within MNCs are staff who are experienced at managing cross-functional teams, often across many national boundaries and who collectively provide an integrative capability. Separating the key functions, as shown in Figure 8, would make it difficult to achieve high levels of collaborative teamwork among so many independent players, with a significant risk of externalities.

### **Diffusion of Medical Technology and Marketing**

In comparing public versus private models for manufacture and supply, it is often implicitly assumed that, not only would the sizeable proportion of revenues that end up as profit in MNCs be saved, but also that there would be dramatic cost savings by avoiding ‘wasteful’ expenditure on marketing. This may also be a questionable assumption in terms of truly improving patient access. As programs such as the TB DOTS campaigns show, it is probably more difficult to change doctors’ behavior in terms of diagnosis and treatment patterns in rural areas of developing countries than in sophisticated developed ones.

Whilst evidence on diffusion, or uptake of new therapies in developing countries may be largely anecdotal, there is evidence from statistical analyses that, in Europe for example, for genuinely significant advances in medicines, the diffusion of use in general practice after three to five years is often no more than 20%-30%, despite the large expenditures often by several competing MNCs to market the new concept or treatment.

This suggests that upgrading traditional treatment patterns and behavior across a national population is both expensive and time-consuming regardless of whether undertaken through private or public sector mechanisms. These costs and timescales are an integral component of the MNC model, whereas, in public sector ones it is often far less clear as to where the capabilities and resources for these activities lie and what the aggregate costs across many countries might be.

### **International Licensing and Supply Contracts**

Access to the latest currently available modern drugs in areas such as HIV/AIDS has become a *cause célèbre*, played out at the WTO in the spotlight of the world media. A comprehensive analysis of the economics of R&D sunk costs and returns to innovators and the associated issues of exhaustion of patent rights and global price differentials for such products, is beyond the scope of this paper. However, it may be of some value to comment briefly on the implications of proposed international strategies, based upon compulsory licensing of manufacturing technology for selected products and countries in the context of this analysis.

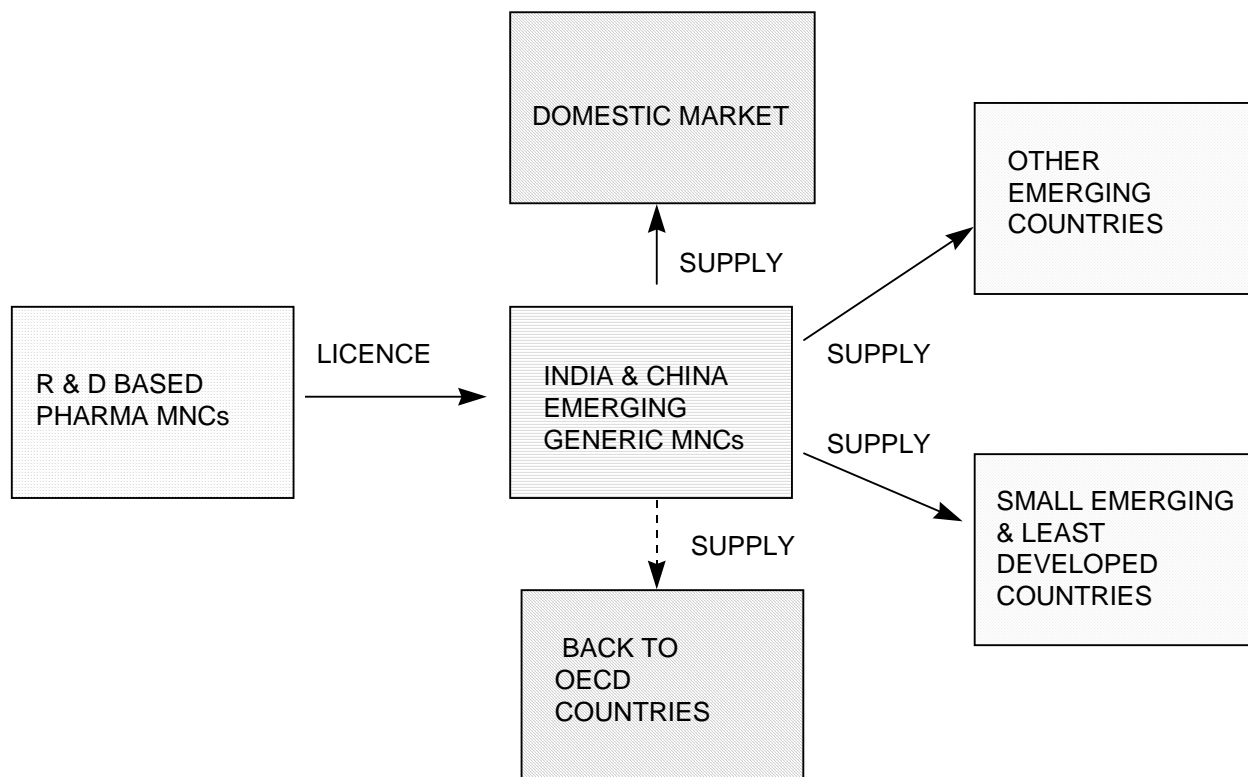
The essential thesis being advanced is that, as it is clear that many smaller emerging economies and virtually all LDC countries lack the necessary infrastructure to provide nationally the resources necessary to invest in and successfully operate pharmaceutical plants, it would be impossible for them to avail themselves of the provisions of the WTO-TRIPS agreement that allow patents to be ‘over-ridden’ and compulsory licenses for manufacture granted in specific circumstances. It has been proposed, therefore, that to help these countries, they could nominate; or maybe independently manufacturers in other emerging countries could apply for, such licenses to supply them on an international trade basis.

In the light of our analysis, the obvious candidates for such licenses would be the emerging industry sectors in India and China. As noted above in our brief review of trade patterns, these countries are likely to play a pivotal role in any future global manufacturing scenario.

As shown below in Figure 9, under such an agreement and depending upon *future* interpretation of international trade law on patents and price differentials, potentially there could be four choices open to these companies to supply the world market.



**Figure 9: The Emerging Country Contract License and Supply Model**



As the leading companies here evolve into generic MNCs over the next decade, they would appear to be best placed in terms of international supply and distribution capabilities to take advantage of these provisions. Increasingly, however, these companies will also have the characteristics of the R&D based MNCs in terms of responsibility to international shareholders and corporate governance. In consequence they will also be under the same obligations, as many already are now, to seek to optimize the profitable growth of their business.

Highest priority will be given to supplying the most attractive and accessible OECD and more affluent emerging markets. Once *de facto* manufacturing technology transfer and freedom from patent constraints has been established, it will be extremely difficult to write and enforce contracts with individual private sector companies, which would require them to utilize limited plant capacities to supply only, or even give priority to, the least or non-profitable LDC markets. To summarize and conclude this section on future international options for improving access, in the light of a best forward view of the international supply side industry, we have evaluated some of the current issues related to extending public agency roles, public-private partnerships and other experimental forms of organization and contracts. In doing so, we have drawn attention to the importance of taking a realistic view of the need to have the right capabilities within an organization to implement successfully new strategies and the difficulties of writing and managing contractual relationships between independent profit- or rent-seeking private sector entities in a varied and uncertain world environment.

In the following section, we will look more specifically at manufacturing and supply from the perspective of formulating national policies for improving access.

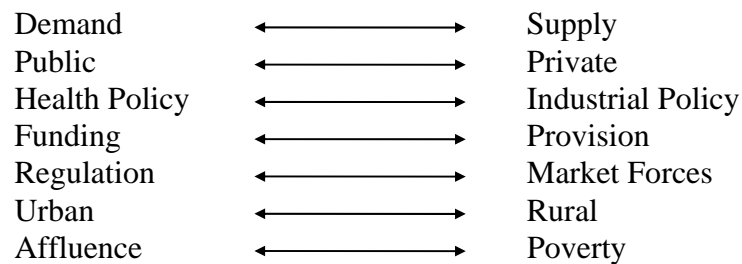
# NATIONAL STRATEGIC OPTIONS FOR MIDDLE-INCOME AND LDC GOVERNMENTS

## OVERVIEW

### Key Policy Dimensions

As already noted, national strategies depend very much upon the local context, and the local context varies enormously across these countries. In consequence, as our primary aim is to highlight where economic theory might provide useful insights, we shall undoubtedly overlook many facets of this subject.

In outline, formulating strategic options encompasses the following important dimensions:



Above all, forward strategies must clearly acknowledge the realities of the current situation as a starting point. We will take as our two key reference points for this analysis, the rudimentary ‘international-national’ model shown in

We have included the funding options here because, in the final analysis, improving access inescapably depends upon the economics of supply, in terms of balancing costs and the flow of funds available. Self evidently from this picture, there are a multiplicity of combinations of funding, manufacture and distribution available. In NIE terms all of these offer different combinations of activities, some carried out under corporate governance and some contracted for under market or quasi market conditions. Clearly a rigorous application of TCA principles to compare transaction costs and evaluate their relative merits represents a formidable challenge.

For the purposes of this discussion, we focus attention on the following components:

- R&D based MNCs
- emerging International Generic Suppliers
- national manufacturer and distributors
- alternative public sector combinations
- new public-private partnerships (PPPs).

Figure 7 and the basic ideas from TCA.

### Country Categories and Strategy Options for Manufacture and Trade

We will examine in turn the following categories of country situations:

1. LDC’s and small emerging markets
2. large emerging markets
3. former Communist Block countries

4. other Latin American and Asian countries.

The presumed ‘generic’ objective of all national systems is to improve access to the best modern medicines at the lowest possible prices, compatible with industrial policies that optimize the potential for investment and development of a competitive national industry sector. In terms of strategic options for manufacture and supply, we will evaluate the following general approaches:

- a) National self-sufficiency
- b) Importation with primarily Public Sector supply systems
- c) Importation with mixed Private-Public Sector supply systems.
- d) Open Market with ‘niche’ investment strategy
- e) Major global investment centre for MNCs

We accept that these country categories constitute relative crude and ill-defined stereotypes, but they will hopefully provide an adequate framework for making some important distinctions. The following discussion also assumes broad appreciation of the macro-environment in the country categories and the overall situation with regard to healthcare systems and policies. We will now discuss each in turn.

## **STRATEGIES FOR COUNTRY CATEGORIES**

### **LDCs and Small Middle-Income Markets**

There is a broad consensus that the options available for these countries are few. The lack of realistic scope for cost efficient local manufacture, at least for the foreseeable future, suggests that the primary objectives need to be:

- To seek the maximum support in terms of aid funding from international agencies
- To invest funds in improving public sector demand side health infrastructures for diagnosis and treatment
- To develop a central government expert capability (technical and commercial) for public sector purchases of medicines from international markets
- To provide appropriate incentives for private sector distributors to purchase and distribute under market governance
- Where funding is available for major public sector treatment programs, consider the use of national government tender
- Participate in international bulk purchase initiatives
- Seek donations plus educational training packages from R&D based MNCs on a selective basis to address high priority needs.

### **Large Middle-Income Countries**

We have already discussed the particular strength of India and China in global manufacturing. Both of these countries will seek over the next decade to build R&D capabilities onto their existing generic manufacturing and export industry platforms. Their respective governments are committed to strategies aimed at becoming leading world centers for manufacture and

international supply, based upon growth of their indigenous industries and through inward investment from Western companies.

However, from a health policy viewpoint, both of these countries have massive rural and growing urban poor populations, who appear to have little access to medical facilities and essential drugs.

*Prima facie*, this would suggest a potential conflict between a health policy aimed at providing essential drugs much more widely domestically and an industrial policy aimed at exporting generics and ultimately innovative products, for which the primary market is the OECD. Of course, it may be argued that, the rate controlling step to improving access lies with public sector investment in demand side healthcare capabilities and not with supplying cheap medicines and that the funds for such investment will only be available when the country has achieved economic growth through a globally competitive industrial base, of which pharmaceuticals is an important component.

For other large countries, such as Brazil or Indonesia, the future appears much more problematic. Brazil would appear to be very much in a pragmatic experimental phase, engaging in publicly funded and owned, not for profit manufacture of some HIV/AIDS drugs, with legislative and tariff requirements to ensure at least secondary manufacture is done locally by MNCs and a highly successful campaign to drive down the prices of these products through hard bargaining with local MNC affiliates. Indonesia also persists with a combination of tariff barriers and pharmaceutical regulations to enforce secondary local manufacture. Currently the Brazilian government policy includes a plan to strengthen domestic manufacture.<sup>45</sup>

Based upon our scenarios for the sector, it appears unlikely that these latter countries and others like them will succeed in leveraging a very limited technology base to develop a globally competitive export led industry, even in the generics field.

This will lead to difficult choices for the future. From a health policy perspective, improving access for the large poorer section of society might well be facilitated by removing protectionist barriers to finished product imports, which are used to support a weak national secondary manufacturing base. This could lead to importation of much cheaper, sound quality EDL generic products to support widespread low cost use.

Whilst recognizing that such strategies have a broader economic consequence in terms of trade balance, currency, etc. and hence may be out of line with the overall thrust of industrial policy for the country as a whole, it is likely to be a more viable long-term approach, which will provide more cheap medicines to support access, than retrenching or persisting with a trade policy vaguely aimed at some form of self-sufficiency in an increasingly global market.

### **Former Communist Bloc Middle-Income Countries**

This section does not include China and is primarily concerned with the countries of Central and Eastern Europe. For a broader review of health policy reform in these transition economies see the work of Preker and Feacham.<sup>46</sup>

Under the former Soviet planned economy system, strategies for medicines manufacture and supply, as for many other sectors, was based upon a policy of national specialization. Thus, whilst there was not an absolute embargo on national manufacture, the now infamous five and ten year Comecon plans placed considerable emphasis upon Hungary and Yugoslavia as the prime locations for development and manufacture of medicines.

Particularly in the case of Hungary, this privileged access to the large Soviet market, with only very limited competition allowed from Western companies, primarily due to currency restrictions, fostered the formation of a particularly strong national capability in the form of the Gideon Richter and Chinoin groups, whose organizational development and achievements closely paralleled that of Western companies.<sup>47</sup>

The legacy of decades of this regime has left many CEE countries and most notably, Russia itself, with very limited national manufacturing bases, despite the fact that, in terms of the fundamentals of scientific and medical education systems, engineering and related manufacturing technologies, historically, such an evolution would have been quite feasible.

In consequence, today many of these countries face a painful policy dilemma in the light of our global scenario and in a domestic context of aggressive privatization policies and competitive open markets, as to if, and where, it might be appropriate to subsidize, or protect some elements of what national manufacturing capacity remains. Already for those countries, due to enter the EU in 2004, the more attractive facilities and centers have been acquired and absorbed by Western companies. The remaining independent ones will, in most cases, be looking to establish viable niche positions within the larger but to a degree, still protected EU generics market.

If the prime health objective is to widen access to modern medicines across the national population as a whole at the lowest available prices, the case for an open market policy, at least for active ingredients, would seem to be compelling. However, conversely from an industrial policy viewpoint, there would be little merit in hastening the demise of existing national manufacturers, unless they were demonstrably uncompetitive on price or quality of products. There is also a need in more technologically sophisticated countries to evaluate carefully if there are specialist, technology based centers, public or private, who might have at least *prima facie* potential capabilities to become competitive on a regional, or even global basis.

### **Other Latin American and Asian Middle-Income Countries**

Whilst circumstances can vary enormously, it would appear unrealistic for these countries to embark upon industrial policies involving investment in primary manufacture, based upon (for example) outmoded ideas of national self-sufficiency.

In larger countries, a strong policy of encouraging local manufacturers to merge and invest in modern computer based technologies to improve efficiency may go some way to enhancing competitiveness, especially in areas where there is high asset specificity. Similarly, mutually beneficial joint ventures of local companies with R&D based MNCs, where there is ongoing access to innovative new products and technologies can be an attractive option.

In most emerging countries, there either already exists, or it should be feasible to establish, a competitive market based wholesaler/pharmacy distribution system. The key public requirement is firstly a technical regulatory agency that, within a legal framework, sets out the requirements for such companies to operate to appropriate professional standards, to maintain storage facilities that are secure, and to safeguard quality. A range of WHO booklets and guidance notes are available on these topics.<sup>34,48, 49</sup>

From the perspective of economic regulation, many countries find it is simplest to agree national contracts with pharmacists' associations for the sector rather than allow a laissez-faire market to evolve. This will depend on the degree to which such an infrastructure has evolved. These systems usually involve an agreed formula, incorporating a combination of fees for service and a margin element. However, it can be difficult to audit such systems to avoid or eliminate rent-seeking behaviors.

An efficient and professional state auditing system for both technical standards and financial accounts is desirable.

Table 4 summarizes in a very general manner the broad strategic approaches that might be best suited to the different categories of national markets.

**Table 4: Manufacture and Trade Strategy -v- Country Matrix**

	<b>National Self-Sufficiency</b>	<b>Importation + Public Supply</b>	<b>Importation + Mixed Public/Private Supply</b>	<b>Open Market + Niche Investment</b>	<b>Major Global MNC Investment Centre</b>
<b>LDC + Small MI</b>	D	C	B	C	D
<b>Large MI</b>	C	C	C	C	A
<b>FCB MI</b>	D	C	B	A	D
<b>Other Lat Am Asia MI</b>	D	C	A	B	D

**A = Optimal; B = Acceptable; C = Sub-Optimal; D = Unrealistic**

## **IMPROVING THE EFFICIENCY OF NATIONAL DISTRIBUTION**

The main focus of this paper is upon the international aspects of supply or trade. However in the broader context of improving access at a national level, it is axiomatic (as is apparent in We have included the funding options here because, in the final analysis, improving access inescapably depends upon the economics of supply, in terms of balancing costs and the flow of funds available. Self evidently from this picture, there are a multiplicity of combinations of funding, manufacture and distribution available. In NIE terms all of these offer different combinations of activities, some carried out under corporate governance and some contracted for

under market or quasi market conditions. Clearly a rigorous application of TCA principles to compare transaction costs and evaluate their relative merits represents a formidable challenge.

For the purposes of this discussion, we focus attention on the following components:

- R&D based MNCs
- emerging International Generic Suppliers
- national manufacturer and distributors
- alternative public sector combinations
- new public-private partnerships (PPPs).

Figure 7) that the ultimate delivery of the product to the patient depends critically upon having efficient networks of wholesalers and/or state distribution centers in both urban and rural areas.

Much scope exists to deploy modern information technologies to improve the efficiency of distribution and stock management. In more affluent countries government purchasers have successfully applied pressure for a share of the savings that accrue from these, and also for concentration of the wholesaling sector into larger more efficient units, whilst still retaining adequate scope for competition. The ideal undoubtedly is for a competitive private sector approach, but with strong technical and market regulation, which is demonstrably enforced. If for cultural or infrastructure reasons this is not possible, then especially for distribution of essential medicines, some form of state network, particularly in rural areas may be the only option.

Even in the more advanced middle-income countries, providing the necessary incentives to ensure a competitive private sector supply system for scattered rural populations is frequently a problem, which requires a greater role for the state or regional authorities.

As more sophisticated modern medicines cascade down from OECD countries, there is a growing imperative that professionally trained pharmacists are responsible for dispensing them. There is a common dilemma in deciding on how to organize pharmacy services in primary care, which is the dichotomy between the professional medical-scientific role of the pharmacist, as opposed to the competitive business person, who is rent-seeking as in any other business. Situations vary greatly from country to country. Some incline to the view of the pharmacist role as a professional for which they are rewarded on a fee for service basis, others prefer to see the pharmacists as an integral part of the commercial transaction process, buying and selling medicines for profit.

A more detailed analysis is beyond the scope of this paper, but as for other facets of supply, careful review of transaction costs for alternative models, within the context of what is culturally acceptable and technically feasible might well add value in defining reform policies.

## **CONCLUSIONS**

Many of the issues we have addressed in this paper are not susceptible to formal academic analysis because, for the most part in middle-income and LDC countries, relevant data sets are

limited, of doubtful quality and compiled on different bases. Thus, whilst IMS, the leading international pharmaceutical market research audit company, has excellent long-term data on OECD countries, beyond that it tails off rapidly. In drawing conclusions, therefore, it is important to be clear that the evidence, information and opinions drawn up are not just empirical but, to a degree, subjective judgments.

With regard to the application value of NIE concepts, there would seem to be scope to examine further the following themes:

- Benchmarking transaction costs in alternative public-private models for manufacture and distribution, particularly new hybrid PPP forms,
- Similarly a fuller analysis of the core capabilities needed to undertake different types of long term initiatives in improving access to medicines, as a basis for evaluating alternative organizational structures and setting the balance between corporate and market governance,
- Possible game theoretic approaches to the potential merits and disadvantages of collaborative versus competitive strategies amongst the different types of international private sector suppliers.

We would suggest that, faced with a specific situation in an international agency or a private company, or in defining a national strategy, this analysis provides at least an insight into how ideas of ‘make or buy’ organization boundary setting, writing and managing contracts and the fit between objectives-strategies and capabilities might be used to formulate a relevant and useful framework for high level consensus building and choice of strategies or policies. Also, understanding the nature of the technologies, capabilities and resources needed to operate professionally and efficiently in the pharmaceutical sector, can greatly enhance the quality of decision-making.

More specifically on the issue of public sector engagements, either internationally, in national policies or at the individual company level, it is critically important to understand likely future global scenarios for location of the most efficient, low cost production and the resulting patterns of international distribution or trade.

Finally, there may be much merit in seeking to achieve best value from the worldwide industry in its many guises, thinking not only in terms of regulation and control, but of incentives and capability building.



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HUMAN DEVELOPMENT NETWORK

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