NARROWING THE GAP

between provision and need for medicines in developing countries

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EXECUTIVE SUMMARY

Health and economic development is positively linked. External investments are needed to break the vicious cycle of poor health and poverty plaguing less developed countries (LDCs).

Measured in disability adjusted life years (DALYs)[1], the disease burden suffered per person in LDCs is twice that of people in established market economies (EMEs). The two regions also have distinct disease patterns with almost 40 percent of LDCs' healthy years lost to communicable, maternal, and prenatal diseases as opposed to only 8 percent in EMEs.

The size and pattern of disease burden in LDCs are linked to wider problems of inadequate infrastructure in education, sanitation, transportation, and so on. These infrastructure problems, together with lack of money, prevent populations from using many existing treatments effectively. In many disease areas, however, effective treatments simply do not exist. Here, investments in new research and development (R&D) are critical.

Diarrhoeal diseases, malaria, tuberculosis, and respiratory infections are among the top global 12 disease categories but they occur almost exclusively in LDCs and are therefore not a priority for the investors in pharmaceutical R&D. In 1992, of the $55.8 billion invested in health care world-wide, only an estimated $2.4 billion or 4 percent were allocated towards LDC diseases. In sharp contrast to health care research in general, where the pharmaceutical industry and EME governments are the primary investors, official development assistance organizations and LDC governments paid for two thirds of the small amount of money spent on R&D for LDC issues.

The political challenge, therefore, is to make LDC health concerns a greater priority of EME R&D investors, as this is where the funding and the experience are centred.

R&D investment priorities are a function of market size, the degree of current and future need and the probability of success (a function of the state of science, in-house resources and experience and

1 This measure aims to take into account both the number of healthy life years lost due to premature death and the disability caused by debilitating though non-fatal diseases and injuries.

risk). As the expected number of patients able to pay for medicines is small, LDC-diseases tend not to be prioritised, and this is despite the significant need for new products in these countries.

The public sectors of the EMEs can intervene in two ways to try and correct these market failures. First, they can improve 'push' and 'pull' incentives to try and make it more attractive for private companies to invest in these disease markets. I call this the 'commercial assistance' approach. Second, they can provide direct public funding for research and product development in these areas. Teams of academic and industry scientists from both developed and developing regions could compete for this funding. I refer to this as the 'public-based' approach.

It is a challenge to identify policies that will:

1) incentivize companies to invest;
2) be acceptable to EME governments (i.e. policies which they will be willing and able to legislate and fund); and
3) produce medicines that the LDCs are able to afford.

Also at issue is how to formulate a package of policies that will encourage both 'local' (LDC) and multinational participants.

To motivate private companies, in a 'commercial assistance' approach, a package of incentives, rather than one single remedy, would work best to incentivize both small and large companies and bring public and private resources together. A modified orphan drug policy[2] that puts together R&D tax credits and grants with a significant pull measure might shift the cost-revenue balance of LDC diseases.

From the standpoint of large companies, this pull incentive must be significant and the promise of funds be credible. Companies are likely to find a roaming exclusivity clause or a guaranteed purchase fund attractive. A roaming exclusivity clause would permit companies

2 The standard orphan drug legislation, in place in the US, Japan, and the EU, combines market exclusivity – for the product in the country where the orphan drug status is awarded – with cost saving measures (tax credits, development grants, fast-track approval) to encourage companies to conduct R&D in rare disease areas with low case prevalence.

to extend market exclusivity for any of their approved products in exchange for marketing an approved LDC drug at affordable prices. A guaranteed purchase fund, such as that proposed by Jeffrey Sachs and Michael Kremer for malaria, TB, and HIV vaccines, would provide companies with the assurance that if their R&D were successful, then there would be a market for their product. Given that it takes many years to develop a patentable idea into a marketable product, the effectiveness of any incentive depends on assurance that funders will uphold promises made now in the future.

Following along another, 'public based' parallel track, public money could be used to set up LDC-disease focused research units or to finance competitions for proposals from academic and industry researchers to conduct the necessary research at their respective facilities. The new Medicines for Malaria Venture (MMV) is an example of the latter. Industry participates in these public based ventures contributing in-kind resources such as technologies or experience, especially in the clinical trial stages. Financial rewards from these contributions are not expected, at least in the short to medium term, though companies do stand to be benefit from the positive public relations, networking opportunities, and shared access to new, scientific breakthroughs.

The two approaches (commercial assisted and public based) are not mutually exclusive. Market based incentives for companies may be more effective for certain diseases than others. Differences between diseases in the size of the potential 'market' (i.e. prevalence in LDCs), the state of the science and the type of companies involved (i.e. small biotechnology companies, large multinational pharmaceutical companies) may mean different combinations of incentives are needed. In cases where researchers still do not understand the science, the promise of markets some time in the future may do little to motivate investment. In other cases, developed, patentable ideas may have been shelved because of the lack of a viable market.

From the standpoint of the patients in LDCs, most critical is that the products are affordable and accessible, which raises the importance of combining incentives for research with efforts to improve access

infrastructure and deal, in advance, with pricing questions.

Ultimately, the greatest challenge may be that of how to get the players involved to back verbal commitments with money and resources. EME governments, for example, must convince a complex set of interest groups to agree to make LDC-diseases a priority for any of the above approaches to work. It may be harder to convince the US or UK taxpayer than a large multinational pharmaceutical company that investments in LDC-diseases are worthwhile.

The potential for real action is there. A number of teams with representatives from industry, international aid and activist organizations and academics are currently working to come up with viable alternatives to attract new investments. In order to put their ideas into practice, these groups must move fast to involve all relevant players, especially payers, in the negotiations.

1 INTRODUCTION

Despite improvements in health care over the past century, a significant gap remains in health and life quality standards between established market economies (EMEs) and less developed countries (LDCs)[3]. As an example, Figure 1.1 shows trends in life expectancy at birth.

LDCs have a pattern of disease burden markedly different from EMEs. In particular, one third to one half of healthy years lost in the LDCs are due to communicable diseases, such as malaria, tuberculosis (TB) and HIV. Improving LDCs' health status depends on the development of new tools to eradicate these communicable diseases. New pharmaceutical products are one important and potentially cost-effective component of this package of tools. 'Essential drugs are the foundation for nearly every public health program aimed at reducing morbidity and mortality in the developing world, and pharmaceutical expenditures can account for a high proportion of the total health expenditure of a country' (Pecoul et al., 1999, p. 361)[4].

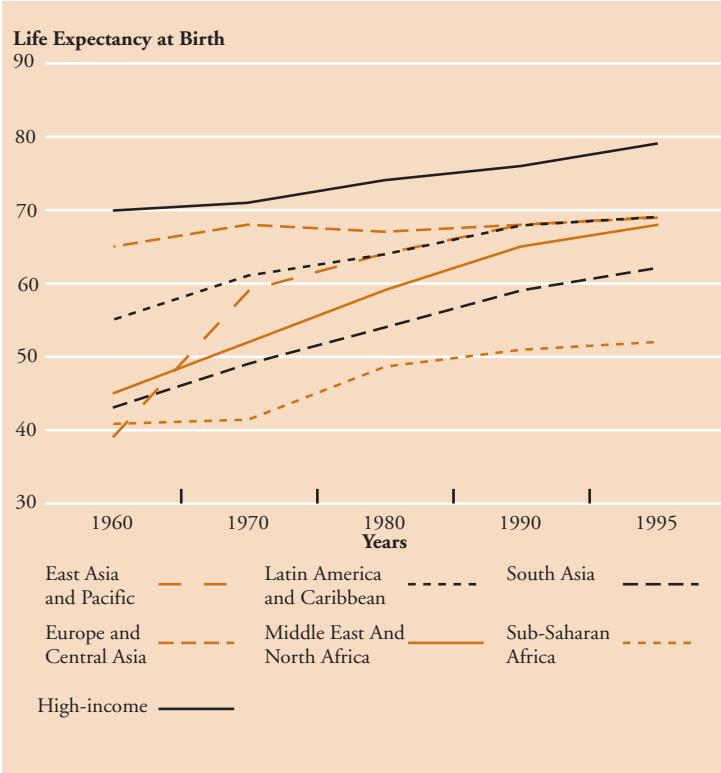
Table 1.1 shows what the World Health Organization (WHO) identifies to be the key sources of observed mortality reduction in LDCs between 1960 and 1990. We see that almost half of the gains in this measure of health result from new technology, an indicator that includes medicines.

The key problem addressed in this paper is that despite the great and obvious need for new therapies in communicable diseases, current private and public investments in new medical research tend to ignore them. After discussion of why this 'market failure' exists, different policy measures that might be enacted to incentivize investor interest are examined. There is currently considerable momentum among differ-

3 The EMEs category includes countries with GNP per capita of $9,361 or more in 1998. Defining the set of LDCs is more difficult. In the statistical tables, unless otherwise specified, the LDCs category includes all countries in the middle- and low-income categories (a GNP per capita of less than $9,361). This without question is too broad a definition as it groups Cameroon and Ghana with the Czech Republic and Hungary. In terms of health care (and economic development in general) the latter two have more in common with the US or EU than with Sub-Saharan Africa. Preferable to categorizing by income would be to group countries according to similar socioeconomic, health and geographic factors. In the text, LDCs refers to the set of countries in the lower income categories with common health care problems from mostly Africa, South Asia, and Latin America.

4 Other key components include investments in education, nutrition, sanitation, vaccines, transportation and basic infrastructure (WHO, 1999a).

Figure 1.1 **Life expectancy at birth, by income group and region**



Source: World Bank, 1999a, p.13.
Notes: 1. The classification of economies is based on gross national product (GNP) per capita for 1998. High-income countries are those with a GNP per capita of $9,361 or more. The regional categories include only the low- and middle-income countries – those with a GNP per capita of less than $9,361. See Appendix I for a complete list of the economies classified by income and region.
2. The life expectancy statistics in this figure do not reflect the impact of HIV on life expectancy (Feachem, 1999).

ent teams of representatives from academia, the WHO and other development research organizations, and industry to identify viable incentive packages, so a critical assessment of different measures is of

Table 1.1 **Sources of mortality reduction, 1960-1990**

Health indicator	Percentage contribution of gains in:		
	Income	Education level of adult females	Generation and utilization of new knowledge
Under-5 mortality rate	17	38	45
Female adult mortality rate	20	41	39
Male adult mortality rate	25	27	49
Female life expectancy at birth	19	32	49
Male life expectancy at birth	20	30	50
Total fertility rate	12	58	29

Source: WHO, 1999b, p.5.
Note: The results are based on analysis of data from 115 low and middle income countries.

particular importance right now. There is no one solution but evidence presented in this paper suggests that there is a need for a mixed set of 'push' and 'pull' incentives that will attract both small and large companies and bring together public and private resources.

Incentivizing the development of new cost-effective medicines[5] is the primary focus of this paper, but key access problems are also identified. A new medicine from the patient's perspective is only as good as his or her ability to access it and afford it.

The paper is organized into six chapters and a conclusion. In chapter 2, an analysis of the global health picture reveals a distinct pattern of disease burden for LDCs. The main difference from EMEs is in the

5 Given the scarcity of public resources, the challenge for policy makers is not just to motivate new R&D but to ensure that the investments produce treatments that are cost-effective relative to existing tools. Cost-effectiveness analysis can be used not only to select between existing technologies and treatments (within or between disease areas) but also to influence decisions about undertaking R&D into new treatments in the first place (Evans, 1996). The WHO (1996) estimates that anything that costs less than US$150 per disability-adjusted life year (DALY) averted to develop, manufacture and distribute would be attractive in low income countries, and anything costing less than US$30 per DALY would be highly attractive.

extent to which LDCs' populations suffer from communicable diseases. In 1998, communicable, maternal, prenatal and nutritional categories of disease made up 36 percent of the LDCs' burden but only 8 percent of the EMEs' health problems.

Many of these diseases are not found in or have been eradicated from EMEs. Treatments may exist but the LDCs are not able to access them and/or the existing treatments are inappropriate given the conditions in the affected regions. Differences in climate and health care infrastructure as well as the LDCs' limited finances may mean that different versions of existing medicines must be developed in order to treat the populations in LDCs.

Where no treatments exist, it seems that insufficient market incentives exist to motivate pharmaceutical companies, the primary investors in new medicine development, to invest in new targeted research and development (R&D). Chapter 3 addresses the question of why LDC diseases (or LDC-targeted treatments for other diseases) are not a priority for pharmaceutical companies.

The numbers of people in need are large. In 1999, for example, the WHO estimated 39.3 million cases of death or disability for malaria and 28.2 million cases for TB (WHO, 1999b). However, the affected regions' poor ability to access medicines and pay prices that will cover R&D costs equate to low market value estimates for these disease areas. To bring private companies' investment interests in line with these global health concerns, policy mechanisms must focus on reducing the risk and costs of drug development, on the one hand, and increasing the market for treatments for these medicines, on the other.

Chapter 4 and chapter 5 examine mechanisms that EME governments might use to shift the cost-revenue balance in favour of LDC diseases. It is a true challenge to identify policies that will: 1) incentivize companies to invest; 2) be acceptable to EME governments (i.e. policies that they will be willing and able to legislate and fund); and 3) that will produce drugs that the LDCs are able to afford. Also at issue is how to formulate a package of policies that motivates both 'local' (LDC) and multinational participation. The current international debate over compulsory licensing of HIV treatments in South Africa,

for example, raises many complex questions about how to support intellectual property, a key incentive for multinationals' R&D, while allowing LDCs to meet their great and urgent need for affordable medicines. Chapter 4 looks at policies that motivate private companies while chapter 5 considers the pluses and minuses of setting up new, publicly funded R&D centres that focus exclusively on LDC-specific diseases. The most effective approach may be to combine both types of policies.

Developing new treatments is only beneficial if the targeted population can access them. LDCs lack the finances and infrastructure (political support, health care systems) necessary to pay for and distribute medicines for LDC-specific diseases as well as those prevalent in both EMEs and LDCs. The barriers to access are numerous and inter-connected. After a summary of the important barriers, chapter 6 looks at the potential value of a tiered pricing scheme. Already in place for some vaccines, tiered pricing might be used to make new medicines more affordable in LDCs while at the same time allow pharmaceutical companies to cover R&D and production costs. Conclusions are drawn in chapter 7.

2 GLOBAL PATTERNS OF HEALTH AND DISEASE

Data presented in this chapter show that LDCs suffer a greater disease burden per person on average than EMEs and that a large percent of this disease burden is caused by communicable, maternal, and prenatal diseases that do not greatly affect the EMEs. In general, the disease burden patterns are linked to the regions' relatively poor state of development in areas of wealth, health, education, nutrition and, sanitation.

2.1 The health and wealth relationship

Significant variation in infant and child mortality rates and life expectancies exists between countries. The regional patterns are correlated with income levels. A comparison of Japan and Sierra Leone shows the two extremes where the life expectancy of a baby born in 1990 was 79 years and 38 years respectively. Table 2.1 compares life expectancies and child mortality rates for high-income countries and low- and middle-income countries from six demographic regions.

All regions experienced improvements in life expectancy and mortality rates over the 1980-1996 period though significant gaps remain between high and lower income regions. Among the countries in the low- and middle-income category, health standards vary directly with wealth. The poorest regions of Sub-Saharan Africa and South Asia exhibit the highest mortality and lowest life expectancy figures. Feachem (1999) and others have argued that there is a positive dynamic link between income and health. This implies that pro-growth and development policies should produce improvements in health status over time (and investments in health should produce improvements in economic development).

2.2 Levels and patterns of disease burden across countries

To measure the burden of disease, development agencies employ the indicator disability-adjusted life years (DALYs). This measure aims to take into account the number of healthy life years lost due to premature death and the disability caused by debilitating though non-fatal diseases

Table 2.1 **Health care indicators for global regions**

	Child mortality rates[1]			Life expectancy at birth			Gross national product	
	Per 1,000 live births			Years			Billions of dollars	GNP per capita, dollars
	1980	**1996**	**% Change**	**1980**	**1996**	**% Change**	**1999**	**1998**
World	80	54	–33%	63	67	6%	28,862	4,890
High income	13	6	–54%	74	77	4%	22,599	25,510
Low and middle income	87	59	–32%	60	65	8%	6,263	1,250
East Asia and Pacific	56	39	–30%	65	68	4%	1,802	990
Europe & Central Asia	41	24	–41%	68	68	0%	1,039	2,190
Latin America & Caribbean	59	33	–44%	65	70	7%	1,978	3,940
Middle East & Northern Africa	96	50	–48%	59	67	12%	586	2,050
South Asia	120	73	–39%	54	62	13%	556	430
Sub-Saharan Africa	115	91	–21%	48	52	8%	304	480

Source: World Bank, 1999a, various tables.
Note: Includes deaths of children under five years of age.

and injuries[6]. Table 2.2, which draws on WHO data, shows that in 1998, populations in the poorest region of Sub-Saharan Africa bore more than four times as much burden per person than populations in the richest countries. Sub-Saharan Africa, which constitutes 10% of the world's population, suffers 23% of the globe's lost healthy life years.

6 For a detailed discussion of methods and problems with measuring DALYs see Murray, 1996.

Table 2.2 **Disease burden by region, 1998**

Region	Income classification	Population (millions)	Percent of region's population	Percent of the world's population	DALYs (millions)	DALYs lost per 1,000 population
World	Total	5884.5			1382.6	235
	High income	907.8	15%		108.3	119
	Low/middle income	4976.7	85%		1274.3	256
AFR		601.7		10%	325.2	540
AMR	High income	304.8	38%	5%	36.9	118
	Low/middle income	497.9	62%	8%	93.9	189
EMR		473.6		8%	122.9	260
EUR	High income	392.4	45%	7%	51.2	130
	Low/middle income	477.7	55%	8%	91.5	192
SEAR	India	982.2	66%	17%	269.0	274
	Other low/middle income	502.8	34%	9%	121.7	242
WPR	High income	198.5	12%	3%	20.0	101
	China	1255.7	76%	21%	208.7	166
	Other low/middle income	197.0	12%	3%	42.4	216

Source: WHO, 1999b, pp.104-109.
Notes: AFR – Africa; AMR – Americas; EMR – Eastern Mediterranean; EUR – Europe; SEAR – South East Asian Region; WPR – Western Pacific Region.

The pattern of burden between the LDCs and the EMEs is also significantly different. In particular, the importance of communicable diseases is inversely related with income level. Figures 2.1a and 2.1b

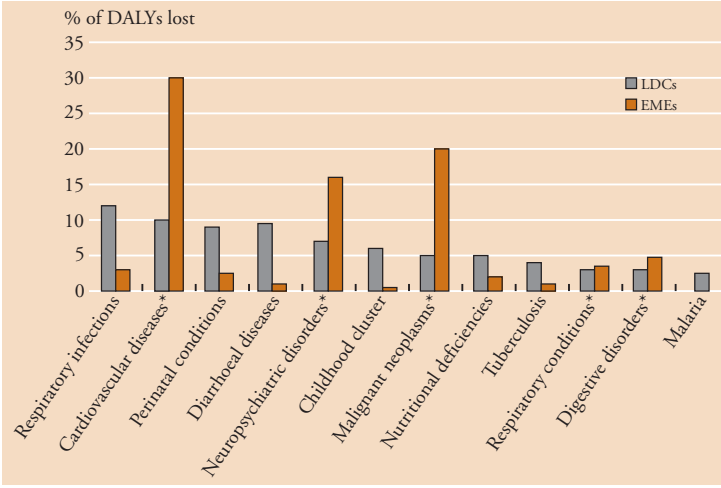
compare the 12 leading non-injury burdens of disease for 1990 and 1998.

From these two figures we can draw a number of important patterns and trends. First, the key differences between the top 12 diseases in 1990 and the top in 1998 are the addition of HIV/AIDS and the disappearance of TB. The number of HIV DALYS lost in the developing world increased 60 percent between 1990 and 1998 from 23.5 million to 69.9 million (77 percent of those new cases were found Africa)[7]. As a result, HIV jumped from a 2.7 percent share of non-injury LDC DALYs lost in 1990 to a 5.5 percent share of non-injury LDC DALYs lost in 1998. Meanwhile, the total number of TB DALYs fell from 45 million to 28 million, its share of LDC DALYs dropping from 4.3 percent to 2.2 percent[8].

Second, for both years, the top 12 diseases account for a significant share of non-injury disease burden in both LDCs and EMEs: 95 percent for both regions in 1990 and around 82 percent for both in 1998. However the diseases among these 12 which are important differ between the two regions. In both years, only the LDCs suffer significantly from communicable diseases. In 1990, the top six communicable diseases accounted for 48 percent of all the LDC non-injury DALYs lost but only 8 percent of EME non-injury DALYs. Communicable diseases' share of LDCs non-injury DALYs lost was somewhat lower in 1998 at 38 percent of LDC. Nonetheless, these diseases remain an LDCs issue. Of the total 565.5 million healthy years lost from communicable diseases, and maternal and perinatal conditions, 99 percent occurred in the low and middle-income countries[9]. To further highlight this regional difference, Figure 2.2 contrasts the disease burden pattern of Africa and the EMEs.

7 Only 1 million or 0.9 percent of the total HIV DALYs lost occurred in high-income countries.
8 99.9 percent of TB cases were in the LDCs.
9 The threat that these diseases will spread to other regions by way of travellers, migration and forced population movements, and global climate change will continue to increase as long as treatments are not found.

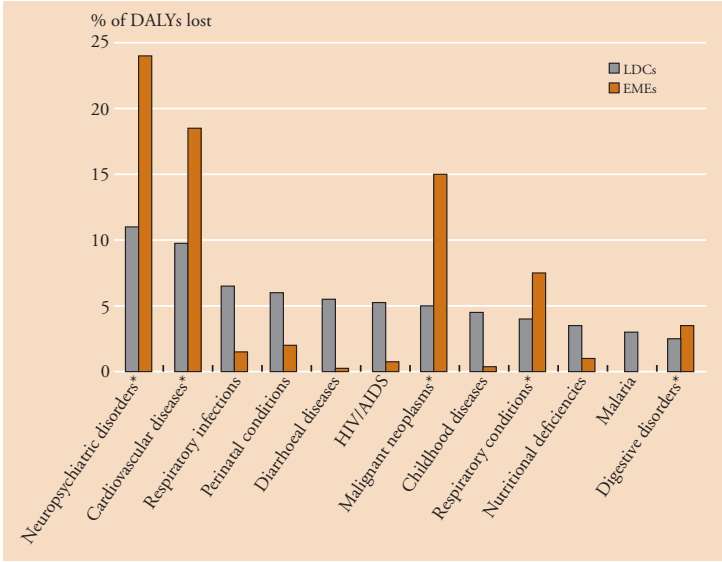
Figure 2.1a **Top burdens of disease, 1990**



Source: World Bank, 1993a, Table B.2 and B.3.
Notes: LDCs = low and middle income countries, EMEs = high-income countries. See Appendix I for countries by income category.
*Non-communicable disease.

Figures 2.1a and 2.1b do suggest a trend of convergence between the disease burdens in the LDCs and EMEs. This is line with WHO predictions for the 2020 disease burden patterns. Murray and Lopez (1996) show the share of total DALYs attributed to communicable, maternal, prenatal and nutritional conditions for LDCs falling from 48.7 percent to 22.2 percent and the non-communicable disease share increasing to 56.7 percent from 36.1 percent. These authors attribute the increase in the relative importance of non-communicable disease DALYs to two trends. First, as fertility falls, 'the proportion of the population that is adult (both young adults and older adults) increases sharply, so the proportion of the total disease burden in the population that is due to adult conditions, largely non-communicable diseases, also rises' (Murray and Lopez, 1996, 136). Second, people's exposure to certain known risk factors for non-communicable diseases (such as tobacco, high-fat diets, and alcohol) is increasing in many

Figure 2.1b **Top burdens of disease, 1998**



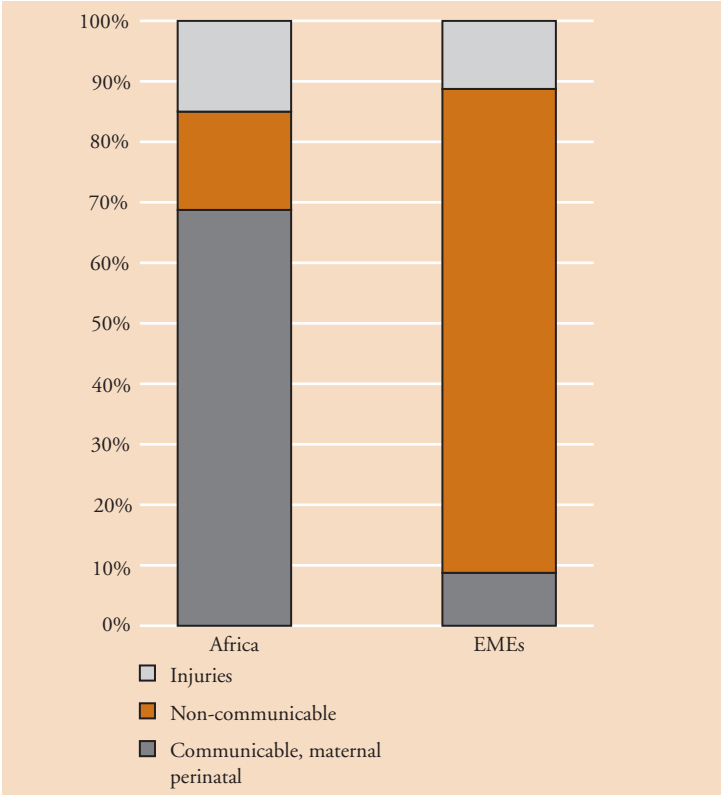
Source: WHO, 1999b, Annex Table 3.
Notes: LDCs = low and middle income countries, EMEs = high-income countries. See Appendix I for countries by income category.
*Non-communicable disease.

regions, while in some low-income countries risk factors for some communicable diseases have been reduced (ibid.).

The decline in communicable diseases between 1950 and 1990 (with the exception of HIV and TB) 'is a function of rising income, increasing education and technological improvements. As income, education attainment and technology are all expected to continue to improve over the next 30 years, the projected burden from this group of disease will also continue to decline' (ibid., 137).

This predicted convergence in disease patterns is not inevitable and depends on further developments in medical research. Also, one must keep in mind that even with convergence, the scale of the LDC DALYS means that communicable disease will remain a major global

Figure 2.2 **Disease burden by cause for selected regions, 1998**



Source: WHO, 1999b, Annex Table 3.

killer. Total DALYs lost in the LDCs exceeded total DALYs in the EMEs by more than one billion in 1998. Therefore, even if the share of DALYs attributed to communicable diseases fell to 4.3 percent in the LDCs (the share currently found in the EMEs) they would still impact more people than all those suffering from cancer in the EMEs (53 million versus 27 million).

2.3 Dealing with the problem of distinct disease burden

To start to deal with the distinct pattern and intensity of disease in the LDCs, we must first identify why the burden exists. The Adhoc Committee of the WHO (1996) identified three key reasons:

1. The failure to use existing tools effectively (referred to broadly as access problems). Here interventions exist but are not being employed effectively and efficiently in LDCs;

2. Inadequate tools. Here the treatments that do exist are inappropriate for the targeted environment where there are resistant strains or where more cost-effective solutions such as vaccines might be used;

3. Inadequate knowledge of disease process and causes. Here no treatments exist.

Different types of research and investment are required for each problem: investment into health systems and policies to address access problems; investments into biomedical R&D to reduce the cost of existing interventions to address inadequacy of existing tools; and investments into biomedical R&D to identify new interventions where no treatments exist. The relative importance of the three problems and the investment priorities differ across diseases. Some examples are presented in Table 2.3.

In the case of diarrhoeal diseases, for example, resources should be channelled into education and infrastructure to ensure better use of existing products. By contrast, scientists still know relatively little about HIV. The few products on the market to tackle it are expensive and require a well developed health care infrastructure to be effective. This combination makes them practically inaccessible to many LDCs.

The next three chapters focus on the problem of attracting R&D into new and more cost-effective treatments. I return to the problem of access in chapter 6.

Table 2.3 **Why certain diseases persist in LDCs**

Condition/risk factor	Inadequate knowledge of disease process and causes	Inadequate tools	Failure to use existing tools effectively
Pneumonia		+++	+++
Diarrhoeal disease		++	++++
VPCI*		++	++++
Malaria	+	++	+++
Malaria in future with severe drug resistance	+	++++	+
Malnutrition	+++		+++
Helminth infestations		+	++++
HIV	+++	+++	
Other STDs		+++	+++

Source: WHO, 1996, chapter 3, various tables.
Notes: VPCI = Vaccine preventable childhood infections. STD = Sexually transmitted disease.
The estimated rating ranges from little importance ('+') to extremely important ('++++'). A blank means not significant.

3 WHY PHARMACEUTICAL R&D INVESTORS NEGLECT LDC DISEASES

Despite the high medical need, the low expected market size of LDC diseases makes them low investment priorities for pharmaceutical producers whether measured by total investment, total number of projects or approved products per disease category. EME governments make financial contributions to basic health care R&D but it is primarily the private pharmaceutical companies that take research ideas and develop them into new, marketable medicines (CMR International, 1999).

3.1 Global R&D patterns

Data on the pattern of global pharmaceutical R&D expenditure show that investments in diseases and conditions that burden LDCs in particular occupy a low priority. Michaud and Murray (1996) 'estimate that in 1992, 4 percent ($2.4 billion) of global R&D health expenditures ($55.8 billion) were devoted to communicable, maternal, perinatal and nutritional disorders – the maladies that dominate the disease burden in the low-income and middle-income countries' (218)[10]. Pecoul et al. (1999) show that only 13 (1 percent) of the 1,223 new chemical entities commercialized between 1975 and 1997 were specifically for tropical diseases and that two of these 13 were updated versions of existing products.

Between the end of the 1980s and the end of the 1990s there was a shift in the balance of R&D expenditure away from anti-infectives and cardiovascular projects towards anti-cancers and biotechnology products[11]. See Table 3.1.

The therapeutic categories presented in this table are highly aggregated so the information does not give the direct R&D effort in LDC disease categories specifically. Research for treatments in communicable

10 Michaud and Murray used a two step process to calculate this estimate. They ascertained what health problems represent the majority of current or future burdens in low- and middle-income countries and then what fraction of research for these health problems would yield solutions that are sufficiently cost-effective to benefit those countries.

11 The absolute number of anti-infective projects increased slightly between 1988 and 1998 from 1,145 to 1,167. The increase can be attributed to an increase in the number of HIV projects (Currie, 1999).

Table 3.1 **Percent of private R&D projects by therapeutic class, worldwide**

Therapeutic class	1988 % of total	1998 % of total	% Change in number of projects 1988-1998
Anti-cancers	10.9	12.6	49%
Neurologicals	11.3	11.9	35%
Biotech products[a]	9.8	11.1	45%
Anti-infectives[b]	13.3	10.6	2%
Anti-parasitics[b]	N/A	0.4	N/A
Formulations[a]	7.0	8.4	53%
Musculoskeletal	5.4	7.1	69%
Alimentary/metabolic	6.0	7.0	50%
Cardiovasculars	12.5	6.9	–29%
Immunologicals	N/A	4.3	N/A
Genito-urinary/sex hormones	N/A	4.0	N/A
Respiratory	4.5	4.0	14%
Blood and clotting	6.0	3.7	–22%
Dermatologicals	N/A	3.2	N/A
Sensory	N/A	1.7	N/A
Hormones	N/A	1.4	N/A
Other[c]	13.3	1.7	N/A
Total number of projects	8,603	11,054	28%

Sources: Ballance, R. et al., 1992, Table 4.7, p.99 and Currie, 1999, p.66.
Notes: R&D projects include pre-clinical or clinical trials, and drugs launched in the specified year.
a. Refers to technological categories.
b. In 1988, anti-parasitics were included in the anti-infectives figure. In 1998 they were listed separately.
c. 'Other' for 1988 refers to all projects outside the top ten categories. In 1998, it refers to all projects outside the 16 categories listed.

disease areas would fall into the category of anti-infectives, and more specifically, into the subcategory anti-parasitics. In 1998, anti-parasitics made up only 0.4 percent of the projects in process. According to Currie's survey in the Scrip Magazine (1999), only 5 percent of the pre-clinical anti-infectives research expenditure was aimed specifically at the anti-parasitic area. LDCs are also burdened by many of the diseases afflicting developed countries. Michaud and Murray (1996) estimate that around 5 percent of research expenditure into all areas will yield products that LDCs can afford (219).

3.2 Major investors in R&D

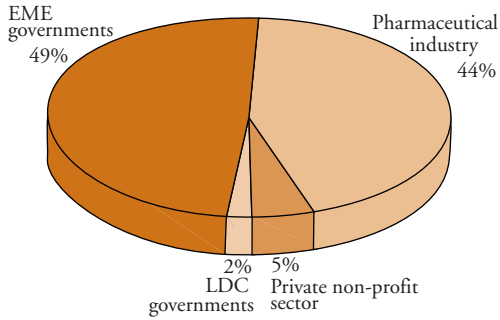
To understand why LDC diseases and health concerns are neglected one must identify the primary investors in new medicines and the factors that motivate their R&D decisions.

Figure 3.1 shows that EME governments and pharmaceutical companies financed 93 percent of the $55.8 billion invested in global health care R&D in 1992.

Most of the major research-based pharmaceutical companies are based in a handful of EMEs. In 1992, seven countries – the United States, Japan, the United Kingdom, Germany, Switzerland, France, and Italy (in descending order) – conducted 97 percent of all worldwide R&D by pharmaceutical companies. Other EME countries contributed 2.6 percent. The pharmaceutical companies in all non-EME regions combined invested less than US$100 million or a mere 0.4 percent of total pharmaceutical R&D expenditures (Michaud and Murray, 1996).

The large multinational companies spend only a small share of their R&D dollars outside the EMEs. In 1997, US-owned pharmaceutical companies spent $3.5 billion on R&D abroad, of which $86.5 million or 2.5% went to LDCs (PhRMA, 1999, 104). See Figure 3.2. The Republic of Korea, India, Indonesia, South Africa and Taiwan were the only LDCs contributing significantly to pharmaceutical R&D. They spent an estimated US$38 million in 1992 (Michaud and Murray, 1996).

Figure 3.1 **Sources of funds invested in global health care R&D, 1992**

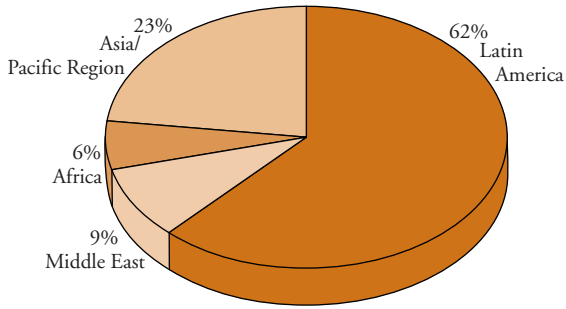


Source: Michaud and Murray, 1996, p.218.
Note: Total R&D expenditure = $55.8 billion.

As this pattern of R&D financing would predict, close to 100 percent of the new medicines launched over the past three decades were developed in EMEs. 45 percent of the 152 global drugs launched between 1975 and 1994 were developed in the US alone.

Public and private organizations in EMEs play different, complementary roles in the R&D process. Mansfield's study (1991) on public-private innovation showed that 27 percent of all the US pharmaceutical companies' new products launched had direct links to public sector research. The earliest stages of discovery are often highly speculative and not directed towards a particular end. No single party is able to expropriate all of the benefit of this basic research. The fact that advancements in the science base can be utilized by many parties simultaneously (non-rivalry in consumption), and are difficult to restrict access to (non-excludability), gives basic research the characteristics of a public good. Private researchers on their own, driven by the need to appropriate private returns from new knowledge, are therefore likely to under-invest, from a social standpoint, in basic

Figure 3.2 **US pharmaceutical company spending on R&D in LDCs**



Source: PhRMA, 1999, p.104.
Note: Total US R&D spend on pharmaceuticals in LDCs was $86.5 million.

research or the science base[12].

The expense and large amount of resources required to conduct clinical trials, however, discourage most public organizations from bringing new products to market on their own. Public sector scientists' involvement tends to be in the early phases of the R&D process and it is the private companies that invest the money in developing scientific ideas into marketable products[13]. In the US, universities and 'not-for-profit' organizations have discovered only 1 in 20 of the new compounds approved by the Food and Drug Administration (FDA).

12 See Office of Technology Assessment (1993) for details of US government support and involvement in pharmaceutical R&D.

13 The division is not absolute and the interaction of public and private sectors is more complex than a simple basic/applied research dichotomy would suggest, especially in the early discovery research phase (Cockburn and Henderson, 1995, p.3). The private sector also invests in basic research, viewing it as fundamental to the maintenance of a productive research effort. Public and private scientists also work together on, and co-author, discovery research. Still, there are distinct reward and incentive structures that motivate the scientists' research priorities differently in public and private organizations that must be taken into account.

The other 95 percent have been discovered, or patented, by the private sector (PhRMA, 1999).

3.3 What motivates private sector R&D decisions?

In selecting therapeutic areas for R&D, companies consider three main criteria:

- expected market size (i.e. number of patients and availability of funds to purchase medicines);
- degree of unmet current and future medical need; and
- the probability of success (Cockburn and Henderson, 1995; Meyer, 1998).

Probability of success is a function of the existing level of competence (science, technology, and research base including personnel and experience in the area) and the risks associated with a certain indication. It changes over the course of the R&D process, starting out low and increasing as time goes on.

Expected market size and medical need (based on the availability of other existing treatments) together determine the sales potential and commercial value of developing a medicine in any given area. Figure 3.3 presents a simplified matrix of potential patient population and medical need combinations. A more sophisticated model would indicate what kinds of medicines are still needed for different conditions – symptomatic treatments, cures, or prevention for example.

Certain research areas, such as hypertension, represent large and growing markets but are already crowded with successful therapies; thus the medical need for further innovations is considered low. At the other extreme are diseases like multiple sclerosis where the need for therapies is great but the number of patients is smaller. To motivate sufficient investments in this bottom right quadrant, additional financial incentives might be needed, given the added risk of research in uncharted areas for an unpredictable market. In general, companies try to design a portfolio to maximize commercial value with a combination of products from different categories.

Potential commercial value must, of course be balanced with the

Figure 3.3 **Balancing potential patient population and medical need for drugs**

Potential patient population	**High**	hypertension, NSAID, ulcers, angina, common cold	asthma, bacterial infection, lipid lowering, MED, type 2 diabetes	obesity, cancer, osteoporosis, atherosclerosis, rheumatoid arthritis
	Medium	contraception	irritable bowel syndrome, incontinence, epilepsy, migraine	heart failure, chronic bronchitis, stroke, schizophrenia, Parkinson's, dementia
	Low	emesis	arrhythmias, diabetes type 1, fungal infection, herpes	AIDS, multiple sclerosis, emphysema, hepatitis
		Low	**Medium**	**High**
			Need for drugs	

Source: Lehman Brothers, 1997, 14.

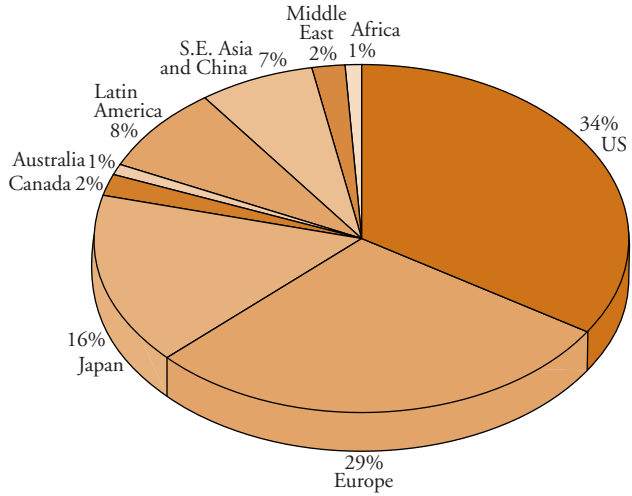
probability of success. To succeed in a therapeutic area where need is great could be highly profitable – consider the case of HIV – but the risks and required investments are also high.

From the company stand point most of the LDC-specific diseases fall in the bottom row and middle and right two columns of this diagram (medium and high need for drugs, small patient population). The total market for pharmaceuticals for all LDC disease areas is relatively small and the effective demand for new therapies for a single disease area even smaller. Two facts support this claim.

First, LDCs make up 80 percent of the world's population but purchase at most 18 percent of the world's pharmaceuticals. See Figure 3.4.

Second, while pharmaceutical expenditures per capita differ signif-

Figure 3.4 **World pharmaceutical market, 1997**



Source: CMR International, 1999, p.50.
Note: Total 1997 sales = US $297 billion.

icantly across countries in the 'LDC' category, in general there is a significant gap between what they spend on medicines versus what populations in the EMEs spend on medicines. In 1990, Japan spent $149 (in 1990 dollars) per person on average while some countries in Africa spent less than $2 per person. As a result, despite its large population share, the LDC total consumption of pharmaceuticals is only one fourth that of the EMEs. See Table 3.2, which shows the total consumption of (generic plus in-patent) medicines in the different regions of the world.

The fact that pharmaceutical spend as a percent of GDP is similar across countries despite low per capita spend in the LDCs reflects the fact that LDCs spend a greater share of total health budgets on pharmaceuticals. 'Among the 19 European and other established market

Table 3.2 **World pharmaceutical consumption, 1990**

Region	Total per capita *1990 $US*	Estimate of total market[d] *million 1990 $US*	% of GDP	Share of population 1991 *percent*	Population 1991 *millions*
EMEs	70.6	60,067	0.95	15.9	851
North America	66.9	19,331	0.87	5.4	289
EU 12[a]	55.6	18,744	0.71	6.3	337
Other Europe[b]	46.3	1,487	0.42	0.6	32
Japan	149.4	19,187	1.62	2.4	128
Others[c]	19.2	1,233	0.46	1.2	64
Transitional economies	20.0	7,705	N/A	7.2	385
LDCs	3.8	15,637	0.67	76.9	4,115
Latin America	11.0	5,003	0.72	8.5	455
North Africa	4.9	734	0.67	2.8	150
Other Africa	1.8	867	0.65	9.0	482
South and East Asia	2.7	4,623	0.60	32.0	1,712
China	2.6	3,019	N/A	21.7	1,161
Others	9.7	1,505	0.81	2.9	155
World	15.6	83,476	N/A	100.0	5,351

Sources: Adapted from Ballance et al. 1992, Table 2.3, pp.30-31, and Table 2.4, p.33. Population figures are from World Bank, 1993a.
Notes: a. EU 12 comprises Belgium, Denmark, France, Federal Republic of Germany, Greece, Ireland, Italy, Luxembourg, The Netherlands, Portugal, Spain, UK.
b. Other Europe includes Austria, Finland, Iceland, Norway, Sweden, and Switzerland.
c. Other EMEs includes Australia, Israel, New Zealand, South Africa.
d. The estimate of total market = consumption per capita multiplied by population.

economies for which data are available, the median expenditure for pharmaceuticals is 13 percent of total health expenditures. In contrast, pharmaceutical expenditure represents 35 percent of total public and private health expenditure in Thailand, 39 percent in Indonesia, 45 percent in China, and 66 percent in Mali. Comparisons of per capita pharmaceutical expenditures and per capita health expenditures sug-

gest that drugs may account for over 50 percent of total expenditures on health in a number of African countries' (Bennett et al., 1997, 32).

Given these already high shares of health budgets spent on pharmaceuticals, prospects for increased pharmaceutical expenditures through shifts in health care priorities are certainly limited in the short term. Only large increases in total health care budgets driven by increased economic prosperity will have a significant impact on pharmaceutical purchases.

At the disease level, companies estimate expected revenues for a new product using information about market size (patient population * access rate), expected market share (reflects competition in the market) and price. The access rate reflects the patient's ability to see a doctor, get a correct diagnosis, and get access to the necessary product. Good data on access in LDCs is scarce, but estimates can be as low as 10 percent.

So assuming that the development costs and risks in the LDC-specific disease areas are comparable to those in other areas, the interest of companies in these diseases, from a strict financial standpoint is small. A number of changes in the industry over the past 20 years may have led companies to shift their priorities even further away from LDC disease areas.

First, pharmaceutical R&D costs have increased dramatically. According to DiMasi et al. (1991), compounds entering clinical trials in the 1970s and early 1980s cost twice as much to bring to market ($312 million per NCE in 1997 dollars) as compounds entering clinical trials ten years earlier. Increased development times by one third, increased input costs, and static success rates, despite large investments in new technologies, suggest that products entering clinical trials in the 1990s cost between $400 and $600 million to bring to market (Kettler, 1999).

Second, companies see their ability to cover these costs as increasingly under threat. Follow-on, competing products are entering specific therapeutic categories more rapidly, allowing the market leader less time to reap the benefits of being first in class (Kettler, 1998). Some have argued that entry of these follower products, as well as

changes in health care provision (the introduction of managed care practices in the US for example) have increased price competition among patented products prior to patent expiry. The impact of generic competition on sales of branded products when off patent is also now much greater than 20 years ago (Towse and Leighton, 1999).

At the same time, the demand for treatments for non-communicable diseases such as ulcers, cardiovascular conditions and depression has increased dramatically over the past 15 years (PhRMA, 1999). 'To cope with large investments and reduce duplicate spending, pharmaceutical companies started an unprecedented cycle of industrial consolidation and mergers at the end of the 1980s. This consolidation focused on the most profitable segments of the market (HIV, cardiovascular conditions, cancer, dermatology, and neurology), leaving tropical medicines largely out of the equation' (Pecoul et al., 1999, 364).

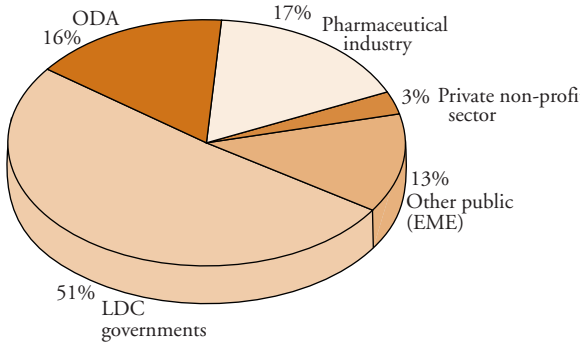
3.4 Conclusion

LDC health concerns are not the focus of the major, i.e. private sector, actors in pharmaceutical R&D. In sharp contrast to the pattern of R&D funding shown in Figure 3.1, Michaud and Murray (1996) find that LDC countries and official development assistance (ODA) organizations provide 80 percent of the funds for R&D in problems specific to the LDCs[14]. See Figure 3.5.

Pecoul et al. (1999) find that only three of the 13 tropical disease medicines developed between 1975 and 1997 may be considered to be the direct results of new R&D activities by the pharmaceutical industry. For the rest, 'two are updated versions of previously approved products, two are the result of military research, six come from veterinary research' (364).

14 ODA refers to financial aid provided to low- and middle-income countries by governments in the EMEs. Half of ODA health R&D funding came from bilateral agencies such as USAID. The rest was split between the EU, UN, development banks and other multilaterals.

Figure 3.5 **Sources of funds for R&D on selected health problems in LDCs, 1992**



Source: Michaud and Murray, 1996, p.222.
Notes: Total R&D spend = $2.4 billion.
Selected health problems = parasitic diseases, the childhood cluster and maternal and perinatal conditions.
Other public = other publicly funded R&D, EME; ODA = Official Development Assistance.

Most LDCs lack sufficient basic science infrastructure, enough highly qualified people and the private sector R&D-based companies needed for new medicine development. Multinational pharmaceutical companies, supported by EME governments, are the major drivers of research and new medicine development. Their input and involvement is therefore essential to develop treatments for LDC-specific health problems. To motivate companies to re-evaluate their R&D investment decisions in favour of LDCs, policies must work to reduce risk and R&D costs in these areas (push actions) and/or increase expected revenues (pull actions). Examples of both push and pull measures are explored in the next chapter.

4 MOTIVATING PRIVATE COMPANY INVESTMENT INTO LDC DISEASES

In order to attract new pharmaceutical R&D investment into LDC disease areas, policy makers in industrial countries (both national and international organizations) must either intervene to affect the companies' investment decisions ('introduce public health criteria into R&D strategies') or finance the R&D directly. In this and the following chapter, I review a range of policy options. Many of these policies are currently under consideration by different working groups or commissions with a common goal to incentivize research into LDC health issues[15]. I conclude that collaboration between public and private actors is essential and that a combination of a strong pull incentive for private companies and a disease-focused, publicly funded research 'push' would be an effective approach. A model, presented at the end of this chapter, supports this conclusion. It measures the impact of different incentive packages on individual companies' investment decisions.

The incentive policies explored in this chapter can be categorized as 'push' and 'pull' measures. Table 4.1 summarizes the specific policies.

Table 4.1 **Incentive measures**

Push	Pull
Improved intellectual property protection for LDC medicines	Market exclusivity[1]
R&D tax credits[1]	Price and purchase guarantees
R&D grants[1]	Roaming market exclusivity

Note: 1. Orphan Drug Legislation in the US combines the tax credits, grants, and market exclusivity measures to encourage investment in 'rare diseases'.

15 For example, in 1999, the pharmaceutical industry, represented by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA), and the WHO set up three working groups to analyse the problems of counterfeiting, access, and new drug development. Preliminary findings and a commitment to continue talks in 2000 were presented in Geneva on November 3, 1999. At the same time, a team of academic led by Jeffrey Sachs of Harvard University is dealing exclusively with the question of how to incentivize research in new vaccines for HIV, TB, and malaria. Other initiatives are being discussed at the World Bank and Institute for Global Health in San Francisco.

4.1 Intellectual property protection

Intellectual property protection (IPP) is considered a necessary precondition to stimulate R&D. Without it exact chemical copies of new medicines can be produced at much lower costs than the original (R&D expenditure in order to make the copy would be minimal), and sold at prices below those of the innovator who seeks to recoup her R&D costs. The rapid entry of generic copies of drugs following the expiry of patents demonstrates the ease with which many products can be copied. Indeed, the fear alone that patents will not be honoured serves as a major disincentive for R&D.

Many LDCs protect process but not product patents. Seen from the stand point of LDCs, failure to protect product patents 'makes it possible for companies with limited financial resources to develop new processes for the same active principal as an original drug but more cheaply' (Velasquez and Boulet, 1997). At issue is whether the LDC population's gain in the short term of cheaper copies (assuming that the local population get access to the locally produced products) outweighs or is outweighed by the long term loss of new products as multinational pharmaceutical companies and local researchers are discouraged from risking investments in R&D for products targeted at these markets.

According to a recent report by the IFPMA (Bale, 1999), since the late 1980s, there has been a significant increase in the number of developing countries that have extensively changed and improved their patent systems. See Table 4.2.

Meanwhile, the US (1984), Japan (1987), the EU (1992), and Australia (1998) have added four to five years onto the standard 20-year nominal patent life of pharmaceutical products[16]. These developments mean that 18 member countries of WHO provide protection above and beyond that which is required by the WTO Trade Related

16 This change is a response to the fact that increased regulatory and clinical trial requirements and a lengthy approval process mean that products with a 20 year patent life often enjoy fewer than 10 effective patent years on the market (Kettler, 1999).

Table 4.2 **LDCs promoting pharmaceutical IPP**

Year new patent policy enacted	Country
1987	Korea
1990	Czech and Slovak Republics
1991	Belarus, Bulgaria, Chile, Indonesia, Mexico
1992	Romania, Russia, Taiwan, Thailand, Ukraine
1993	China, Macedonia, Philippines, Poland, Slovenia, Yugoslavia
1994	Andean Pact, Hungary
1996	Brazil

Source: Bale, 1999.

Agreement on Intellectual Property Rights (TRIPS) standard of 20 years and this number is likely to increase in coming years as more countries join the EU[17].

In the long term, it is argued that LDC countries stand to benefit from improved patent protection in a number of ways:

1. It will potentially globalize the effort to find cures for disease, spreading the effort to emerging economies that have core scientific skills but currently lack the incentives to use them. In countries with emerging pharmaceutical industries such as India, Korea, Brazil, and China, it should encourage researchers to switch from a strategy of molecule copying to one for innovative research of new drugs and LDC-versions of existing drugs;

17 Under TRIPS, as of 2000, industrialized countries will adopt additional intellectual property rights laws and regulations, including new anti-counterfeiting measures. By 2005 (or 2006 for some LDCs), all WTO member countries are supposed to have adopted full product patent protection for pharmaceuticals and biotechnology medicines. Despite these advances one must not ignore the real problems involved in reforming countries' laws in line with the deadlines and ensuring that companies comply with these laws.

2. It should improve the transfer of, and access to, technology and information from EME companies to LDC researchers;

3. It will create jobs for skilled labour and perhaps limit the 'brain drain' from LDCs to EMEs;

4. It will improve international credibility for, and prospects for joint ventures and direct foreign investment in, LDC research.

From the standpoint of the multinational companies, however, improved global protection of patent rights (in LDCs in particular) provides a necessary but probably not a sufficient condition for investing in LDC disease areas. For one thing, there are articles within the TRIPS Agreement that allow countries, under certain special circumstances, to bypass the patent holder and to grant compulsory licences to produce cheap generic versions (Velasquez and Boulet, 1997). The heated, international debate set off by the recent move by South Africa to grant compulsory licences for certain AIDS drugs demonstrates how sensitive this issue is for multinational companies (Boseley, 1999; Hilton, 2000).

But even when intellectual property is secure, companies still see the market size for these patented products in most of these disease areas as too small to justify investments. Additional incentives are needed.

4.2 Orphan drug legislation

In designing a package of public incentives, orphan drug legislation, such as that which exists in the US and Japan and has been approved in December 1999 for the European Union, might be used as a model. This legislation combines market exclusivity rights with cost saving measures (tax credits, development grants, fast-track approval) to encourage companies to conduct R&D in rare disease areas with low case prevalence. An important question is how these programmes could be modified to attract investment to LDC diseases as well.

Table 4.3 summarizes the orphan drug packages in the US, EU, and Japan.

All three regions' programmes combine market exclusivity with a package of measures designed to reduce the average total cost of R&D for orphan drugs. 'The (US) Orphan Drug Act creates market condi-

Table 4.3 **Orphan drug legislation: criteria and incentives**

	US	Japan	EU
Year initiated	1983	1993	Approved by the European Parliament, December 1999*
Qualification criteria	a. Condition affecting fewer than 200,000 in the US, around 1 case per 1,000 people; or b. Proof of no expectation to recover R&D costs from US sales even if the disease affects more than 200,000	Condition affecting fewer than 50,000 Japanese, around 1 case per 2,500	a. Condition affecting fewer than 1 per 2,000 people in the EU with no 'satisfactory method authorized'; or b. For selected serious conditions, proof that sales in the EU will not recover investment costs
Market exclusivity	7 years of exclusive approval rights	Post-approval monitoring period is extended to between 6 and 10 years before re-examination	10 years of exclusive approval rights
Tax credits	Tax credit equal to 50% of qualified clinical research expenses for the taxable year	A 6% tax credit for orphan related R&D expenses incurred in Japan and a maximum 10% reduction in the corporate tax rate	Orphan drug is eligible for EU and member state incentives to support R&D and, when applicable, small and medium sized enterprises (SME)
Development grants	Annual budget approx. $12 million. Clinical trials awarded from $100,000 to $200,000 per year in direct costs for up to 3 years	Grants available to subsidize orphan drug development	See above
Regulatory review	Approval requirement assistance including access to fast-track approval, and waived or reduced FDA user fees	Expedited regulatory review	Fast-track approval process considered. Fund to waive part or all of user fees

*Note:** Important technical issues, including funding, remain to be solved (Scrip, 22 December, 1999).

tions in which a reasonable expectation of profits exists that did not exist before' (Peabody et al., 1995, 382). Studies of the US programme find the market exclusivity measure to be the most attractive incentive. Relative to the total R&D costs, the impact of the combination of development grants, tax credits and time costs saved through fast-track approval is small (ibid.)[18].

Exclusive approval is awarded to designated orphan products whether or not the medicine is 'patentable' or, if patentable, if that patent is set to or has already expired. The seven years (in the US) of exclusive rights are not guaranteed however. In 1992, the FDA introduced new regulation specifying when physical properties or structural features render two products 'the same' under the orphan scheme. If a second sponsor can provide evidence that its drug 'A' is 'clinically superior' to an orphan drug 'B' already on the market, 'A' can be deemed 'different' and become eligible for FDA marketing approval as an orphan even if it is structurally the same and intended for the same indication as Drug A (Shulman and Mannochia, 1997, 322). The new EU legislation also leaves open the possibility for a new, superior product to earn market approval after six of the ten years of exclusivity for the original product have passed.

Technically, LDC-specific diseases already qualify for orphan drug status because of their low prevalence in the US, Japan or EU (despite high global prevalence). The US legislation also explicitly states that drugs requiring foreign clinical testing can qualify for tax credits and research grants as long as the company can demonstrate that there is an insufficiently large testing population in the US. As of July 1999, 25 US orphan designations were targeted at tropical diseases (3 percent of the total 850). Eleven of these medicines have been approved (6 percent of the total 195), one for two different conditions (FDA, Office of Orphan Products Development). See Table 4.4.

Steps must be taken to make LDC-specific diseases a greater priority among orphan drug diseases. Peabody et al. (1995) proposed devising an index that prioritises orphan diseases by prevalence, level of pain and suffering associated with the disease, and the availability

18 The economic studies reviewed in the rest of this section are based only on the US case.

of alternative therapies. 'One of the Orphan Drug Act's incentives, the research grants (in an expanded form to make a more significant impact on R&D costs), could be awarded for research and development directed at those diseases having high priority' (ibid., 383). LDC diseases are likely to rank high on such an index.

Giving companies priority access to research grants is, on its own, unlikely to prompt much response, however. Analyses (including one by Peabody et al.) of the US orphan drug legislation have found the market exclusivity right to be the most important incentive. The research grants and tax credits taken together make little impact on the high R&D costs involved. The biggest problem with the orphan drug incentive packages currently on offer is that market exclusivity in the US, EU, and Japan, for a LDC-specific disease medicine is not worth much because there are few patients outside the LDCs.

LDC markets need to be made more secure. Companies are unable to sell LDC-specific products at high enough prices to earn profits (especially as the final objective of any policy is to develop products these populations can afford). Appendix II shows how the different demand conditions for a standard orphan drug compared to those for a LDC-specific disease lead to different impacts on expected revenues being produced by the orphan drug incentive package. The package has little impact on the LDC-specific disease case because demand for products in these areas is relatively price elastic.

4.3 Purchase guarantees and prize funds

To improve the orphan drug package for LDC diseases, a convincing 'pull' mechanism must be put in place. One way of enhancing that market might be for international aid organizations to subsidize the products of the targeted R&D. This would offer companies 'profitable' prices and LDC populations 'affordable' ones. For example, Sachs proposed in a recent article in The Economist that EMEs 'pledge to purchase an effective malaria vaccine for Africa's 25 million new born children each year if such a vaccine is developed. A guaranteed minimum purchase price – say $10 per dose – would be promised

Table 4.4 **Orphan designations and drugs for WHO targeted diseases**

Disease	Generic name	Sponsor(s)	Designation date	Approved	Other indications
Malaria	Artesunate	WHO	July 1999	July 1992	
	Halofantrine	SKB	Nov 1991		
	Mefloquine HC1	HL Roche[1]	April 1988	May 1989[2]	
	Sodium dichloroacetate[3]	Stacpoole	Nov 1994		2
Leishmaniasis	Aminosidine	Kanyok	Sept 1994		2
	Liposomal amphotericin B	Fujisawa USA	Dec 1996	Aug 1997	1
Meningitis	Cytarabine liposomal	DepoTech Corp	June 1993	April 1999	
	Liposomal amphotericin B	Fujisawa USA	Dec 1996	Aug 1997	1
Tuberculosis	Aconiazide	Lincoln Diagnostics	June 1988		
	Aminosalicylic acid	Jacobus Pharm. Co.	Feb. 1992	June 1994	
	Aminosidine	Kanyok	May 1993		2
	Rifalazil	PathoGensis	April 1999		
	Rifampin	HMR	Dec 1985	May 1989	
	R,I,P[4]	HMR	Dec 1985	May 1994	
	Rifapentine	HMR	June 1995	June 1998	2
	Thalidomide[5]	Celgene Corp	Jan 1991		7[6]
Trypanosoma	Eflornithine HC1	HMR	April 1986	Nov 1990	
Hepatitis B	CY-1899	Cytel Corp	March 1994		
	FIAU	Oclassen Pharm Inc	July 1992		
	Hep B IGI[7]	NABI	March 1995		
	Mono Antibody	Protein Design Labs	June 1991		
	Thymalfasin	SciClone Pharm Inc	May 1991		1

Table 4.4 ***(Continued)***

Disease	Generic name	Sponsor(s)	Designation date	Approved	Other indications
Leprosy	Clofazimine	Novartis/Ciga-Geigy Corp	June 1984	Dec 1986	
	Thalidomide	Celgene Corp	July 1995	July 1998	7
	Thalidomide	Pediatric Pharm	Nov 1988		2
Totals			25	12	

Source: FDA, Office of Orphan Products Development website, *http://www.fda.gov/orphan*, December 12, 1999.
Notes: 1. Mepha AG was awarded the first orphan designations for Mefloquine HC1 in July 1987.
2. Mefloquine HC1 was approved as a treatment of acute malaria due to Plasmodium falciparum and Plasmodium vivax and as a prophylaxis for Plasmodium falciparum malaria that is resistant to other available drugs.
3. Stacpoole aimed to use sodium dichloroacetate to treat lactic acidosis in patients with severe malaria.
4. Rifampin, isoniazid, pyrazinamide.
5. In this application, Celgene Corp looked to use Thalidomide to treat mycobacterial infections caused by tuberculosis.
6. Celgene Corp was awarded seven different orphan designations for Thalidomide. One, to treat leprosy, was approved for marketing. Pediatric Pharmaceuticals and Adrulis Research Corporation also have two designations apiece for Thalidomide.
7. Hepatitis B immune globulin intravenous.

for a vaccine that meets a minimum profile, with possibly a higher price for a better product' (Sachs, 1999, 21). Sachs specified that no money would need to be spent by any government until the vaccine actually existed.

Under the Sachs proposal[19], clearly developed in two discussion

19 The Sachs/Kremer proposal is set up specifically to address the problem of vaccine development. With some modifications the idea seems applicable to medicines as well. An important difference is in the way medicines and vaccines are purchased and distributed in LDCs. Setting up a centralized (public?) purchasing agent is more feasible for vaccines than medicines. In the latter case, a complex administrative infrastructure would be needed to ensure that the LDC purchasers make a contribution to the price of the new products and that the products reach the patients who need them. Given the current state of the science in malaria and TB, industry experts expect that new medicines could be developed more quickly than new vaccines. That suggests that the purchase fund would have to be in place sooner to cover medicines than it would need to be to cover vaccines.

papers by Kremer (1999a and 1999b), a purchase fund, based on pledges from governments and aid organizations, would be set up and made available to companies producing a vaccine for malaria, TB or HIV that meets three pre-specified requirements:

1. Candidate vaccines would have to be approved by some regulatory agency, such as the US FDA;

2. Candidate vaccines would also have to meet a market test – developing countries wishing to purchase vaccines using program resources would be required to contribute a co-payment and draw down an account that they would hold within the programme;

3. Any vaccines meeting these basic requirements would be eligible for purchase at some minimum price. Vaccines exceeding these requirements would receive bonus payments linked to vaccine effectiveness, perhaps as measured by the estimated number of lives or DALYs saved by the vaccine (Kremer, 1999b, 1).

By setting these guidelines, the pre-committed purchase fund seems to be better linked to product quality than a research cash prize that might be awarded to a company that gains approval for a product in a specified area. Under a cash prize scheme, if the product is later found to have adverse side effects, it might be difficult to get the money back. By contrast, the vaccine purchases could be suspended if countries choose to cease purchasing them for quality reasons. 'Similarly, if a superior vaccine came on the market, countries could switch their purchases to that vaccine[20]. A cash prize, on the other hand, would already have been awarded' (Kremer, 1999a, 29).

The Sachs/Kremer proposal assumes that companies have or can obtain the up-front money for the research so that the money in the fund will only be spent if a product meeting the above qualifications comes to market. They contrast their idea with that of a research fund competition (or an advance share of the guaranteed purchase fund for research). In the latter case, if the research project is killed or fails to produce the product within a pre-specified time period, the money

20 This is similar to the orphan drug policy where market exclusivity is guaranteed only so long as a superior product is not available for sale.

would, at least in theory, go back into the general pot. There are problems with this scenario. First, it requires that the committee overseeing the fund correctly assesses the quality of early research proposals and picks likely winners, a difficult task for even the industry experts. Second, it requires that the committee constantly monitor the research underway to assure that the money is not spent in other areas (ibid.).

For the purchase fund idea to serve as an effective incentive, a number of features must be clarified or addressed.

First, companies must consider the promise of future funds as credible. Given the likelihood that governments and policy priorities will change during the R&D period, governments would probably need to commit funds up-front before companies would risk investing in the R&D. Companies are also looking for a viable market, not a specific price, so in the case of a price guarantee the size of the subsidy would have to be flexible and reflect the number of people affected at the time the product is launched[21]. The number of people affected by many LDC-diseases, other than TB and malaria, is relatively small[22] and thus high prices per treatment would have to be offered to create a viable market.

Second, it is necessary to specify which parties are to be responsible for overcoming the access barriers. One of the Sachs/Kremer criteria is a 'market-test'. What is unclear is whether this test implies that if an individual country decides that they will not use a vaccine, or will refuse to co-pay for it, or they lack the infrastructure to inoculate their population, then the company that did the R&D will not win the fund after all. For companies to initiate the research, this possibility must be avoided.

Linked to this question is that of what happens when a follower product comes on to the market? Will the fund be transferred in full to the new product or will the two companies compete for it, allowing the

21 As will be discussed in chapter 6, a guaranteed price will also not guarantee product access. Other, non-financial, barriers must be addressed too in order for the affected populations to benefit from the new product.

22 In 1999, the total DALYs for the five LDC-specific infectious diseases ranked as priorities after malaria and tuberculosis by the WHO – LF/onchocerciasis, leishmaniasis, schistosomiasis, African trypanosomiasis, and chagas disease – is 11 million. That compares with 39.3 million DALYs for malaria and 28.2 million for tuberculosis (WHO, 1999b).

purchasing countries to decide which of the two products they will use?

Third, and related to the country contribution problem, is the task of identifying which parties in the LDCs are responsible for purchasing and distributing. Here, differences between vaccines and medicines are important. Governments are more likely to oversee a centralized purchasing and distribution system for vaccines than for medicines. Data on the financing of health care and pharmaceutical expenditures in different countries show that the contribution made by private sources increases as national income falls. See Table 4.5. This suggests that the purchase fund's administrators would have to be prepared to deal with a decentralized set of actors in the developing world for their programme to succeed for medicines.

Finally, Sachs and Kremer assume that small pharmaceutical research companies would be able to obtain private, outside funding for their R&D because they argue that venture capitalists would back a research proposal in the TB, HIV or malaria area on the promise of such a purchase fund. To confirm these investors' commitment to the scheme, venture capitalists should be represented on the purchase fund's administrative committee.

Table 4.5 **Health expenditures by source**

Region	**Health expenditures by source (%)**			**Pharmaceutical expenditures by source (%)**	
	Public	*Private*	*Aid flows*	*Public*	*Private*
Established market economies	77.0	23.0	–	59.9	40.1
Transitional economies	72.7	27.3	–	N/A	N/A
Middle Eastern Crescent	54.2	42.9	2.9	26.0	74.0
Latin America and Caribbean	54.9	37.4	7.6	28.5	71.5
Asia and Pacific Islands	40.9	48.1	11.0	18.6	81.4
Sub-Saharan Africa	33.4	37.6	28.8	33.2	66.8

Source: Bennett et al., 1997, 31, 32.

4.4 'Roaming' market exclusivity

Another 'pull' incentive likely to find favour with major pharmaceutical companies is to allow companies to transfer the market exclusivity awarded in the orphan drug package from the LDC-specific drug to another product of their choosing. Presumably, this second product would be marketed predominantly in the EMEs. This measure would motivate companies to do R&D in one of the LDC disease areas and offer to sell any new products coming out of that research at affordable prices that LDC populations can afford while still earning a return on their investment[23].

In a hypothetical set up, a team of experts, perhaps housed at the WHO, would be responsible for preparing a list of qualifying disease categories. This list would have to be updated as new treatments are developed and new infectious diseases (or drug resistant strands) are discovered. This international body would approve applications for this special orphan designation but individual countries would be responsible for providing the research grants, tax credits, and exclusivity rights. The number of 'extra' exclusivity months this company would be awarded for product B (their already existing drug) would depend on the expected R&D costs of product A (the new LDC drug) and the expected added revenue per month earned from sales of product B in an uncontested market. Alternatively, a cap could be set on the additional funds companies could earn from the granted market exclusivity.

The main problem with this proposal is that the burden of financing the roaming exclusivity measure falls predominately on the users of drug B. EME governments are likely to face opposition from strong domestic patient groups opposed to the idea of their being singled out, making such a measure hard to legislate[24]. Another problem with this

23 The US Drug Demand Reduction Bill, now before the Senate Committee for the Judiciary, sets a precedent for transferring the patent extension to a different product. This bill seeks to encourage the development of new drugs for treating dependence on a controlled substance by offering extended market exclusivity rights to an 'on-market' drug that 'need not be related to substance abuse and addiction'.

24 A proposed remedy to this problem is to have the governments reimburse the patients the difference between the expected generics price and the protected price for the months of extended exclusivity. This would transfer the burden back to the general taxpayer. The generics industry might also demand compensation for the extra months they are denied access to the market.

proposal is it will only be of valuable to companies that already have approved products. This would exclude small biotechnology companies, for example, that have no other products to transfer the exclusivity rights.

There is little argument that under any policy, EMEs will have to subsidize the costs for LDCs to benefit. The two key issues are first, whether the work is done by public or private organizations (in this case the private companies do the work) and second, whether the subsidy will be 'hidden' (extra costs to payers and patients in the EME funding and using the products with the extra months of exclusivity) or 'open' (a grant paid out of general taxation, say, to the WHO to set up a purchase fund for example).

4.5 The impact of incentives on companies

To anticipate how companies would respond to different incentive policy packages, one can set up a model where a company's expected returns (net product value (NPV)) are calculated using different input assumptions. Table 4.6 sums up the findings from such an exercise, purely for illustrative purposes. The standard case represents a product for an 'EME' disease. Relative to the LDC base case, this product has a significantly larger expected market size thanks to a larger patient population and a higher access rate. For the standard case 43 percent of a patient population of 200 million are expected to access the product. In the LDC case only 11 percent of the 8 million afflicted with the disease will have access. (The assumptions behind each case are set out in Appendix III).

Columns 3-6 show what happens to sales, total and R&D costs, and the NPV for the LDC-disease product under different incentive scenarios. For example, assuming the same market size but market exclusivity and tax breaks, the orphan drug legislation would increase total sales of a LDC-drug from £67 million to £139 million and reduce costs from £132 million to £112 million. These changes, however, are not enough to create a positive, NPV. In the case of a purchase fund, where companies are guaranteed peak sales of £250

Table 4.6 **The impact of different incentive packages on net product value**

	1	2	3	4	5	6
Million £	**Standard case**	**LDC base case**	**Orphan drug**	**Fund, no exclusivity**	**Fund with exclusivity**	**Standard drug with 3 years of 'transferred' exclusivity**
Total sales	4,134	67	139	1,083	3,281	12,526
Total costs	2,395	174	187	661	1,717	6,970
Total R&D costs	132	132	112	132	132	132
Net product value	198	–60	–50	14	174	734

Notes: 1. The orphan drug package includes seven years' market exclusivity, fast track approval (one year off the development time), a development grant and FDA approval waiver worth £369,000, and a 50% tax credit on development.
2. The guaranteed fund assumes that sales peak at £250 million. In Column 4, firms face the same likelihood of sharing the market as is assumed in Column 2. In Column 5. It is a 'winner take all' scenario where the first company to launch a product gets exclusive rights to the market.
3. In Column 6, the inputs are the same as in Column 1 but the company that launches a LDC drug can transfer three years of exclusive marketing to this product.
4. See Appendix III.

million regardless of the real population size and access rate, NPV becomes positive.

In general the exercise makes clear how important market size is for company NPV estimates. The guaranteed fund and the transfer of market exclusivity to the standard drug are the only incentive packages presented here that are likely to make investing in the LDC disease area attractive to companies.

Industry is not the only hurdle to bringing about new R&D investments however. Significant and difficult political processes also

stand in the way of operationalizing any of these incentive packages. Discussions must involve all key payers (representatives from EME governments, venture capitalists, charities and foundations, aid organizations) as well as representatives from LDC governments, research universities, and small and large companies.

4.6 Conclusion

This chapter has outlined incentive proposals for boosting incentives to private companies to invest in R&D for medicines for LDC-specific diseases. The absence of a market means that granting marking exclusivity for a product in the targeted disease area – a key incentive of the orphan drug package – will be of little help on its own. How well a combination package resembling the orphan drug legislation would work depends on the size of the research grants (cost discounting) and the size of the purchase funds (revenue enhancing). Companies must also consider the programmes to be credible for the long term.

It is also important to emphasize that the focus of most of these incentive packages has been on incentivizing private companies to increase R&D. They have not dealt with the access problems within the LDCs that keep the afflicted populations from getting treated. The roaming exclusivity and purchase fund ideas have the potential to increase a company's NPV but until these access problems are tackled, the DALY figures will remain the same (and in the case of the Sachs fund, the companies will not get a return on their investment).

Rather than seek to rectify the market failure in private sector R&D investment in LDC-specific disease areas with incentives for private companies, another option is for the R&D to be funded directly by the public sector. This option is discussed in the next chapter.

5 CREATING PUBLICLY FUNDED R&D PARTNERSHIPS

This chapter considers ways that public organizations (national or international) might increase their direct participation in new drug R&D. At the moment, public funds tend to be invested in the basic research stage. To take over the responsibility of developing and then bringing new therapies for LDC diseases to market, governments would need to increase their sponsorship of scientists doing applied research and drug development. This could involve the transfer of more funds into LDC-targeted research organizations already in place or the establishment of new institutes with such a focus. I look at examples of each in this chapter and conclude that research for new treatments is probably most effectively dealt with through public and private collaboration rather than exclusive reliance on public funds and public sector organizations.

5.1 Features of an effective public sector R&D institution

Until now, we have considered policies that would encourage private companies to shift their R&D priorities towards LDC-specific diseases. Public organizations could fund and conduct R&D into medicines for LDCs themselves, though this approach has its own challenges.

Publicly owned organizations (such as universities and research institutes) must compete with the private sector for top researchers and scientists. This means that they need to offer attractive remuneration packages and allow researchers to come up with their own solutions and to maintain research on a promising lead long enough to develop a useful product. They must have enough independence from political interest groups to select projects that meet criteria for scientific excellence and cost-effectiveness. They must also be able to kill projects when they are no longer productive. This is not always easy as it may be unpopular with taxpayers who feel that money has been wasted on a 'bad' project (rather than applauding a decision not to waste more cash) and with the researchers who may argue that success was 'just around the corner'. The work of the public body must also be transparent enough so that finance providers can check that their

Table 5.1 **Voluntary contributions to the TDR, 1974-1995**

Contributor	Donation (millions US$)	Share of total budget %
Denmark	53.1	11.2
World Bank	48.3	10.2
Norway	46.6	9.8
USA	46.0	9.7
Sweden	45.8	9.7
UNDP	42.3	8.9
The Netherlands	23.5	5.0
WHO	23.4	4.9
Germany	21.6	4.6
Canada	21.4	4.5
UK	19.2	4.1
Switzerland	18.3	3.9
Belgium	10.4	2.2
Australia	8.7	1.8
Italy	6.3	1.3
MacArthur Foundation	6.1	1.3
Japan Shipbuilding Industry Foundation	5.9	1.2
France	5.8	1.2
IRDC	3.3	0.7
Finland	2.8	0.6
African Development Bank Group	2.3	0.5
Others (total)	12.9	2.7
Total contributions	474	100.0

Source: TDR website, www.who.int/tdr, August 1999.

money is being invested efficiently with cost-effective treatments as the research targets.

As examples of public based research organizations, I look first at a special unit at WHO that was set up to invest in LDC-specific diseases. Second, I examine a new public-private initiative called Medicines for Malaria Venture (MMV), that aims to combine public funds and private resources to research new malaria medicines.

5.2 The special program for research and training in tropical disease (TDR)

The WHO's Special Program for Research and Training in Tropical Disease (TDR) is unique for its focus on tropical diseases. Its annual budget averaging $30 million is financed through voluntary contributions by more than 40 countries and foundations; the key ones being from Scandinavia, the World Bank, and the US. See Table 5.1.

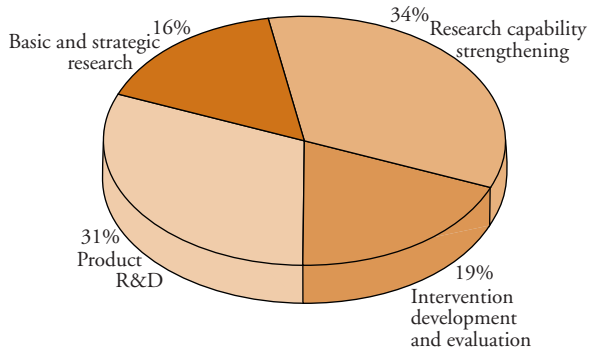
TDR resources and staff are divided into four research areas covering eight disease groups. See Figures 5.1 and 5.2.

Malaria, the top disease priority, makes up 54 percent of the total budget and 47 percent of the product R&D budget.

TDR facilitates and coordinates scientific and technical collaborations between a variety of public organizations, charities, foundations, and international aid agencies as well as private pharmaceutical companies. A list of more than 50 collaboration partners, excluding direct recipients of TDR grants, includes organizations such as the Agency for International Development in Washington DC, the National Council of Scientific and Technological Development in Brazil, the US National Institutes of Health, the Ministry of Public Health in Beijing, and 22 pharmaceutical companies (Adhoc, 1996, 253). Despite its small annual R&D budget of around $10 million,[25] TDR has made some important medical developments through its collabo-

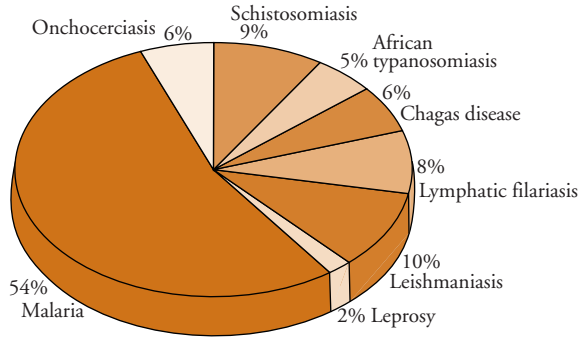
25 In comparison to this figure of $10 million, the top pharmaceutical companies each invested more than $1.5 billion in R&D in 1999.

Figure 5.1 **TDR budget[26] by research area, 1997-98**



Source: TDR website, www.who.int/tdr, August 1999.

Figure 5.2 **TDR budget[27] by disease area, 1997-98**



Source: TDR website, www.who.int/tdr, August 1999.

26 Across all disease research areas.
27 Across all research areas.

rations. These include: the development of Praziquantel drug combinations for multi-drug therapy for schistosomiasis; the field and clinical trials of Ivermectin to treat onchocerciasis; and the development of Eflornithine for treating African trypanosomiasis. TDR attributes these accomplishments to the combined and balancing influences of the scientific community, the managing secretariat, and its outside investors.

Much of the actual work occurs outside TDR's borders (and budget). It uses its limited funds to 'lubricate' the development process in other organizations. These resources multiply through the drug R&D cycle by attracting matching grants and funds from outside partners. In cases where TDR assists in the enhancement of markets, private industry is also encouraged to collaborate. This is because companies that contribute towards a research project that realizes a marketable product are guaranteed a share of the TDR supported market.

5.3 The Medicines for Malaria Venture (MMV)

In an alternative model, industry and public organization representatives have set up a disease focused research institute. The experience illustrates some of the difficulties involved in designing and managing a fruitful partnership.

In 1997, representatives from the pharmaceutical industry, WHO, and World Bank initiated work to devise a public-private scheme to address the lack of R&D in tropical diseases. The original idea was to set up a virtual company to focus exclusively on tropical diseases, starting with malaria. Industry and public organizations would jointly provide the funding for the discovery and early clinical trial phases for a number of candidates along a 2:1 private/public split. Private companies would license-in any successful compounds at Phase III clinical trials stage and finance these large trials plus subsequent marketing and distribution. Returns from successfully launched products would be distributed according to participants' contributions.

Under the finally approved initiative, the funds for the public venture capital fund (that the advisory board will manage) to finance the discovery and early clinical trial phases for a number of projects will

come from governmental funding agencies, foundations, and philanthropic donations. The pharmaceutical industry will contribute in kind: access to combinatorial libraries, high throughput screening systems, laboratory space, and so on. The goal for the MMV advisory board is to license-out successful compounds to pharmaceutical companies for late stage clinical trials, and to manufacture and market.

The list of MMV Partners as of December 1999 included:

- International Federation of Pharmaceutical Manufacturers Associations (IFPMA);
- Global Forum for Health Research;
- The Netherlands Ministry for Development Cooperation;
- The Rockefeller Foundation;
- The Swiss Agency for Development and Cooperation;
- The United Kingdom Department for International Development;
- World Health Organization;
  - Roll Back Malaria;
  - TDR;
- World Bank.

Source: www.malariamedicines.org/partners.htm, December 20, 1999.

Under the original idea, academic institutions (sometimes teamed up with pharmaceutical companies) compete for the funds. It is anticipated that the winning projects will be housed in academic institutions, though some may be pharmaceutical company based.

The most promising development candidates will be fed into a 'virtual' drug development unit, also financed and administered by the MMV. This unit should be capable of taking compounds through to registration but its management would seek industrial partners for the final phases of clinical trials, and for the manufacturing and commercialization phases. Such partners might be either large or small pharmaceutical companies. The MMV and its academic and industry partners will jointly own the intellectual property rights to any compound patented through this initiative (Dr. Trevor Jones, Interview, June 1999).

In the short term, MMV seeks to create a portfolio of properly funded and adequately resourced projects on a par with industry-run discovery projects. In the long term, once fully operational, the goal would be to secure the production on average of one registered new anti-malarial drug every five years. The predicted costs to manage this number of projects are $30 million p.a. As of January 2000, MMV had cash promises of $10 million for 1999/2000 (MMV Presentation, January 13, 2000).

In terms of attracting researchers' attention, the MMV has already been a success. For the autumn 1999 competition for the first round of discovery funds, the office received over 100 letters of interest from 27 different countries. Seven of the academic proposals had links to major pharmaceutical companies; six others had links with biotechnology companies. Eighteen letters originated from biotechnology companies independent of academic centres. The three proposals selected for full funding all involved a joint university and major pharmaceutical company team. The winners of the first round are:

Table 5.2 **The key components of MMV**

- Discovery research: public venture capital funds for winning joint academic/industry proposals ($2.5-3.5 million p.a. each).
- Intellectual property rights: jointly owned by MMV and the academic and industrial partners in the research project.
- Development: managed through a virtual[28] development company. Early phases MMV financed. Phase 3 trials done in partnership with intended commercial partner ($1-2 million p.a. each).
- Production and commercialization: pharmaceutical company financed and managed, under licence from MMV and the academic and industrial partners who own the IPR.
- MMV's royalties/other payments: retained by the MMV Fund.

28 The virtual drug development unit would contract its work out on a competitive basis. The WHO/TDR have established such a unit and could take on this responsibility, at least initially.

1. GlaxoWellcome and the University of Bristol

2. SmithKline Beecham and the University of California San Francisco

3. Roche and the University of Nebraska (Rob Ridley, Correspondence, December 2000).

A number of important issues need to be resolved, however, to guarantee that the initiative successfully brings new research ideas to market. First, until the research projects bear fruit, the credibility of the initiative (and its ability to raise additional monies) will rest with the reputation of the MMV's advisory board responsible for selecting the projects and overseeing the use of the funds. Thus the composition of that board and the inclusion of representatives with the relevant commercial, regional, and disease area experience is critical. Similarly, the location of the headquarters is important. If the venture is to have an institutional affiliation this must be considered neutral by all parties involved (industry, government, academic).

Second, in selecting projects, the MMV board must resist political pressure and remain 'region' neutral, and through a transparent selection process choose proposals based on science and cost criteria not nationality.

The MMV board must also make clear from the start that this is a competition and that even the winning proposals are not guaranteed full funding unless their early research proves successful. The public must also be made aware of the high failure rate in drug discovery and development. This means that some, and possibly all, of the original winners may fail to produce a compound for human trials. Without making these risks clear from the outset, the venture risks criticism later when they may appear to have 'wasted' public funds on unsuccessful projects.

Finally, MMV must still find a way to make it attractive for private industry to step in and license compounds at the later stages of development while guaranteeing that LDCs can afford the final result[29]. As

29 An alternative might be to try and raise additional public funds to cover the expensive Phase III clinical trials, manufacturing and marketing stages.

was discussed in the previous chapter, the creation of a market may be an effective way to attract industry participation. Price guarantees or tiered pricing and purchase funds are options that the MMV board is exploring for creating a market for malaria. A tiered pricing system that reflects populations' ability to pay would allow companies to charge one price in the EME travellers' market and another (or a range of prices) in the LDC markets. See chapter 6 for more details of this option.

5.4 Conclusion

Initiatives such as TDR and MMV and the incentive packages discussed in chapter 4 are not mutually exclusive activities and should be pursued in parallel. All depend on a complex network of contributors to succeed. Under the schemes based on incentive packages, it is private companies who will actually conduct the R&D but collaborations with governments and aid organizations will still be essential. Under the MMV scheme it is public academic organizations that will conduct the research but private industry will contribute in kind. There is a key difference between the two approaches. In the second case, companies' motivation is primarily that of charity and public relations rather than commercial return, at least until the late clinical trial stages.

For patients in LDCs to benefit from new R&D, attention must also be given to the barriers that inhibit access to existing and future medicines. Improved access will also greatly influence companies' assessment of the market. Some of the main barriers to access are discussed in the next chapter.

6 ACCESS TO EXISTING MEDICINES

Up until now, this report has focused on the problem of filling gaps in treatment regimes for LDC populations especially but not exclusively in LDC-specific diseases. This chapter examines some of the problems that block LDCs' access to affordable, effective medicines and treatments[30].

A complex set of issues affects these countries' access to health care. The list includes but is not limited to: physical barriers, financial barriers, political barriers, costs and price barriers, information barriers, and social barriers. Access problems may be most effectively dealt with on a case by case basis but in parallel rather than sequentially, taking the relevant combinations and interdependencies into account. For example, policies to provide existing products at concessionary rates to LDCs must be combined with policies to monitor their distribution to ensure that the cheap products are delivered to the targeted populations and not re-exported at slightly higher prices that undercut the same product in other markets. Similarly, investments in physical infrastructure building must be matched with investments in educating both doctors and patient populations about the most cost-effective treatments and the use of drug regimes.

After a broad overview of the problems, I give the multi-tiered pricing policy a closer analysis as the MMV and the Sachs/Kremer incentive packages both propose tiered-pricing as one of the ways in which effective demand for new medicines or vaccines might be enhanced.

6.1 Overview of access problems

The most serious of the access problems is the lack of sufficient **financial resources** (public and private) in LDCs to meet health care needs for the majority of their populations. The lack of adequate financial resources leads not only to inadequate resources to purchase

30 This chapter serves only as an introduction to a broad spectrum of complex access issues. See Madrid (1999) for more detailed coverage.

medicines, but also to an inadequate number of medical professionals and hospital facilities to deliver health care. Governments may not be able to assign priority to or have sufficient resources available for, building the **infrastructure** necessary to improve health status and provide access to health care. Basic investments in transportation, sanitation, and education are also needed to support health care specific infrastructure.

Facility and staff shortages are particularly acute in remote rural regions. The distribution of physicians and health care facilities is skewed toward urban areas. Physicians are often from urban centres and more likely to select urban locations in which to practice. 'In one Asian country, 36 percent of the population reside in rural areas, but only 8 percent of the physicians are located in these rural areas' (Bale, 1999, 14). Poor roads and transportation systems make it difficult for patients to get to the centres that do exist. These transport infrastructure problems also hinder doctors' efforts to get to patients and suppliers' efforts to deliver medicines, equipment, diagnostics, and basic supplies in a timely fashion.

Under these conditions, complex treatments that require regular doctor visits close supervision, and combinations of products (combination therapy for HIV/AIDS for example) cannot readily be administered even if the treatments were made available at affordable prices.

Lack of **information** about the types of treatments available, the need for treatments, and where to seek treatment are serious barriers to access as well. Self-medication by poorly informed patients may lead to ineffective drug utilization and to the growth of drug resistance (consider HIV or malaria drug regimes). Physicians may not always be aware of the most cost-effective therapies or, because they are short of resources, they may be forced to treat with 'outdated' or inappropriate medicines.

In some countries there is inconsistent information about the quality of generic products. Unsure of the safety and reliability of these products, doctors and patients frequently choose the more expensive brand name products. This may be linked to poor intellectual property protection and the existence (and rumours) of substandard coun-

terfeit products in LDCs[31].

Economic policies such as domestic industry protection, failure to protect product patents, and price controls are often considered means to improve affordable access to pharmaceuticals and support the local industry. They may instead push up drug cost margins, limit the supply of certain products, and discourage major pharmaceutical companies (and local companies) from investing in LDC-targeted R&D and, in the case of the former, from marketing existing products in these countries.

6.2 Tiered pricing

Price may not be an access barrier for LDC purchases of off-patent drugs but is clearly critical in the case of new, patented products. As we have discussed above, nearly all new drugs, even those addressing LDC-specific diseases, are likely to be developed by commercial firms in EMEs. LDCs still lack adequate and effective intellectual property rights and most lack the infrastructure to discover new drugs that would address important disease indications prevailing in their own countries[32]. Companies may consider concessionary prices for poorer populations in cases where they can sell the product at higher prices in EMEs for the same or some other condition. The tiered pricing policy is only relevant in cases where some non-LDC specific market exists.

A multi-tiered pricing strategy has been advocated by WHO and the World Bank as a way to make vaccines available at affordable prices to all countries while maintaining an environment that encourages companies to invest in R&D to develop new vaccines (Batson, 1998; Mercer, 1993 and 1997). Vaccine companies would charge different prices in different markets, reflecting the patients' ability to pay in

31 Feachem (1999) argues that existing aid policies for improving access problems may be misdirected because they do not engage the appropriate set of actors. As the figures in Table 4.5 suggest, some kinds of aid might be better directed at private organizations than governments.
32 See the discussion of intellectual property in chapter 4, section 4.1.

those markets. Charging full costs – including corporate overheads and R&D costs – to EME markets allows companies to cover the expensive costs of R&D investments. Charging prices closer to marginal costs to other markets allows producers to expand volume and reduce unit costs of production.

International aid organizations are also promoting this strategy as a way to make new vaccines available to LDCs at affordable prices more quickly (Kremer, 1999a). Traditionally, companies launched vaccines at low volume and high prices in EMEs and only expanded production and distribution over time. 'The use of multi-tiered pricing has enabled European manufacturers (of vaccines) to price products in their core markets to cover the full cost of production, investment in R&D, marketing, and all overhead costs, while also allowing them to sell large volumes of low-price vaccines to the poorest countries of the world. These global sales have, in turn, enabled manufacturers to take advantage of economies of scale in production and for the cost per dose' (Institute of Medicine, 1997, 31).

At issue is whether such a solution would be transferable to medicines. Parallel trade issues are perhaps a greater concern in the case of medicines. Parallel importing refers to cases where the recipient of the product at low prices resells it in higher price band markets at prices below full-cost prices but above the price they originally paid. 'Multi-dose packaging of vaccines and complex, controlled, delivery services largely negated the danger of resale into higher-priced markets' (Rosegrant, 1998, 5).

Multi-tiered pricing is presented as a 'win-win' situation. Companies sell higher volumes at lower unit costs but are assured that R&D costs are covered because of continued 'full-cost' pricing in EMEs. LDC populations gain access to vaccines at an affordable price soon after they are launched. Under a parallel-importing scenario, the LDC populations may not get the products and the pharmaceutical companies' products are undersold in higher price band markets, thus depriving them of full-cost returns. The bottom line is that companies will not agree to such a scheme if the products will come back.

Multi-tiered pricing is also only useful in cases where markets for

the LDC-specific disease product also exist in EMEs, thereby providing companies with a range of markets. That excludes the diseases focused on in much of this report but is certainly important for treatments in non-communicable disease areas which are expected to become ever more important in the disease burden structure for LDCs (see chapter 2).

7 CONCLUSION

An imbalance exists between the need for new medicines to treat LDC-specific diseases and the level of investment allocated towards R&D for new medicines in these areas.

Private industry tailors research to the needs of patients where effective demand is sufficient to finance large costs of R&D. LDC markets are generally not large enough to attract a significant share of that private sector investment. To a limited extent, the LDCs' governments could increase their expenditure on health care, including pharmaceuticals, by improving purchasing efficiency. However, given the extremely low absolute level of expenditure on health care in many LDCs, and the fact that many of these countries are already spending a significantly higher proportion of their national income on pharmaceuticals than developed countries, their ability to obtain substantial new resources for new medicine purchases from this source is limited.

The public sectors of the EMEs can intervene in two ways to try and remedy these market failures. First, they can improve the push and pull incentives to try and make it more attractive for private companies to invest in these disease markets: the 'commercial assistance' approach. Second, they can provide direct public funding for research and product development in these areas. Teams of academic and industry scientists from both developed and developing regions could compete for these funds. We can refer to this as the 'public-based' approach.

In both approaches, public organizations and private industry must work together. Who is conducting and funding the primary R&D and what is motivating industry are two ways to distinguish the approaches. In the 'commercial assistance' approaches, companies are drawn by the prospect of financial return. In contrast, while contributions in kind or money to public-based projects might bring benefits in terms of reputation, networking opportunities, and shared access to new, scientific breakthroughs, companies do not generally expect financial rewards to materialize directly from them, at least not in the short to medium term.

The goals of 'commercial assistance' approaches are to **lower expected costs, lower risk** and **increase the expected revenues** for

companies making R&D investments into the relevant disease areas. One possible method is to introduce a modified form of the orphan drug legislation to reflect the unique circumstances of the LDC diseases. As we showed in chapter 4, the standard orphan drug legislation used in the US, for example, would be insufficient to attract serious attention from companies for R&D in LDC medicines. In particular, the important market exclusivity component, which applies to sales in the market where the orphan disease status is awarded, is relatively ineffective in the case of LDC diseases. The legislation would have to be modified in the following ways:

- rather than define eligible candidates according to disease incidence or prevalence, a list of designated target diseases such as those specified in the WHO 1996 report, would be more appropriate;
- clinical trial expenditure incurred in developing world settings must be allowable in the tax credit calculation. With few, or no, cases of LDC diseases in the developed world, the large Phase III clinical trials are probably not feasible there;
- grant funding should extend beyond applied research to basic research;
- the role of coordinating collaborative ventures and the provision of prevalence and aetiology information should be undertaken specifically for developing country diseases, probably by a unit similar to the Orphan Drug Development Office in the US;
- the pull incentive must be enhanced, perhaps through a purchase fund or a roaming market exclusivity clause. With some modifications to reflect the differences in purchasing and distribution systems and the shorter expected time lines, the Sachs/Kremer purchase fund proposal should work as an incentive to encourage R&D into new medicines as well as vaccines.

If experience from US orphan drug legislation serves as a predictive example, the commercial assistance approach seems most likely to influence the investment decisions of smaller pharmaceutical companies. As of 1995, 75% of the 256 company sponsors of orphan drugs were small and medium sized companies (Shulman and Manochhia, 1997). Without a great deal of funding and a strong pull, the assisted

commercial environment may fail to attract the attention of the 'big players', the multinational companies. To harness the expertise of these companies, the public sector could adopt a more proactive approach to funding the necessary R&D.

For a publicly funded R&D effort to be successful, it would require a collaborative effort with the industry. This means industry becoming actively involved in these projects, albeit not on a fully commercial basis. Their contribution could include: providing access to sophisticated technology; making available appropriate expert advice; and foregoing some of the patent rights on compounds that the public sector would like access to. An important question is whether diseases specific initiatives, such as MMV, should be set up or a broader based 'infectious disease' unit. Such a unit could coordinate and contract for the R&D and could build on the experience of the Special Program for Research and Training in Tropical Disease (TDR).

The two approaches – commercial assisted and public based – are not mutually exclusive. Market based incentives for companies may be more effective in certain diseases than others. Differences between diseases in the size of the potential market (prevalence in LDCs), the state of the science and the type of companies involved (small biotechnology companies, large multinational pharmaceutical companies) may mean different combinations of incentives are needed.

Studies of what types of incentives might motivate company R&D in HIV vaccines and TB, for example, have produced dramatically different results. In the case of HIV vaccines, companies still see science as the important barrier and emphasize the importance of push incentives, such as support for expensive and highly uncertain clinical trials. Though crucial in the long term, the provision of a guaranteed market right now will have little impact on companies' investment decisions there (Mercer, 1998). By contrast, companies interviewed for a WHO study of the incentives and disincentives for new anti-TB drug development emphasized the perceived lack of commercial return. Here, pull mechanisms might have a more immediate impact on investment decisions (Chang Blanc, 1998).

These findings add to the debate over whether disease specific

approaches such as MMV or legislative changes to provide incentives for a broader set of diseases would be more effective.

For the affected populations to benefit from any new investments, a complex set of access barriers must also be eliminated. Policies to deal with access problems, however, must take into consideration their impact on R&D. So, for example, moves to permit compulsory licensing or to impose price controls to cut costs for existing products in the short term might discourage industry involvement in long term R&D investment projects.

Ultimately, the greatest challenge of all is how to get the actors involved to back verbal commitments with money and resources. EME governments, for example, have complex sets of interest groups that all need to make LDC diseases a priority for any of the approaches to work. It may be harder to convince the US taxpayer than a large multinational pharmaceutical company that investments in LDC diseases are worthwhile. The current teams exploring policy initiatives behind closed doors must move quickly to be more open and involve all relevant players, especially the payers.

A complacent attitude that populations of EMEs are immune to these diseases is not only reprehensible but also naive and dangerous (Institute of Medicine, 1997). Increased international travel means increased risk of transferring the diseases across borders. Between 1987 and 1992, a total of 8,353 cases of imported malaria were reported in the UK (WHO, 1999a). According to this same study, since 1980, 18 new infectious diseases have been identified; a list that includes Lyme's disease and HIV, conditions clearly not restricted to the developing world. All countries can benefit from the advances in science that can help eradicate these infectious diseases. Furthermore, lessons learned from setting up public and private collaborations and incentives to deal with these problems can probably be transferred to other welfare issues concerning all regions.

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APPENDIX 1

Classification of economies by income and region, 1999

Income group	Subgroup	Sub-Saharan Africa		Asia		Europe and Central Asia		Middle East		Americas
		East and Southern Africa	West Africa	East Asia and Pacific	South Asia	Eastern Europe and Central Asia	Rest of Europe	Middle East	North Africa	
Low income		Angola	Benin	Cambodia	Afghanistan	Armenia		Yemen, Rep.		Haiti
		Burundi	Burkina Faso	China	Bangladesh	Azerbaijan				Honduras
		Comoros	Cameroon	Indonesia	Bhutan	Kyrgyz Republic				Nicaragua
		Congo, Dem. Rep.	Central African Republic	Korea, Dem. Rep.	India	Moldova				
		Eritrea	Chad	Laos PDR	Nepal	Tajikistan				
		Ethiopia	Congo, Rep.	Mongolia	Pakistan	Turkmenistan				
		Kenya	Côte d'Ivoire	Myanmar						
		Lesotho	Gambia, The	Solomon Islands						
		Madagascar	Ghana	Vietnam						
		Malawi	Guinea							
		Mozambique	Guinea-Bissau							
		Rwanda	Liberia							
		Somalia	Mali							
		Sudan	Mauritania							
		Tanzania	Niger							
		Uganda	Nigeria							
		Zambia	São Tomé and Principe							
		Zimbabwe	Senegal							
			Sierra Leone							
			Togo							

Classification of economies by income and region *(continued)*

									Belize
									Bolivia
									Colombia
									Costa Rica
									Cuba
									Dominica
									Dominican Republic
									Ecuador
									El Salvador
									Guatemala
									Guyana
									Jamaica
									Paraguay
									Peru
									St. Vincent and the Grenadines
									Surinam
									Antigua and Barbuda
									Argentina
									Barbados
									Brazil
									Chile
									Grenada
									Guadeloupe
									Mexico
									Panama
									Puerto Rico

Middle income

Lower

Djibouti
Namibia
South Africa
Swaziland

Cape Verde
Equatorial Guinea

Gabon

Fiji
Kiribati
Marshall Islands
Micronesia, Fed. Sts.
Papua New Guinea
Philippines
Samoa
Thailand
Tonga
Vanuatu

Maldives
Sri Lanka

Albania
Belarus
Bosnia and Herzegovina
Bulgaria
Georgia
Kazakhstan
Latvia
Lithuania
Macedonia, FYR[a]
Romania
Russian Federation
Ukraine
Uzbekistan
Yugoslavia, Fed. Rep.

Iran, Islamic Rep.
Iraq
Jordan
Syrian Arab Republic
West Bank and Gaza

Algeria
Egypt, Arab Rep.
Morocco
Tunisia

Middle income

Upper

Botswana
Mauritius
Mayotte
Seychelles

American Samoa
Korea, Rep.
Malaysia
Palau

Croatia
Czech Republic
Estonia
Hungary
Poland
Slovak Republic

Isle of Man
Turkey

Bahrain
Lebanon
Oman
Saudi Arabia

Libya

Classification of economies by income and region *(continued)*

Middle income	*Upper*									St. Kitts and Nevis St. Lucia Trinidad and Tobago Uruguay Venezuela
Subtotal	157	26	23	23	8	26	2	10	5	34
	OECD			Australia Japan New Zealand			Austria Belgium Denmark Finland France Germany Greece Iceland Ireland Italy Luxembourg Netherlands Norway Portugal Spain Sweden Switzerland United Kingdom			Canada United States
High income										

Classification of economies by income and region *(continued)*

High income	*Non-OECD*	Réunion		Brunei		Slovenia	Andorra	Israel	Malta	Aruba
				French Polynesia			Channel Islands	Kuwait		Bahamas, The
				Guam			Cyprus	Qatar		Bermuda
				Hong Kong, China[c]			Faeroe Islands	United Arab Emirates		Cayman Islands
				Macao			Greenland			French Guiana
				New Caledonia			Liechtenstein			Martinique
				N. Mariana Islands			Monaco			Netherlands Antilles
				Singapore						Virgin Islands (US)
				Taiwan, China						
Total	211	27	23	35	8	27	27	14	6	44

a Former Yugoslav Republic of Macedonia.
b Federal Republic of Yugoslavia (Serbia/Montenegro).
c On July 1 1997, China resumed its sovereignty over Hong Kong.
Source: World Bank 1999b, pp.290-291.

APPENDIX II – THE ECONOMICS OF AN ORPHAN DRUG VERSUS A LDC DRUG

Differences in the shape and location of the demand schedules for a drug to treat a standard orphan disease and one for a LDC-specific disease, mean that the orphan drug incentive package that works to make investing in the former case attractive, may not work in the latter case.

The standard orphan disease case:

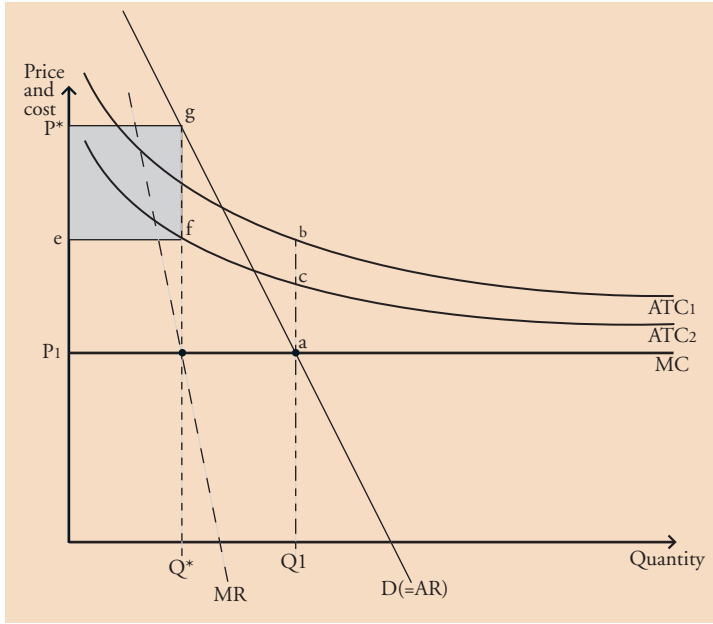
Peabody et al. (1995) provide a clear description of the economics of a 'typical' orphan drug market. The low prevalence of orphan diseases influences demand and makes it difficult to sell orphan drugs beyond limited, invariably low, quantities. As a result, demand schedules for most orphan drugs do not reflect substantial revenue potential. However, because orphan diseases are often severe diseases for which alternative treatment is limited or non-existent, the quantity of orphan drugs demanded is generally insensitive to fluctuations in price over most of the orphan drug's demand curve. The cost structure for an orphan drug, however, is assumed to be consistent with that of other pharmaceutical products.

These demand and cost schedules combine to form a market that appears quite attractive to a monopoly supplier of orphan compounds. This market quickly becomes unattractive to firms in a competitive open market with multiple producers and no barriers to entry. Competition lowers prices or volumes sold of the drug and producers are then unable to realise any profit in the typical orphan drug market because average total costs lie substantially above price level for any achievable quantity of sales.

Thus, the 'first' monopolist is unlikely to materialise unless there is some assurance that the original monopoly status will be preserved. The market exclusivity provision of the orphan drug legislation ensures this monopoly status for several years, allowing companies to factor prospects for profits into their investment decisions for initiating R&D in the orphan disease area (Peabody et al., 1995, 375-76).

Figure AII.1 illustrates how the standard orphan drug market works. The demand (average revenue) curve in this market is shown by D (=AR). The corresponding marginal revenue curve is MR. The

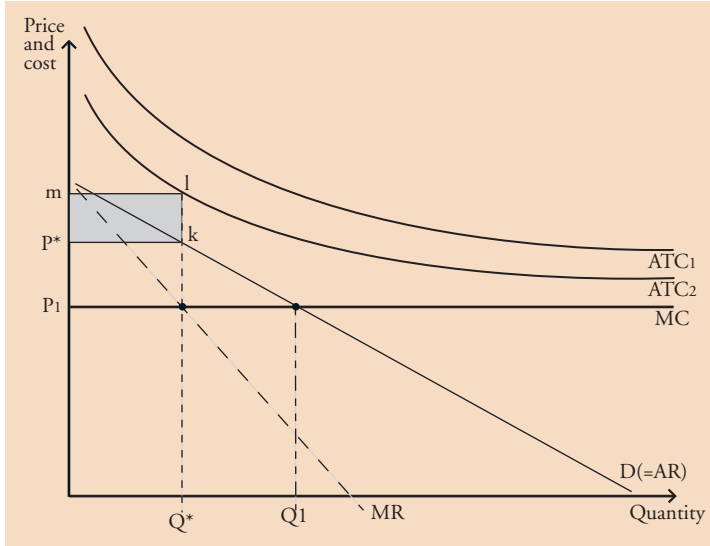
Figure AII.1 **Standard orphan drug case**



initial average cost curve for producing the standard orphan drug is ATC1 before the introduction of any orphan drug legislation incentives. The marginal cost of producing the drug is shown by MC. If the market is competitive, with more than one rival producer, price would be forced down to the level P_1 at which average cost would exceed average revenue by the amount ab and so producers would make a loss. Producers will not willingly enter such a market and will thus avoid R&D investment in such areas.

The cost incentives within the orphan drug legislation package might reduce the average cost curve to ATC_2 but this would still be insufficient to stimulate investment in R&D as long as the market was expected to be competitive. However, the market exclusivity provision allows the first firm in the market to charge a monopoly price of P*

Figure AII.2 **LDC disease case**



and so earn profits equal to the shaded rectangle *efgP**. By creating conditions for a reasonable expectation of profit, the orphan drug legislation incentivizes companies to invest in orphan drug R&D.

The LDC disease case:

The key difference between the standard orphan drug described above and the LDC-drug is in the shape and position of the demand curve. Given the poor economic conditions in the targeted markets, and the existence of other – though perhaps inadequate – treatments, the demand curve is likely to be less steep, reflecting payers' greater sensitivity to price fluctuations. This means that even under conditions of market exclusivity, there is a greater prospect that the monopoly price could remain below ATC (even after cost has been shifted down), resulting in a loss for the company. Such an example is illustrated in Figure AII.2. Even though the standard orphan drug legislation has

reduced average costs from ATC_1 to ATC_2 and created market exclusivity, the best a monopoly producer could hope for would be to charge P* and sell Q*. But she would then still be making a loss equal to the area of the rectangle *P*klm*.

To make the LDC disease area attractive, therefore, additional policies might be needed. These could take the form of additional cost subsidies to shift the ATC curve down further or demand enhancing policies that shift the demand curve out to the right.

APPENDIX III – ASSUMPTIONS FOR THE SENSITIVITY ANALYSIS OF NET PRODUCT VALUE UNDER DIFFERENT INCENTIVE PACKAGES

The key inputs that distinguish the different cases in Table 4.6 are:

- patient population;
- access rate (a function of the rate at which patients can seek physician advice, the chance that that physician correctly diagnoses the problem, and the chance that that physician can access the specified treatment);
- price per treatment;
- whether the company has market exclusivity and, if so, for how many years;
- the time it takes to research, develop, and launch a drug;
- whether tax credits or grants exist to help cover R&D costs, and their magnitude.

The model assumes that the base R&D spend is the same for each case: £200 million. Total R&D costs to the company in every case are less than this because of tax credits earned on R&D spends prior to earnings. Marketing and production costs are assumed to be a percent of sales and so are much lower for the LDC drugs.

Table AIII.1 sums up the key inputs for each of the cases. The patient population for the purchase fund scenarios was increased from 8 million to 25 million and the access rate was assumed to be 100% to capture the effect of a guaranteed market of £250 million.

Table AIII.1 **Inputs into the net product value sensitivity model**

	Standard case	LDC base case	Orphan drug case	Fund, no exclusivity	Fund with exclusivity	Standard with 3 years of 'transferred' exclusivity
Patient population (m)	200	8	8	25	25	200
Access rate	43%	11%	11%	100%	100%	43%
Market size	86,000,000	880,000	880,000	25,000,000	25,000,000	86,000,000
Price per treatment	£10	£10	£10	£10	£10	£10
Market exclusivity	No	No	Yes	No	Yes	Yes
If yes, how many years			7		7	3
Years in R&D before launch	10	10	9	10	10	10
Tax credit	No	No	50% on D	No	No	No
Grants	No	No	£.367M	No	No	No

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