Final Report
for the WHO Commission on Intellectual
Property Rights, Innovation and Public Health

What Type of Innovation is Required and How Can We Incentivise the
Private Sector to Deliver It?

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Executive Summary

- Innovation has a number of characteristics or dimensions and that advances along any one dimension or a combination of dimensions can be of value. Therefore, the distinction sometimes made between incremental and breakthrough innovation is not a particularly meaningful one. What matters is to identify the attributes of innovation that are important and seek to find products that will provide them.

- Most of the research in neglected diseases is now conducted by a range of players through the vehicle of public private partnerships (PPPs) which, on the basis of funding from philanthropic sources, are able to harness the skills of different organisations at different stages of the R&D process. Large companies play an important role, albeit in a semi-commercial basis; small companies require a commercial return.

- To generate the innovations needed, commercially-based incentive mechanisms, if carefully designed, have the potential to complement the activities of PPPs.

- Drawing on the experience of two existing incentive mechanisms – orphan drug legislation and the paediatric initiative we conclude that the following “pull” incentives have the greatest potential to generate the innovation needed:
  - transferable/roaming intellectual property rights (TIPR), whereby a company is awarded additional IP on a product of its choice in exchange for developing a given neglected disease product;
  - transferable fast track/priority review/accelerated approval (TFT) whereby a company receives more rapid regulatory review for a product of its choice in exchange for developing a neglected disease product (effectively lengthening the period of patent protection for the chosen product);
  - advance purchase commitments (APCs) provided through a guaranteed purchase fund.

- The ability to trade these rights will be important so that in all three cases it should be possible, for example, for a small biotech company involved in early stage development to sell its product to a larger company after (say) completion of Phase I or Phase II trials.

- These mechanisms can be used for diagnostics, vaccines and pharmaceuticals. For example, a TIPR for a pharmaceutical could be given for the development of a diagnostic kit meeting relevant regulatory requirements in a target disease area.

- Each of the three has strengths and weaknesses. For example: APCs can most easily be fine tuned and hence may be most cost-effective; TIPR has most credibility with the industry; TFT delivers efficiency gains to developed countries. All can be made complementary to existing “push” approaches such as PPP funding. They are not mutually exclusive measures and could be designed to address different innovation needs.
1 Introduction

1.1 Terms of Reference for the Study

The World Health Organisation (WHO) has established the Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH) with a mission to “examine in depth how to stimulate the creation of new medicines and other products for diseases that mainly affect developing countries.”

Its terms of reference include requirements to:

“consider the importance and effectiveness of intellectual property regimes and other incentive and funding mechanisms in stimulating research and the creation of other new products against these diseases;

analyse proposals for improvements to the current incentive and funding regimes, including intellectual property rights, designed to stimulate the creation of new medicines and other products, and facilitate access to them.”

The Framework Paper published by the CIPIH in July 2004 includes as a relevant question: “How effective have exclusivity-based systems (such as orphan drugs, paediatric extensions or data confidentiality rules) been in stimulating research where market incentives are otherwise weak?” Alternative proposals for consideration might include “modifications and alternatives to patent and other exclusivity based systems (including drawing on orphan drug and similar legislation) …Advance purchase commitments/patent buyouts and similar approaches, (and) tax credits” (CIPIH, 2004).

OHE Consulting has been commissioned to provide a review of market and intellectual property (IP) related proposals to stimulate more innovation in combination with a study of the importance of incremental versus breakthrough innovation.

The terms of reference for the OHE Consulting study are to examine:

• what type of innovation is required to tackle global health problems? In particular what mix of incremental innovation and breakthrough innovation is required?

• whether existing IP (patents plus other forms of exclusivity) could be modified to provide incentives for R&D into global health diseases. Although the main emphasis will be on IP related incentives, the study will also analyse how these IP laws compare with other methods of funding / incentivising R&D for diseases of poverty. The study will include, as a minimum, consideration of orphan drug legislation, paediatric initiatives, patent buyouts and tax credits. Other proposals will be identified and explored subject to discussion with the secretariat of the CIPIH (the Commission).
how these proposals are likely to impact on incentives for incremental and breakthrough innovation respectively.

1.2 Methods

The work has involved:

• an analysis of incremental (or what is sometimes called ‘me-too’) versus breakthrough innovation issues in the context of R&D for global health diseases. This is based on a literature review on innovation and materials from relevant websites;

• interviews with disease experts within WHO to explore the type of innovation required in a number of disease areas. A list of those interviewed is set out in Appendix 1;

• setting out the details of, and commentaries on, the various proposals for IP-related measures to incentivise the private sector to deliver the innovation required to improve global health. These were obtained from our own files, from a literature review using Pubmed, a trawl of relevant websites, and discussion with the Commission secretariat;

• an analysis of the likely cost-effectiveness of the different proposals for incentivising research for global health in the light of the balance of needs as between incremental and breakthrough innovation.

1.3 Outline of the report

Sections two and three set out the characteristics of innovation in general terms and as it relates to pharmaceuticals specifically. Section four considers innovation in the context of developing countries and presents the innovation needs for a selected group of diseases. Section five presents an overview of the R&D process and the various organizations involved, while section six considers how the private sector might be more effectively engaged and presents conclusions. Appendix 1 is a list of interviewees, Appendix 2 summarises some of the key drug developments in neglected diseases and Appendix 3 sets out established incentives mechanisms for orphan drugs and for paediatrics, while Appendix 4 discusses other proposed incentive mechanisms.

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1 We carried out the literature review using Pubmed and Econlit. The search criteria include the following key words:

• ‘breakthrough and innovation’ and (medicines or pharmaceutical or drug or technology or therapy or treatment or molecule or intervention or system or device or procedure)

• “me too” and innovation and (medicines or pharmaceutical or drug or technology or therapy or treatment or molecule or intervention or system or device or procedure)

• and other words with similar meaning, such as “incremental and innovation”
2 Characterising innovation in general

In order to understand the characteristics of innovation in pharmaceuticals we need to examine the nature of innovation elsewhere. Innovation happens in all areas of economic activity. Where there are effective consumer markets, it is the ultimate consumers of goods and services who determines whether a new product is innovative or not. Newness alone does not imply innovativeness. It must be combined with consumers’ willingness and ability to pay for it.

Innovation is generally defined as a process concerning “the search for, and the discovery, experimentation, development, imitation, and adoption of new products, new processes and new organisational set-ups” (Dosi, 1988). It covers a variety of disciplines, including the basic science, economics, corporate management and marketing, as it proceeds through “the exploration and exploitation of opportunities for a new or improved product, process or service” (Pavitt, 2003). Thus discovery (i.e. the invention) drawing from basic and applied research becomes an innovation if it is implemented in the market or used within the production process, and adopted or used by other parties beyond the discoverers. Innovation implies not only a technological advance but also one that brings social and economic consequences.

Thus innovation can be on a large or small scale, and can have any of a very broad range of socially-relevant characteristics. Innovation is not ‘on or off’, ‘black or white’; it is a matter of degree. Neither is innovation limited to a narrow range of aspects; it can include anything that people find useful.

2.1 Drivers of innovation

Innovation in the private sector is driven by a combination of the following:

- market needs and demand;
- the institutional environment;
- scientific knowledge and technological opportunities.

We review these in turn.

2.1.1 Market forces

Commercial innovation is substantially driven by demand side factors: what consumers may be willing to pay, or pay more, for. The innovation process undertaken by profit-motivated agents involves the perception of an unexploited economic opportunity and an expectation that there exists a market to justify the R&D outlays.
Some authors emphasise the role of “demand-pull” factors (see Schmookler, 1966) and have provided empirical evidence on the primacy of market demand forces within the innovation process. However, the appeal to demand-pull arguments does not always provide a useful insight into the complexity of the innovation process, because whilst innovation might respond to existing patterns of demand, it can also create a new demand previously unrecognised by the consumer. For example, in the late 1970s, households did not perceive the home computer as a useful item and could not remotely anticipate how many applications it could have. Garcia and Calantone (2002) highlight that new technology “acts as the catalyst for the emergence of new markets and/or new industries”.

Schumpeter’s famous analysis of technical change (Schumpeter, 1942) highlights that strategic decisions on innovation are based on expected profits due to a temporary competitive advantage originating from a patent or the length of time it will take competitors to imitate the innovation. In the Schumpeterian world the innovation process is the modus operandi driving markets: firms compete through innovation, as it allows them to obtain higher profits than their competitors. As Rosenberg (2001) points out, this simplified model of innovation overlooks the fundamental element of uncertainty associated with new technologies (as we discuss in 2.2 below) and assumes that an innovator firm has only to introduce a new technology into the market for it automatically to increase profits.

Also, the Schumpeterian analysis does not consider the role of market forces in the financial markets. A profit maximizing firm undertakes an inventive effort only if the (discounted) future earnings derived from market demand is likely to exceed the (discounted) R&D costs. R&D investment decisions require finance and so are also crucially driven by perceptions of stock market investors on the potential profits associated with the marketing of new products in development.

Thus market demand drives innovation subject to an expectation of profit on the part of investors given uncertainty, and a recognition that innovation can create a market by introducing products that are so different in character to those currently available that it is difficult for consumers to anticipate the benefits they will derive from them.

2.1.2 Institutional factors

National institutions and structural conditions determine the broad parameters within which innovative activities are carried out. This general institutional environment, which comprises legislative settings, financial institutions and educational systems, affects the innovation process by setting the rules and range of opportunities for innovation (OECD, 1997). Edquist and Johnson (1997) observe that the institutional set-up shapes innovative activities by:

- reducing uncertainty, as it can provide information and increase the degree of economic appropriability of innovation;
managing conflicts and aiding cooperation, as it can ensure stability and respect of societies’ rules, and support the economic restructuring necessitated by high rates of innovation;

- providing incentives, both pecuniary (e.g. wage schemes, tax allowances, intellectual property rights, government subsidies for R&D) and non-pecuniary (e.g. prestige, status);

- introducing obstacles which raise hurdles to innovation, such as rigid rules that have to be observed².

In addition, institutions may help to channel resources to specific areas, in particular through collaborative-sponsored programmes for R&D (Pavitt, 2003)³.

2.1.3 Scientific knowledge

Technological innovation exploits scientific knowledge, which often provides the essential understanding and theoretical basis for research that translates basic science into product or process innovation. Knowledge can suggest possibilities for designing new products, or improving the performance of existing ones, or producing those products at lower costs. However, investment in basic research is in part driven by identifiable gaps in the market place. And there is an element of serendipity as technical needs have influenced and stimulated scientific activity which has led to innovation in unrelated markets. A famous example is Louis Pasteur’s development of the science of bacteriology, which “emerged from his attempt to deal with problems of fermentation and putrefaction in the French wine industry” (Rosenberg, 1982).

2.2 Innovation is an uncertain activity

There are four major kinds of uncertainty in innovative activity:

- whether the scientific challenge can be met;
- the costs of development;
- demand for the innovation;
- the potential for follow-on applications.

Some of these are faced by both the innovator and the final user. We discuss these four elements briefly below.

The innovative process, involving the activities of search and experimentation, entails major uncertainty, so that its outcome cannot easily be anticipated ex ante. Innovators

² Of course if these are of social value then the hurdle may be appropriate and may ultimately stimulate innovation. For example, there is evidence that the introduction of efficacy requirements for pharmaceutical products by the FDA in the 1960s helped to increase the innovative capacity of the US pharmaceutical industry.

³ The Public Private Partnerships to tackle Global Health Problems are examples of these in the area of pharmaceuticals and vaccines.
aim to successfully develop and exploit technical and economic opportunities, the
performance and cost of which cannot be accurately predicted in the early stages of
the innovative process. Even after a new technology has proven to be workable and
has been brought on to the market, it is difficult to forecast its eventual social and
economic impact.

Thus, at the time of launch of a new innovation, the final user also faces an
uncertainty: whether or not the innovation provides the expected benefits. Connected
to the uncertain impact of innovation is “the inability to predict the rate at which
performance improvements and cost reduction can take place, as well as the speed
with which new uses are discovered for new capabilities” (Rosenberg, 2001).
Technological improvements and cost reductions may result in price reductions and
technology diffusion but they may also encourage improvements in products from
older technologies and the introduction of yet newer ones.

The fact that new technologies come on to the market in a primitive form which are
often improved and widely adopted only after its first introduction highlights another
important aspect of innovation: successive improvements. As Lipsey and Carlow
(1998) argue, “major radical innovations never bring new technologies into the world
in a fully developed form. Instead, these technologies first appear in a crude and
embryonic state with only a few specific uses.” The point here is that successive
improvements derive a significant economic impact through the processes of
“learning by doing” and “learning by using”. These can be defined as follows:

- “Learning by doing”, which can occurs at the manufacturing process level as
  workers improve their skills in using a technology to make the product (Arrow,
  1962);

- “Learning by using” improvements, originating from the utilisation of the new
technology by the final user. The importance of this aspect of learning is
particularly important when the scientific knowledge or techniques cannot predict
accurately some performance characteristics (Rosenberg, 1982). For example,
much of the essential knowledge in aircraft design and construction derive from in-
flight learning. Indeed the “extensive use of an aircraft may eventually lead to the
discovery of faults in components or design, as in the discovery of metal fatigue
that lead to considerable loss of life in the Comet, or the unusual resonance that
eventually weakened the engine mounts of the Electra and also led to fatal crashes”
(Rosenberg, 1982).

2.3 Innovation is a cumulative activity – small steps are important too

Complementary to the learning aspects of innovation is its cumulative and iterative
nature. Rosenberg (1982) highlights that “the total growth in productivity takes the
form of a slow and often invisible accretion of individually small improvements in
innovation”.

There is a tendency to associate major innovations with an individual inventor at a
precise date. But that is misleading. It is important to understand the cumulative
impact of the many small improvements that occur over time which help to meet the needs of users better than the early versions of a product. Thus a breakthrough in basic science or in translational research producing a “first in class” product will be followed by additional innovation with very important cumulative impacts. In the case of electric power generation, which has one of the highest rates of growth of total productivity in the twentieth century, Kline and Rosenberg (1986) argue that no single major innovation occurred. Instead, “slow cumulative improvements in the efficiency of centralised thermal power plants have generated enormous long-term increases in fuel economy”.

2.4 **Summarising the characteristics of innovation**

Thus innovation in general is characterised primarily by a drive to meet market needs subject to the requirements to make a commercial return given cost and risk. The institutional environment, including incentives, together with scientific knowledge, play key roles in influencing the amount of innovation that emerges and the market needs that are met. However, in some cases new markets are created. Consumers did not anticipate the potential value of a new product. In others there is serendipity – scientific knowledge pursued for one purpose has spin-off applications in others. And there is an interaction between the science and translational research. Basic science is pursued in many cases to find knowledge that can be translated into innovation that will meet market needs.

Innovation in some cases provides a major departure from established technologies, such as the steam engine, the petrol engine, the telephone, the semiconductor and the jet engine. In most cases however, innovation comprises small but important steps which, cumulatively, lead to major improvements in products within a market. The element of serendipity extends to the benefit of technologies even after initial adoption. Use can lead to the development of knowledge about additional applications which, in some cases, may be more valuable than the initial market application.
3 Characterising innovation in pharmaceuticals

3.1 The drivers

Innovation in the pharmaceutical industry is a complex phenomenon that significantly contributes to society’s wellbeing and health. It involves different stakeholders (including industry, patients, physicians, academics, governments, and third party payers) and its influence is not restricted to the pharmaceutical sector but is crucial for the entire economic and political system.

We have argued that, in general terms, an invention becomes an innovation when it is successfully implemented and adopted in the market place. This implies that consumers, as the final users, have both to value the invention and be willing to pay for it. For pharmaceuticals, however, there is a need to make a distinction between the final user (i.e. the patient) and the payer, as these usually do not coincide, because of the use of third party payer private and social insurance and tax-based systems in many parts of the world. Where third party payers (or doctors as the agents of the payer or of the patient) are the key to adoption then it is their willingness and ability to pay and to use new pharmaceuticals and vaccines that will drive private sector innovation.

In many parts of the world there is medical need but no ability to pay and no third party insurance system. The purpose of this paper is to explore how the private sector can be incentivised to deliver innovation in these circumstances. In this context, the ability to alter the institutional environment by providing incentives will be crucial. We return to these issues in later sections of the report.

In the remainder of this section we explore the relevance to pharmaceuticals of two other key aspects of innovation in general: uncertainty and learning by using; and the cumulative nature of innovation.

3.2 Uncertainty and learning by using

Uncertainty about the ability to generate successful drug and vaccine candidates from scientific research is central to the development process. The costs and failure rates associated with the development process from candidate generation to successful licensing of a product have been well documented, although disputed, and we return to this element in section 5.

Of particular importance to an understanding of innovation in the pharmaceutical market is the process of ‘learning by using’. After a medicine is launched and used in real life settings, two types of improvement can result:

- better use for the original indication;
- additional indications.
Kettler (1998) shows how experience gained after market approval can lead to new or better uses of the same products. There are three main routes:

- new formulations can provide improved safety and efficacy or extend the range of indications in the original therapeutic area;
- there can be an extension of therapeutic areas of use by application of known pharmacological actions;
- there can be unexpected new therapeutic uses discovered mainly by chance.

Gelijns and Moskowitz (2000) reinforce the last point by arguing that innovation in general, and in medicines in particular, involves a high degree of serendipity and creativity which cannot be planned. Thus there is an element of uncertainty not only at the R&D stages but also long after new products are introduced into practice. They argue that many new indications have been discovered only after drugs and devices have been introduced into clinical practice. They show that for the top 20 best-selling drugs in the US in 1993, 40% of their revenues were, by 1995, coming from secondary indications. Pritchard et al. (2001) undertook a similar analysis for the top 50 UK products and found that secondary indications accounted for a smaller but still significant 25% of sales. However, Pritchard et al. find a skewed distribution, with a significant number of products having no subsequent indications and others having very substantial further uses.

For any particular medicine or family of medicines the relevant attributes can change over time, both positively and negatively. The importance of ‘learning by using’ in the pharmaceutical market implies the need for an element of flexibility in any institutional arrangements designed to encourage innovation in order to capture the unexpected medical benefits that are only revealed through market use.

### 3.3 Incremental versus breakthrough innovation – a false dichotomy

Traditionally, in the pharmaceutical industry new medicines have often been referred to as being either a ‘breakthrough’ or a ‘me-too’. Using this classification, a breakthrough or major innovation could be defined as a first agent with a particular clinical action or pharmacological action or the first with the same clinical effect as existing agents but a different mechanism of pharmacological action. Me-too or incremental innovation could then be defined as a follow-on modification in molecular structure or dosage formulation having similar, but not identical, pharmacological action or a different absorption, metabolism or excretion profile.

One of the main problems arising from this binary classification is the pejorative sense the term ‘incremental’ takes. We would caution against classifying innovation in pharmaceuticals and other health technologies using this dichotomy, given its complexity and multi-dimensionality. A broad perspective needs to be taken when evaluating innovation in health care products; otherwise, we run the risk of ignoring some, or all, of the advantages of follow-on products.
The debate around “me too” products has been conducted mainly in relation to developed country markets. Three distinct concerns have tended to be conflated, as to whether:

a. a follow-on product within a therapy class brings any additional benefits to patients or payers;

b. a follow-on product within a therapy class is attracting a price premium that exceeds the value of any additional benefits it will bring;

c. the practice of “evergreening” (where a company is able to obtain an extension to the patent life of a molecule) enables it to prevent generic entry with no additional value to patients or payers.

We explore issue a. in the next section within a general framework for assessing the value of pharmaceutical innovation. We seek to apply this framework in the remaining sections of the report to explore what type of innovation is required to tackle diseases of poverty and how this can be incentivised.

Our view on b. and c. is that they may be issues of limited relevance in low income countries because lack of market demand means that a central role will need to be played by the international community as third party payers or funders of those payers. Their willingness to reward companies will be crucial. We do not consider issues b. and c. further in this paper.

### 3.4 Attributes of pharmaceutical innovation

The innovation attributes we have identified that need to be taken into account in any assessment of the value of innovation in the health care industry can be grouped under three general headings:

- health gains;

- patients’ convenience, either in its own right or because it leads to better patient adherence to treatment (which will often be linked to better health outcomes);

- cost savings or other economic gains.

Figure 3.1 summarises the possible characteristics, or attributes, of innovation.
Figure 3.1 *Characteristics of innovation in pharmaceuticals*

Under the heading ‘health gains’, improvements in any of the following dimensions as a result of introducing a new medicine can imply an innovation:

- health outcomes as compared to existing treatments, which may comprise one or both of quality of life and quantity of life. In the context of developing countries, tackling resistance may be a particularly important source of health gain;

- safety, which here we treat as strictly related to improved side effects and tolerability profiles;

- possibility of better treating one or more different patient subpopulations, which represent the groups at greater risk in developing countries (e.g. children);

Health gains can arise either when a new medicine starts treating a new condition for which there has hitherto been no effective prevention or treatment (i.e. first-in-class) or when it offers some form of additional health gain compared with existing treatments.

‘Patients’ convenience’ (shaded yellow in Figure 3.1) includes any attributes that can lead to better outcomes by improving adherence to treatment and/or which simply lead to greater satisfaction. Examples of such attributes can include new delivery methods of existing molecules (e.g. patches), and enhanced regimens (e.g. shorter duration and/or smaller number of doses); the opportunity for patients to treat
themselves at home instead of having to go to the hospital and/or physician; and special pharmaceutical presentations for children.

‘Releasing other health care resources’ (shaded red in Figure 3.1) is a benefit that accrues mostly to the providers of health care services, rather than to the individual patient, although where the patient is making significant out-of-pocket payments for treatment there may also be benefits to them. Other resources can be freed as a result of the introduction of new medicines, now or in the future through disease prevention and/or slower progression of the condition. If new products enable a change in the way that health care is provided to a group of patients then other resources (including non-health care resources, such as social care) may be released. An example is when medicines reduce hospitalisation costs by reducing lengths of inpatient stays or by eliminating altogether the need for admission.

New medicines can also lead to productivity gains (also shaded red in Figure 3.1) as a result of patients or carers returning faster to work or not missing work at all, or to them being more productive when they are at work. This brings benefits to employers and to the economy as a whole, as well as to patients and carers. It is also important in this context to think of process innovation that may reduce the costs of production of a treatment, so enabling a new version of the technology to be lower priced and thereby releasing resources within the health care system.

Not all new health technologies bring improvements in all dimensions, but it should be emphasised that improvements on any of the dimensions can be socially valuable.

Within a wide perspective, these dimensions could represent targets meant to be achieved through innovative health technologies, including not only pharmaceuticals but also diagnostic tools and vaccines. For example, in the context of developing countries the emergence of resistance to existing treatments could be in principle prevented or reduced by introducing new effective drugs but also by developing new sensitive diagnostic tests which can result in the administration of more appropriate therapies.

We now look at the requirements for innovation to tackle the diseases of poverty using this framework.

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4 The benefits to patients and carers will arise from their ability to build “human capital” (particularly important for young people who would otherwise miss education) and their earnings from employment. In many middle and low income countries there are not social insurance schemes or obligations on employers to provide replacement earnings during absence from work.
4 Innovation for neglected diseases

4.1 Attributes of innovation for neglected diseases

The world’s poorest countries are afflicted by many diseases associated with high level of mortality and/or morbidity but, because of their inability to pay for commercial products, “there is a lack of effective, affordable, or easy to use drug treatments” (Yamey, 2002). These diseases are generally regarded as ‘neglected’ and include conditions such as malaria, tuberculosis, leishmaniasis and African trypanosomiasis. Neglected diseases, also known as ‘diseases of poverty’ and ‘endemic diseases’, have “particular research needs, global public health implications, and market dynamics” but share the urgent need of new and more appropriate treatments (Yamey, 2002). They differ in:

- the loss of disability adjusted life years\(^5\) (DALYs) caused, with some conditions accounting for significant proportion of the global burden of disease (e.g. HIV-AIDS) and others having a public health importance only in some particular parts of the world (e.g. African Trypanosomiasis);
- the geographical areas they occur, e.g. visceral leishmaniasis is prevalent in Bangladesh, India and Nepal, while Chagas disease is endemic in Latin American countries;
- the imperfections of the currently available treatments, e.g. the antimalarial Coartem has been shown to be highly effective but is derived from a relatively costly natural source, while drugs used to treat tuberculosis are effective and inexpensive but require a long treatment course.

Although each condition has specific characteristics requiring targeted solutions, it is possible to use the framework of innovation attributes we have set out in section 3 to categorize the types of innovation required to accomplish the goal of better health outcomes in poor populations. We set this out in Figure 4.1, illustrating with examples from diseases of poverty.

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\(^5\) “WHO, the World Bank and many other organizations have for the past 10 years used and promoted Disability Adjusted Life Years (DALYs) as an integrated measure of mortality and disability. The indicator combines mortality and morbidity into a single measure. One DALY can be thought of as one lost year of ‘healthy’ life and the burden of disease as a measurement of the gap between current health status and an ideal situation where everyone lives into old age free of disease and disability” (WHO, 2004).
Under the heading of ‘health outcomes’, we included the need to develop and introduce effective medicines that may reduce or prevent the emergence of drug resistance. For example, R&D efforts ought to be concentrated on effective products for the treatment of chronic phase of Chagas disease, for which no treatment is available, and malaria, which has become variably resistant to most drug classes used in developing countries, and will in time become resistant to the new Artemisinin Combination Therapies (ACT) now being deployed.

In poor countries, the lack of new and safe products means that patients are still treated with old medicines limited by toxicity and serious side effects. Human African trypanosomiasis (HAT) is a typical example of a condition occurring only in sub-Saharan Africa currently treated with old compounds having serious adverse reaction, i.e. a fifth of patients develop encephalopathy, which is fatal in 50% of cases (Barrett et al., 2003).

As a number of global diseases occurring in developing countries disproportionately affect specific subgroups of patients, there is an urgent need to obtain new products matching these particular patients’ needs. The treatment of HIV-infected children could be simplified and enhanced by developing new and more adequate formulations of existing products, such as breakable or chewable tablets (MSF, 2004). Similarly, alternative formulations to use in pregnancy and in children may reduce substantially the burden of malaria.
To facilitate the implementation of effective medicines and improve patients’ adherence to treatment, appropriate regimes (i.e. smaller and/or few doses) and more convenient modes of administration (i.e. oral rather than injectable drugs) ought to be developed. In particular, the treatment of tuberculosis could be substantially improved by new products reducing the therapy time to four months and requiring less frequent doses (Nwaka and Ridley, 2003).

For innovative medicines to be used routinely in countries facing limited resources, they must be easy to adopt in the health care facilities available in endemic countries. This could in principle result from process innovation, which may lead to reduction of the costs of production, or more general improvements of health technologies, releasing health care resources. For example, the use of the most effective antimalarial combination drug, currently limited by the high cost and shortage of the key ingredient artemether, derived from a Chinese plant, could be facilitated by developing alternative synthetic antimalarials.

Endemic diseases, such as HIV-AIDS and malaria, pose serious threats to economic growth in many countries due to their high mortality and morbidity reducing the quantity and the quality of labour available to contribute to the gross national product. It follows that new vaccines and better therapeutic interventions may lead to improved economic productivity and may thereby help to break the link between poverty and poor health outcomes.

4.2 Choice of case studies

Neglected diseases can be divided into the following categories, suggested by the Commission on Macroeconomics and Health (CMH, 2001):

- diseases with global public health impact and a global market (e.g. HIV/AIDS, pneumonia, and diarrhoeal diseases);
- diseases, predominantly tropical diseases, that have public health importance for the developed world as well as the developing world, but for which the global market is less significant (e.g. tuberculosis, malaria, intestinal parasites and leprosy);
- parasitic diseases of public health importance in the developing world, but of little public health and economic significance in the developed world (e.g. African sleeping sickness, Chagas’ disease, schistosomiasis, lymphatic filariasis, onchocerciasis, and leishmaniasis).

To illustrate the types of innovations required to better treat, and in some cases prevent, neglected disease we have selected three disease case studies, one from each of the CMH categories. These three diseases have been chosen because they account for a significant proportion of the global burden of disease and because we believe they can provide a useful illustration of:
• the limitations of existing treatments;
• how a different profile of products could be beneficial in developing countries compared with the profile needed in developed countries;
• the need for a mix between short term and long term objectives – e.g. between innovation that would improve adherence to existing treatments and innovation that might transform the way the disease is tackled – and a mix of drugs, vaccines and diagnostics;
• the potential impact of different types of incentive on commercial R&D to tackle these diseases.

The infectious diseases on which we are proposing to focus our attention, together with their DALY burdens, are set out in Table 4.1.

Table 4.1 *Burden of selected infectious diseases (WHO, 2004)*

<table>
<thead>
<tr>
<th>Group</th>
<th>Cause</th>
<th>Global (DALYs)</th>
<th>Total</th>
<th>% total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Global impact and global market</td>
<td>Respiratory Infections - pneumococcal disease</td>
<td>94,603,000</td>
<td>6.3%</td>
<td></td>
</tr>
<tr>
<td>2 Global impact and limited global market</td>
<td>Malaria</td>
<td>44,715,596</td>
<td>3.0%</td>
<td></td>
</tr>
<tr>
<td>3 Developing countries impact</td>
<td>Leishmaniasis</td>
<td>2,089,888</td>
<td>0.1%</td>
<td></td>
</tr>
</tbody>
</table>

We now consider in turn the innovation requirements for these three diseases.

### 4.3 Innovation required to tackle ARI and pneumococcal infections

Acute respiratory infections (ARI) are one of the leading causes of death in children under 5 years. It is estimated that 3.9 million people die from ARI annually and 1.9 million of these are young children in low and middle income countries (Williams et al. 2002). The global burden of ARI is estimated at 94,603,000 DALYs and Africa and South-East Asia account for 70% of the total worldwide burden (WHO, 2002).

The bacterium Streptococcus pneumoniae, also called pneumococcus, causes the most severe pneumonia cases (i.e. bacterial pneumonia) and is responsible for a number of other serious systemic infections including meningitis and bacteraemia. While in developed countries the burden of pneumococcal infections occurs among the elderly,
in developing countries the disease is predominant among children. Bacterial pneumonia is associated with substantial mortality among young children not treated with antibiotics, particularly when they are malnourished or have other diseases.

The implementation of standard control programmes is hindered by unfavourable circumstances strictly linked to poverty that include:

- emergence of bacterial resistance to antibiotics;
- increasing numbers of people with chronic disease or HIV infections, who are at high risk of invasive pneumococcal disease. In South Africa, children with HIV infections are 20 to 40 times more at risk of getting pneumococcal pneumonia (pneumoADIP).

In addition, in developing countries large numbers of people do not have access to diagnosis (i.e. chest x-ray) and basic curative health care.

Thus, widespread use of effective pneumococcal vaccine might significantly enhance the treatment of this infection and contribute to the realisation of the United Nations Millennium Development Goals (MDGs) of reducing child mortality. In addition, an alternative diagnostic test might enable more targeted use of existing antibiotics, reducing the growth of resistance, and also encourage research to identify whether alternative existing antibiotics might have applications to the treatment of pneumonia.

### 4.3.1 A new vaccine

A 14-valent pneumococcal polysaccharide (PS) vaccine was licensed in the US in 1977 and a 23-valent PS vaccine in 1983. Although PS vaccines are immunogenic and protective in most adults and children over 5 years of age, they do not protect children under 2 years of age reliably and do not result in immunological memory. These vaccines use capsular PS, which relies on T-cell-independent antigens, and young children lack mature B lymphocytes necessary for T-cell-anybody-mediated immunity (Lucero et al., 2004). The vaccine is currently recommended for patients who have had pneumonia, are at risk of developing pneumonia, or are aged 65 years or above.

Based on the approach of the successful conjugate vaccine for Haemophilus influenzae (Hib), vaccines containing the bacterial polysaccharide conjugated to a carrier protein (PVC) have been developed for the treatment of Streptococcus pneumoniae. A seven-valent PCV manufactured by Wyeth Vaccines was licensed in the US in 2000 for the prevention of paediatric pneumococcal disease. However, it has yet to be routinely adopted to prevent pneumococcal disease in children of developing countries. This is because it has a high price, there is no international vaccine procurement in place, but most importantly it may not work in developing countries as there are about 90 different serotypes of pneumococcus and it has not been tested on strains that appear in these countries.

Several new nine- or 11-valent conjugate vaccines using different carrier proteins are undergoing trials. The serotypes included potentially cover about 70% of developing country serotypes. Several candidates have passed the development phases dealing
with efficacy and immunogenicity. As compared with the Hib conjugate vaccine, PVC has shown to be protective against invasive disease and also to suppress nasopharyngeal carriage of the pathogen. Furthermore, a number of pneumococcal proteins are currently under pre-clinical evaluation as vaccine antigens. This approach could theoretically induce universal protection against pneumococcal disease, regardless of the serotype involved.

One initiative supporting the evaluation and access to new pneumococcal vaccines is the Pneumococcal Vaccine Accelerated Development and Introduction Plan (pneumoADIP), launched by the global alliance for vaccines and immunization (GAVI) in 2003 to facilitate the introduction and the wide adoption of pneumococcal conjugate vaccine in developing countries. The Johns Hopkins Bloomberg School of Public Health, Baltimore, is the host institution.

### 4.3.2 New diagnostic tools and new antibiotics

The most appropriate way to diagnose pneumonia is chest x-ray but the stethoscope analysis and the observation of respiratory rate and breathing patterns remain the most used methods. The main limitations of existing chest x-ray are:

- the need of laboratory facilities, which makes the access to this test particularly difficult in low income regions;
- the low sensitivity of radiological diagnosis as compared to clinical diagnosis, which leads to under-treatment with antibiotics because radiological changes appear later when the disease has progressed to a severer form. On the other hand the clinical diagnosis is highly sensitive but less specific compared to radiological diagnosis when assessing the nature of ambulatory pneumonia (i.e. viral or bacterial), and this leads to overtreatment with antibiotics, when not necessary (interview with Shamim Qazi, WHO).

No public-private partnership is currently involved in the development of new treatments or diagnostic techniques for pneumonia.

### 4.3.3 Summary of the type of innovation needed for ARI and pneumococcal infections

Growing drug resistance could be prevented through the development of new vaccine strategies, able to enhance health outcomes by:

- increasing protection against a high number of pneumococcal serotypes;

and treat better the high-risk subgroup of patients by providing protection in:

- patient suffering from various states of immunodeficiency (e.g. HIV infections);
- young children.
Alternatively, the emergence of resistance to commonly used antibiotics (e.g., penicillin) could be tackled by the development of affordable, simplified and specific diagnostic techniques, which would ideally result in a more appropriate and sensible use of antibiotics (interview with Shamim Qazi, WHO).

Figure 4.2 summarises the key features of innovation required to reduce the burden of ARI.

Figure 4.2: Types of innovation for ARI

4.4 Innovation required to tackle Malaria

Malaria is an infection transmitted by the bite of the anopheline mosquito and caused by four parasite species of the genus Plasmodium, of which two (Plasmodium falciparum and Plasmodium vivax) are responsible for the majority of infections in human beings. In particular, Plasmodium falciparum causes nearly all the fatal cases and accounts to a large extent for the morbidity due to malaria. Malaria parasites have multi-stage life cycles (pre-erythrocyte, blood stage, mosquito stage) in which they express different proteins at different times (Hoffman, 2004). The complexity of the parasite has resulted in uncertainties and great challenges in developing a malaria vaccine.

Although the disease has now been eradicated from large parts of the developed world, malaria still causes 1,124,000 deaths annually (WHO, 2002) and accounts for 300-500 million new infections every year (see Figure 4.3).
Figure 4.3 Worldwide malaria distribution
Different estimates have been provided for the distribution of malaria among age groups: according to the analysis of Snow et al. (2003) 65% of deaths attributable to malaria occur in children under the age of five, while the WHO reports a corresponding figure of 86% (WHO, 2002).

Malaria causes the loss of 45 million DALYs and accounts for 13% of the DALY burden of all infectious diseases. It also has enormous economic consequences. It is a highly debilitating disease causing loss of productivity in the labour force and reduced educational attainment, consequently discouraging local and foreign investment.

Malaria offers an important example of the need to match short term and longer term solutions. The absence of an effective vaccine and the ability of the causative organism to develop resistance to existing therapy represent the main problems of malaria to be tackled. Therefore the short term objective is the development of fixed-dose combinations of existing drugs with improved efficacy. For example, the combination of an artemisinin derivative and mefloquine has been shown to prevent the emergence and spread of drug resistance, and to interrupt the transmission of P. falciparum (Nosten and Brasseur, 2002). An improved diagnostic test would also improve the targeting of therapy and so reduce drug costs and the growth of resistance.

The medium term objective is the development of new molecules belonging to known classes of drugs. These objectives could be coupled with long term goals, which consist of the development of new classes of antimalarial drugs and an effective vaccine. New insecticides would also be of potential value for improved vector control.

### 4.4.1 New insecticides for vector control

After World War II, vector control campaigns using DDT-based insecticides and effective drugs eradicated the disease in Europe, north America and parts of Asia but were not successful in tropical regions, where the effectiveness of control strategies has been hampered by poor health infrastructure and the development of insecticide resistance. Current vector control efforts to prevent human infection and transmission are based on protection methods, including:

- insecticide treated mosquito nets (e.g. impregnated bed nets);
- indoor residual insecticide spraying, although the use of DDT has decreased because of emerging resistance and environmental concerns;
- environmental and biologic management (i.e. reduction of the breeding of mosquitoes and destruction of larvae).

More information is needed on new combinations of insecticides, which may prevent the emergence of resistance. Further work also ought to be concentrated to develop new approaches of applying insecticides to nets that can avoid the need for frequent re-treatments (i.e. long-lasting insecticide nets) (Riopel, 2004).
Whilst there is much to be gained by greater use of existing insecticides, particularly impregnated bed nets, we have been told that there would be substantial benefit from the availability of new insecticides. However, any development of a new insecticide for use to protect humans is likely to be as a secondary use for a product developed primarily for agricultural purposes.

### 4.4.2 New diagnostic tools

**Microscopy examination** is the most appropriate diagnostic tool. It is simple and inexpensive but requires trained laboratory technicians and adequate facilities in order to reach high sensitivity. As a result, malaria is often diagnosed on the basis of **clinical signs and symptoms**, which has frequently led to over-prescription of antimalarial drugs. Other methods have been developed such as rapid diagnostic test (RDTs) that use a dipstick or test strip. The main limitations of these rapid test aids are their short lives in tropical conditions and their variable sensitivity and specificity.

### 4.4.3 New treatments

Antimalarial drugs have proved effective for the treatment of the disease. They can be grouped into the following families:

- blood schizontocides, which include quinoline-containing drugs and artemisinin-type compounds;
- nucleic acid inhibitors, which include antifolates and atovaquone;
- tissue schizontocides, which include primaquine (Guerin et al., 2002).

First-line treatment for uncomplicated falciparium malaria is best provided by oral formulations of artemisinin-based combination therapies, which effectively prevent progression to severe disease and complications, reduce transmissibility, and are well-tolerated. Because of their relatively high cost, access to these effective treatments has so far been denied to most patients in developing countries, where health ministries continue to recommend older drugs that often no longer work. The inexpensive treatments favoured by the largest proportion of endemic countries have shown several serious drawbacks, which have dramatically decreased their clinical effectiveness. For example, **chloroquine** and a combination of sulphadoxine and pyrimethamine (SP) have been largely used in tropical areas but the emergence of widespread resistance has compromised its use in Africa, where treatment failure reaches 80%, as well as in Asia and South America.

Other newer drugs such as **mefloquine** and **atovaquone-proguanil** also have limitations, including side effects which have not been directly documented in African and other poor populations.

Inadequate treatment of uncomplicated malaria can lead to progression to the severe form of the disease, for which injectable or rectal administration is required. Artemisinin derivates are preferred to quinine but they need further assessment.
For the high risk group of pregnant women the WHO recommends intermittent preventive treatment (IPT) based on SP. Emerging resistance to this drug has, however, decreased its efficacy. In addition, pregnant women are excluded for several reasons from clinical trials so that the development of a safe and effective treatment for this group is still a distant prospect.

Plasmodium vivax causes fewer fatal cases but is associated with recurring and debilitating infections. Current treatment relies on a combination of chloroquine, to which it has shown limited resistance, and primaquine. The two-week regimen accounts for high rates of relapse and poor adherence.

The level of R&D activity for new antimalarial drugs is high. It is significantly supported by the public sector (e.g. the US Walter Reed Army Institute of Research), private-public consortia (e.g. WHO/TDR, the Multilateral Initiative for Malaria, and the Medicines for Malaria Venture (MMV)), and the pharmaceutical industry. The current pipeline focuses on the development of:

- new dosing and combination treatments, mainly artemisinin-based, to address the key issue of drug resistance;
- new formulations of existing compounds which are likely to be safe and effective in subgroups of patients;
- new antimalarial drugs.

Advances in knowledge concerning the genetics of Plasmodium falciparum could lead to the identification of new therapeutic targets and antigens for potential vaccine. However, the translation of this knowledge into product development requires huge investments with the risk that worldwide markets may not materialise.

R&D activity for malaria treatment is an attractive investment principally because of the travellers and military markets. At the same time there is a need for the introduction and availability of new therapeutic tools which are directly tailored to the unmet medical needs of developing countries.

4.4.4 A new vaccine

Malaria vaccine can target different stages of the parasite cycle. Current candidates rely on the following approaches:

- prevention of infection (pre-erythrocytic stage), which is the most heavily funded area of research because of its potential use in developed countries (e.g. for travellers, the military, tourists);
- limitation of parasite replication and severe forms of malaria, which could be particularly useful for children and pregnant women in areas of high transmission;
- prevention of the spread of viable parasites to other people, which could decrease the number of infections in low-transmission areas (Hoffman, 2004).
Currently, 25 candidates are in phase I trials, six are in phase IIa, eight are in phase IIb and only two are in phase III. RTS, S/A is the most promising candidate in development. It is based on the Plasmodium falciparum parasite and targets the pre-erythrocytic stage of infection. In the clinical trial involving children aged between one and four living in Mozambique (i.e. phase IIb), the vaccine reduced malaria infections of 30% and the incidence of severe disease by 58% (Alonso et al., 2004). RTS,S/A was initially developed by GlaxoSmithKline and the US Walter Reed Army Institute of Research and then largely supported also by the Malaria Vaccine Initiative. The encouraging results of clinical trials have catalysed the interest of the UK government, which has recently announced its intention to pre-buy 300 million doses of the future vaccine, but it will probably not be possible to bring it into use before 2010.

It is also worth noting that, in the case of malaria, the targeted populations for new treatments and vaccines in developing countries may differ from those for developed countries. As Hoffmann (2004) points out, “most malaria deaths and severe disease in sub-Saharan Africa occur in infants, young children and pregnant women”; therefore “a vaccine would be worthwhile even if it only limited the severity of disease for those most at risk, without preventing infection or moderate disease. Such a vaccine would probably not be very useful for tourists, but would be beneficial in most parts of sub-Saharan Africa” (Hoffman, 2004).

### 4.4.5 Summary of the type of innovation needed for malaria

An effective approach to combat malaria in endemic countries would couple early detection and confirmed diagnosis with the use of combinations of antimalarial drugs as a mechanism to reduce resistance, which represent the main obstacle to malaria control. To deploy this strategy, there is a need to develop:

- sensitive and rapid tests which can be adapted to field situations;
- new combinations of existing drugs with improved dosage methods, packaging and delivery systems promoting patients’ compliance with treatment;
- new formulations of existing drugs to use in children and pregnant women (Guerin et al., 2002).

Improvement of existing treatments should result in delivering more appropriate, affordable and safer antimalarials to the low income populations afflicted by the disease. One approach aimed at reducing the cost of current treatment relying on a costly Chinese plant (artemisinine) would be that of developing synthetic products (interview with Dr Nafo-Traoré, Director, Roll Back Malaria Department, WHO.).

In addition, new targets and molecules should be identified and included in new discovery projects, consolidating the scientific findings into formal development.
Greater financial support and continued efforts are required to develop an affordable vaccine, able to limit infection in young children and/or pregnant women, and reduce transmission within community (Hoffman, 2004).

To prevent human infection and transmission, new and innovative methods of vector control, such as new insecticides preventing resistance and long-lasting insecticide nets, are also needed.

The attributes of innovation described above are represented pictorially in Figure 4.4

Figure 4.4: Types of innovation for malaria

4.5 Innovation required to tackle Leishmaniases

Leishmaniases are a group of parasitic protozal diseases transmitted by the sandfly. There are four major clinical forms of leishmaniasis:

- visceral leishmaniasis (VL),
- mucocutaneous leishmaniasis (ML),
- cutaneous leishmaniasis (CL),
- dermal leishmaniasis, which occurs up to two years after cure of VL.

VL, known as kala azar in India, is a life-threatening disease, endemic in 62 countries and responsible for 41,000 deaths in 2000. It is estimated to cause the loss of
1,980,000 DALYs per year but, because of poor epidemiological data available, this figure probably underestimates the current burden. As shown in Figure 4.5, Bangladesh, India, Nepal, Brazil and Sudan carry the major burden (90% of VL cases occur in these five countries).

Figure 4.5 Distribution and incidence of visceral leishmaniasis

Risk factors for development of VL include:

- malnutrition;
- immunosuppressive drugs;
- HIV co-infection, which may change the epidemiology of the disease.

The diversity of epidemiological cases (i.e. there are 30-100 subclinical infections for every VL case) complicates further the diagnosis, treatment and control of the disease. Other factors, such as the large number of potential hosts, difficult life conditions of afflicted populations, and environmental changes increasing the exposure to sandfly vectors, hinder effective control of VL.

In the case of visceral leishmaniasis (group 3), which is concentrated in Brazil, Sudan, Bangladesh and India, the available technologies for diagnosis are not easily usable in the field, and current treatments (antimonials) suffer from the limitations of resistance, long treatment courses, parenteral administration, and high prices (Guerin at al., 2002).

The use of existing compounds to discover new indications has been shown to be a successful approach to tackle the “most neglected diseases”, and is a strategic approach that both the Special Programme for Research and Training in Tropical Diseases (TDR) and the Drugs for Neglected Disease Initiative (DNDi) have adopted. A collaboration between the Indian government, TDR and the company Zentaris has
resulted in the first effective oral drug for leishmaniasis, miltefosine, which was initially developed and studied as a cancer treatment (DNDi business plan, 2003).

4.5.1 New insecticides for vector control

Vector control strategies are tailored to the two main epidemiologic entities: anthroponotic, when humans are the sole reservoir, and zoonotic, when animals and in particular dogs, are the main sources of infections.

Vector and host control strategies (e.g. animal reservoir control, insecticides, impregnated bed nets) have been important measures to control VL but have been abandoned due to several limitations. For example, residual insecticides were largely used in the past in India because of their efficacy against leishmaniasis vectors and low cost but they are now discontinued because of the growing resistance of sandfly vectors. However, as in the case of malaria discussed above, any development of a new insecticide for use to protect humans is likely to be as a secondary use for a product developed primarily for agricultural purposes.

4.5.2 New diagnostic tools

Current diagnostic procedures include:

- serological techniques adapted for field use (e.g. ELISA and DAT);
- PCR, especially on peripheral-blood samples.

However, there is no commercial source for DAT, no commercial kit for ELISA, and PCR is not easily usable in the field. In addition, the current diagnosis procedures entail invasive tests and cannot easily implemented in poor clinical settings (Guerin et al., 2002).

4.5.3 New treatment

Antimonials have been used since 1940 and are still the first line treatment of VL in most countries. They have established efficacy for treating VL but exhibit the following drawbacks:

- parenteral administration in hospital for 3-4 weeks;
- toxicity in HIV co-infected patients;
- emerging parasite resistance;
- high cost of branded drugs;
- uncertain efficacy and safety of generic drugs.
The antibiotic **amphotericin B** is the current alternative treatment, particularly used in those areas where resistance to antimonial drugs has emerged and for treating HIV-co-infected people. Its limitations are:

- toxicity;
- high cost;
- limited availability.

**Ambisome** is a lipid formulation of amphotericin B and is the most effective drug available. It was developed through the TDR in order to reduce the toxicity of traditional amphotericin B but the high cost limits its use in developing countries.

**Pentamidine**, which is a second-line drug, is progressively being discontinued because of its toxicity and resistance in India (Liu and Lawn, 2004).

A new therapy has been developed. A successful collaboration between the Indian government, TDR and the company Zentaris has resulted in the first effective oral drug for leishmaniasis, **miltefosine**, which was initially developed as a cancer treatment. It was registered for use in India in 2002 and TDR is now promoting its registration in other endemic countries. Phase III trials comparing miltefosine with amphotericin B have been recently completed. Potential threats to the successful use of this drug are:

- risk of rapid development of resistance;
- possible teratogenicity and therefore concerns regarding its administration to women of child-bearing age.

In addition, there are two other new drug developments:

- **Paromomycin** is an effective, well tolerated and cheap drug, the old formulation of which is not longer available. A final phase III trial necessary for the registration of the new formulation of paromomycin, is still ongoing in India and Africa (DNDi, 2003);
- Development of the second oral drug, **sitamaquine** (GSK), has been proceeding, albeit slowly.

4.5.4 **Summary of the type of innovation needed for leishmaniasis**

Many species of sandflies are responsible for the transmission of visceral leishmaniasis (VL). The use of insecticide-impregnated bed nets could ensure personal protection against sandflies bite at night but are limited by the costs of frequent bed nets reimpregnations. Certainly, new practical solutions for the implementation of vector control strategy in endemic countries ought to be identified and translated into the development of innovative tools (e.g. more cost-effective bed nets).
The morbidity and mortality burden of visceral leishmaniasis (VL) is unlikely to change if current therapies continue failing because of high cost, long courses, toxicity and emerging resistance. Controlling VL in endemic countries requires urgently:

- new formulations of existing drugs with more appropriate administration methods (e.g. oral) and shorter treatment duration to enhance patients' convenience;
- new combinations therapy, in particular for miltefosine and paromomycin, which could lead to better health outcomes by preventing resistance and improving efficacy (Guerin et al., 2002; Torreele et al., 2004).

Given the substantial knowledge on the biology and genome of leishmaniases, there is an opportunity to identify and develop new classes of anti-VL drugs as a long-term objective (Wirth, 2001). Similarly, the development of an effective vaccine remains an ambitious programme, which may prove largely difficult and expensive.

Figure 4.6 shows the type of innovation required to tackle VL.

Figure 4.6 *Types of innovation for VL*
5 The Research and Development Process

In the preceding chapters, we have discussed the kinds of innovations that are needed to help reduce the disease burden of neglected diseases. The key question is how to build solutions to achieve these innovations. The starting hypothesis when working in neglected diseases is that they are characterized by market and public “failures”, where incentives and institutions function in ways that do not encourage sufficient attention and investment by either public or private actors to make progress. Solutions are built from this premise, i.e. how to create a more conducive environment for R&D. Prior to moving to the question of how to do R&D more effectively for neglected diseases, we first review how R&D takes place for innovations targeted at “non-neglected” diseases. Understanding who drives what and why in the “traditional” process helps to inform how better to shape processes for neglected diseases.

5.1 Changing boundaries in the conduct of R&D

The post-war model of pharmaceutical R&D was one of ‘in house’ research, development and manufacture by vertically integrated major pharmaceutical companies (Galambos and Sturchio, 1998). Basic research into disease mechanisms had largely taken place in universities. Indeed Cockburn et al. (1999) have argued that ‘random’ screening did not necessarily require a company to understand disease mechanisms, for example injecting hundreds of randomly selected compounds into hypertensive rats in the hopes of finding something that would lower their blood pressure.

This model of the R&D process, with a rigid separation between ‘basic research’ carried out in universities and ‘applied research’ carried out in vertically integrated major pharmaceutical companies, has been changed fundamentally by three major trends. First, there has been a private sector move towards greater collaboration between the public and private sectors in understanding disease mechanisms. This dates from the 1970s, although there are earlier examples. Second there has been a rise of specialist private sector ‘biotech’ companies in the 1980s, often spun off from universities, followed in the 1990s by the rise of companies specialising in ‘genomic’ technologies. Third, we see a trend by major pharmaceutical companies towards subcontracting R&D, sales and manufacturing activities, first within developed countries but increasingly with a trend into middle income countries. The R&D process as set out in Figure 5.1 is therefore now more likely than in the past to involve different organizations at different stages.

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6 The discussion in sections 5.1 to 5.6 draws on Chapter 3 of Kettler and Towse (2002).
Figure 5.1 Major sub-components of R&D activity through to consumption

Genomic databases
- Understanding disease
  - Identifying targets
    - Library
      - Screening compounds
        - Identify lead series
          - Phase I
            - Toxicology
              - Pre-licensing activities
            - Post-launch safety monitoring
          - Secondary manufacture
            - Post-launch medical support
          - Distribution
            - Post-launch medical support
          - Dispensing
            - Patient presentation and diagnosis
          - Prescribing
            - Patient concordance
          - Serial activities
          - Parallel activities
        - Phase II
          - Pharmaceutical development
            - Maintaining GMP
          - Secondary manufacture
            - Licence variations/new indications
          - Primary manufacture
            - Choice of markets
          - Secondary manufacture
            - Pricing
          - Promotion to doctors/patients
          - Patient concordance
        - Phase III
          - Analytical development
            - Post-launch medical support
          - Post-launch medical support
          - Licence variations/new indications
          - Distribution
            - Patient presentation and diagnosis
        - Phase IV
          - Analytical development
            - Licence variations/new indications
          - Secondary manufacture
            - Post-launch medical support
          - Distribution
            - Patient presentation and diagnosis
        - Post-launch medical support
          - Licence variations/new indications
          - Distribution
            - Patient presentation and diagnosis
        - Post-launch safety monitoring
          - Licence variations/new indications
          - Distribution
            - Patient presentation and diagnosis
          - Primary manufacture
            - Choice of markets
          - Secondary manufacture
            - Pricing
          - Promotion to doctors/patients
          - Patient concordance
          - Serial activities
          - Parallel activities
        - Lead candidate
          - Serial activities
          - Parallel activities
          - Lead candidate
          - Serial activities
          - Parallel activities
          - Serial activities
          - Parallel activities
5.2 Changing relationship between the public and private sectors

Evidence on the origins of new drugs helps to shed light on the changing relationship between public and private sectors. Cockburn and Henderson (1997) looked at 21 drugs identified by two experts as 'having had the most impact upon therapeutic practice' between 1965 and 1992. They found that only 24% (six) were developed with no public sector input into the basic or applied research that was necessary to bring the product to the market place, suggesting that public sector research input was usually essential to private sector drug discovery. They noted that the public sector can also be important in providing insight into new uses for existing drugs. Conversely the discovery of an effective compound by the private sector can provide evidence as to how the body works, providing new avenues for basic research in universities into human physiology and molecular biology.

The typical product coming to market in the 1970s and 1980s therefore involved either direct collaboration between the public and private sectors or indirect ‘collaboration’ via the scientific literature, and this collaboration was crucial to the eventual launch of a successful product. The key public science input is in basic research, but the public sector also funds and undertakes applied research. Conversely, the private sector also undertakes basic research where it sees opportunities to capitalise upon it.

Cockburn et al. (1999) noted the move in the 1970s to ‘science-based drug discovery’ or ‘rational’ drug design aimed at taking advantage of increased scientific understanding about the biological basis of disease. Success in applied research became more dependent on an understanding of basic research. To access such information, companies had to encourage their researchers to interact more closely with the scientific community external to the firm. This was a two-way process. For example, the experiments which identify potentially valuable commercial drugs will also tend to be empirical tests of specific (and most likely previously unproven) biological or biochemical theories. Successful participation involved publishing in the scientific literature. Companies became participants in ‘science’, in a wider sense, rather than just users of scientific knowledge.

Cockburn et al. (1999) concluded that a positive publication strategy and the pursuit of basic research in-house were key for companies seeking to build links with publicly funded scientists and so gain access to leading edge understanding of disease mechanisms. This study offers support for the hypothesis that ability to access and interact with the public sector is an important determinant of the productivity of downstream private sector research.

5.3 The impact of the rise of biotech/genomics companies on the R&D process

Henderson et al. (1997) analysed the impact of the revolution in molecular biology on the structure of the pharmaceutical industry and hence on the structure of R&D markets. They noted that only one company – Syntex – the developer of the oral
contraceptive – succeeded in entering the industry in the post-war period prior to the mid 1970s. The passing of the Bayh-Dole Act in the US in 1980 was a crucial factor in altering the R&D landscape by encouraging the commercialisation of products developed with federal government funds. This piece of legislation, in combination with other policies, was instrumental in launching the biotechnology company boom of the early 1980s. At the same time, the revolution in biomedical science and genetics has posed greater threats to the mainstream pharmaceutical industry because of its potential to challenge some of the established industry’s key competences.

One result of the biomedical/genetics revolution has been the use of biotechnology as a production technique, initially on ‘large molecule’ proteins whose therapeutic qualities were well understood. Of the three biotech products that have been major commercial successes (insulin – Genentech and Eli Lilly, erythropoietin – Amgen and Ortho, tPA – Genentech) the first two were recombinant versions of established products. These products helped launch Genentech and Amgen into the top flight of pharmaceutical innovators. As a production technique (the ability to manufacture proteins), biotechnology enabled new companies to enter the pharmaceutical market. This reflected the difficulty of the processes and the lack of relevance of the existing manufacturing competences of pharmaceutical companies.

In conventional ‘small molecule’ synthetic chemical drugs, genetics and molecular biotechnology can be used to enhance the productivity of the discovery process. In this area, new competencies have reinforced the dominance of the more scientifically sophisticated large firms (particularly some of the US, British and Swiss companies) and not destroyed it (Henderson et al., 1997).

Meanwhile, the discovery and development of biotechnology based large molecule drugs has evolved over the past 20 years. This process combines genetics and molecular biotechnology, drawing on competencies not required (or not primary) for new chemical development. An examination of patenting activity shows that new biotech companies accounted for 41% of US origin patents at the European Patent Office in 1987-1993, compared with 38% from established companies and 21% from universities (Kettler, 2000). New biotech companies were initially also more successful in bringing new biological entities (NBEs) to market. Many of these new NBEs were targeted at orphan diseases and the companies were able to leverage the support, infrastructure and incentives provided by the US Orphan Drug Act to get them to market (Kettler, 2000). The Act thus provided a strategy option for small and medium sized companies to target niche markets of little interest to large pharmaceutical companies.

Of 21 NBEs approved for the US market by 1994 only two came from established pharmaceutical companies operating in their own right. Although some large pharmaceutical companies have sophisticated biotechnology capabilities in-house they have yet to emerge as major independent players in the large molecule drug market. However, the number of large molecule drugs that are approved for marketing each year is still small relative to the number of small molecule drugs. For example, the FDA lists 23 New Molecular Entity New Drug Application approvals in the calendar year 2004, compared with four New Biologic License Application approvals.
Incumbents still have the advantage of competence in clinical trials and commercialisation. Exceptionally (e.g. Genentech, Amgen), new biotech companies may become fully integrated major pharmaceutical companies. The trend over time has been for a market for know-how to develop, with start-up firms positioned as upstream suppliers of technology and R&D to established firms.

5.4 The trend to subcontracting

Kay (2001) comments that it is logical for the pharmaceutical industry to follow the publishing and film industries in separating those responsible for origination, those who deal with ‘publishing’ (co-ordination, project selection, finance and marketing) and those taking on the distribution function. He notes that, in pharmaceuticals, origination and publishing may not be as separable as in other sectors but also points out that the traditional arguments for vertical integration – asset and competence specificity – can be achieved by contract within a market place of independent players.

Independently of the rise of biotech and genomic companies there has been a substantial growth in subcontracting by major pharmaceutical companies at many stages of the R&D process. This subcontracting has occurred in each of the stages of clinical development (Phases I, II, III and IV), in toxicology, and, to a lesser extent, in other aspects of non-clinical development (Kettler, 2001). Companies are also increasingly using co-marketing deals and contract field force organisations to ‘rent a sales force’. The emergence of these contract research and manufacturing organisations (CROs and CMOs respectively) raises the issue as to how important the role of ‘integrator’ is and whether it can be replicated by organisations other than the major pharmaceutical companies.

5.5 How important are the competences of large pharmaceutical companies?

Henderson and Cockburn (1996) sought to explore the relationship between R&D and scale, scope, spillovers and research productivity for large pharmaceutical companies, drawing on a dataset covering 38 research programmes in 10 major R&D pharmaceutical companies over a period of up to 30 years. They concluded that large firms have an advantage in the conduct of research in terms of productivity (measured by patents granted in major markets for the years 1961-1988) but that this comes from economies of scope (to do with the output mix) rather than of scale (to do with size). There are spillover effects between programmes within the company.

In another study Henderson and Cockburn (1994) tested for two broad classes of capability that might act as sources of firm advantage (measured in terms of

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7 Genentech was bought by Roche, but not until it had already become a major player. It continues to be run on an arms length basis as a separate company.
significant patents, i.e. those granted in at least two out of three of the USA, Europe and Japan). Using quantitative and qualitative pharmaceutical research data from 10 major US and European pharmaceutical companies for the period 1975-88, they found that locally embedded knowledge and skills enabled a large firm to acquire one or both of a unique disciplinary expertise or a proprietary knowledge of a particular disease area. They call these ‘competences’. Second, integrative capability was significantly positively correlated with research productivity. By integrative capability they meant a company’s ability to make use of its competences by maintaining an extensive flow of information within and across the firm.

Both of these studies suggest that large pharmaceutical companies retain ‘integrator’ or ‘co-ordination’ skills in discovery that are key to delivering products to the market place. We should note, however, that the discovery activities of large pharmaceutical companies have had to change considerably in order to enable companies to survive. They do not necessarily possess inherent R&D competences that cannot be challenged

Nevertheless, there is some agreement that large pharmaceutical companies will retain a major role in the R&D process. According to Henderson et al. (1997), this is because of their continued role in discovery combined with their competences in the management of large-scale clinical trials, in the process of gaining regulatory approval, and in marketing and distribution. Galambos and Sturchio (1998), while arguing that large manufacturers have adapted their in-house R&D capabilities and will therefore continue to be the dominant players in global R&D markets, acknowledge that networks of biotech – pharmaceutical collaboration “will remain important for many years to come”.

Of more enduring importance may be the competences associated with development and commercialization (bringing the end product to market, sales and distribution). These appear to be hard to replicate. In spite of the rise of subcontracting in clinical and non-clinical R&D, in manufacturing and in marketing, there have been few new entries into this end of the pharmaceutical industry (Kettler, 2001). An exception, as we have noted, has been the introduction by biotech companies of orphan drugs to the US market place (Kettler, 2000). However, in the case of orphan drugs, given the small targeted populations, the existence of active patient groups and the tendency for these often severe diseases to require hospital care, the investment these small biotech companies need to make in sales and marketing infrastructure is relatively small compared with products targeted at larger, broader, markets.

5.6 What will the R&D market place look like in future?

On the basis of the evidence they document on changes to the R&D market place and referred to above, Kettler and Towse (2002) express skepticism with regard to the ‘traditional model’, in which the major pharmaceutical companies use alliances and licensing as a ‘stop gap’ to catch up with new technologies.

An alternative ‘dynamic’ model is the specialist division of labour model set out by Pammolli and others (Pammolli and Riccaboni, 2001). This could take the form of
large companies establishing longer term relationships with biotech companies, either by way of long-term, renewable contracts or by acquiring shares. Although this has occurred, a more likely version of the model is a dynamic network. The R&D process might differ depending on the therapeutic category and the product, leading to more short term, project specific, contracting between biotech suppliers and large company customers for innovative ideas and compounds. In some cases this dynamic model may be more virtual with biotech companies developing products on their own, perhaps through collaborations or alliances with each other, sometimes using major pharmaceutical companies, sometimes not, relying on research organisations and contract sales organisations to do work that major pharmaceutical companies have done in the past.

Kettler and Towse (2002) argue that the available evidence supports the second scenario, of a ‘dynamic’ network model of R&D, but with major pharmaceutical companies playing the central (although not exclusive) role in co-ordinating discovery activities and in bringing products through development to market. Major pharma companies are the “nodes” in the network. As Kettler and Towse (2002) point out, however, the way in which R&D is conducted in future will depend on the relative commercial success of different approaches. Rather than suggest there is an evolution from one single model to a different universally applicable model, however, it is more meaningful to think in terms of a number of competing models, with companies employing a combination of approaches depending on the features of the product concerned and on the company’s environment.

At the same time that different organizational approaches are developing, the global scope of the industry is also evolving. Industries that until recently have served primarily their domestic pharmaceutical demand in countries such as India, China and Brazil, are becoming increasingly global.

In India, under the Indian Patent Act of 1970, only process, not product, patents were protected. As a result of this and other institutional aspects of the Indian market, companies have invested little in new product R&D. Instead, Indian companies are engaged in supplying active pharmaceutical ingredients or generic formulations via reverse engineering for drugs either still under patent in the US and Europe or available elsewhere as generics. However, as the Indian government adapts its IP regime to the requirements of TRIPS, and patent protection is established, Indian companies will no longer be allowed to copy on-patent drugs. The most successful (large) companies are already adapting their strategies to move beyond copies of products sold to domestic and developing country markets, to compete for generics markets in the developed world and to invest more in research – building on their in-house chemical capabilities to develop new formulation and new delivery mechanisms for existing compounds and in some cases to undertake R&D for new chemical entities.

A recent DfID commissioned report (Grace, 2004a) states that Indian companies are already planning to devote more of their revenue to this type of activity, with industry leaders, Ranbaxy and Dr Reddys, planning to increase R&D from 6% to more than 10% of sales over the next five years. A conclusion of the Pharma Futures report
(Tickell, 2004) is that the impact of emerging markets on the global pharmaceutical industry has been “significantly underestimated”. This may well lead to investment by the major pharmaceutical companies in these countries with spin off benefits for local companies. Thus a new type of company, based in middle income and low income countries, may also become a participant in the network model for R&D.

5.7 R&D processes for global health

The above sections describe the nature of the R&D process when there is a sufficient market to motivate the private sector to develop new pharmaceuticals. In countries where global diseases are prevalent but purchasing power is insufficient to generate an adequate return on investment, then, as has been well documented, private R&D is far less. For example, in their review of global drug development between 1975 and 1999, Trouiller et al. (2002) found that only 16 of 1,393 new chemical entities marketed in this period were for tropical diseases or tuberculosis. All of these received some public sector support. In terms of the sums invested, the authors report a previous estimate that total public and private investment in drug R&D for malaria, tuberculosis, leishmaniasis and African trypanosomiasis in 1999 was less than $70 million.

While the incentives for the private sector to undertake R&D into tropical diseases have not altered substantially in the last five years, the sums provided by new philanthropic sources have dwarfed those previously invested. For example, Towse et al. (2004) report funding pledges of US$604 million for product development public private partnerships (PD PPPs) to 2007. This type of organization has now become the dominant player in R&D for neglected diseases.

A general trend towards the greater use of PPPs to address global health issues has been highlighted by the work of Buse and Walt (2000a,b,c) and of the research group the Initiative for Public Private Partnerships for Health (IPPPH). From the point of view of Trouiller et al. (2002), the impact of PPPs has been such that they are deemed to “have altered the international health landscape … as a new paradigm for drug development activities”.

PPPs bring together members of civil society, (a category which includes academia, non-governmental organisations (NGOs), philanthropists and other not-for-profits), the public sector (government agencies and inter-government agencies) and the for-profit sector (pharmaceutical companies, biotech companies and other commercial companies from relevant industries). Contracts can be on a “fee for service” basis or a collaboration with an exchange of money to support R&D projects for a pledge by participating companies to make any final products stemming from their collaboration available to patients in the developing world. This might be achieved by the company delivering the product itself or through the transfer of the product to other companies or organisations for delivery and distribution. Companies may also provide “in kind” benefits of access to in-house resources or release key people to participate in PPP activities.
A recent analysis by the Pharmaceutical R&D Policy Project (PRPP) team at the London School of Economics has documented the way in which PPPs have been responsible for most of the increase in neglected diseases activity observed since 2000 (PRPP, 2005a). Of the 63 drugs registered or in development over this period, there is a roughly equal split between those in which small scale enterprises have been involved on a commercial basis (partnering with PPPs (12) or through subcontracting arrangements with PPPs (17)) and those in which big pharmaceutical companies have been involved (30). All of the latter are classified as non-commercial, a minority being developed by big pharmaceutical companies alone (14) rather than within PPPs (16) (see Figure 5.2). Examples of end products being developed under different approaches are:

- Miltefosine for leishmaniasis: small scale commercial company within a TDR initiative;
- Lapdap for malaria: multinational pharmaceutical company with help from a PPP;
- CoArtem: multinational pharmaceutical company alone.

Figure 5.2 PPPs and ‘pure industry’ participation in neglected diseases R&D

Source: PRPP (2005a)
As we note, none of the 63 projects studied was classified as being conducted by a large pharmaceutical company for normal commercial reasons. However, there may be good business reasons for undertaking the work. In the case of CoArtem, Grace (2004b) sees the benefits to Novartis as indicating its global citizenship role with concomitant public relations benefits, although she also comments that part of the company’s motivation was to test out new partner firms, and that the capacity and relationships built up through the development of CoArtem are now being used for other Novartis products. Learning an ability to leverage may not be unusual and is important. Small and large companies collaborating with PPPs also may get commercial spin-off benefits from trying out R&D routes (e.g. new vaccine technologies) in neglected diseases that may have applications in other disease areas for which there is a developed country market.

Although PPPs have assumed a dominant role in the current portfolio of neglected diseases R&D, Figure 5.2 and Appendix 2 show that established pharmaceutical companies have played the dominant role to date in the development and delivery of new licensed products for neglected diseases. It is important to note that the 63 products are almost all in development. The new PPPs have not yet delivered new products onto the market place. Appendix 2 lists the 12 approvals under the Orphan Drug Act targeted at tropical diseases as identified by Kettler (2002); the 16 orphan designations for malaria, tuberculosis and sleeping sickness, with eight product approvals, listed by Milne et al. (2001); and the tropical disease drug development output 1975-1997 of the TDR. In each case the key companies are listed and the importance to date of the large pharmaceutical companies is clear8.

Of course, this R&D effort largely pre-dates the revolution in the organisation of R&D that we outline earlier in this section. The PPPs are bringing in new small company and academic partners and offer encouraging potential. However it has yet to be realised and there are questions about the sustainability of PPP pipelines in terms of funding. Only TDR has succeeded in bringing new products to market, and then in collaboration with the pharmaceutical industry. Moreover, the PRPP indicates that around half of the 55 products in development involve large pharmaceutical companies (10 are large company only and the balance are in collaboration with PPPs).

Evidence from the R&D process for developed country products suggests that large pharmaceutical companies play a key integrative role in the discovery area, and they continue to dominate commercialisation activities. There is evidence from the US orphan drug market that smaller biotech companies are able to bring products to market, but there are particular characteristics of these markets that may not be applicable to PPP target markets. This means that PPPs may have to contract with large companies at some point, or develop substantial in-house co-ordination competencies if they are to manage these stages on a virtual basis.

8 Work in progress by Moran (private correspondence) and Kettler (2002) indicates that a number of these products were developed some time prior to ODA designation and in some cases were already licensed. The use of the ODA was therefore intended to provide new opportunities for extracting value from the products.
We do not see a conflict in principle between supporting PPPs with more funding and seeking to incentivise the private sector. Indeed, there may be limits to the ability of PPPs, as they seek to increase their funding, to engage further big pharmaceutical participation on a non-commercial or semi-commercial basis. We are not surprised by the PRPP finding that large (and small) companies are not involved in neglected disease R&D primarily for direct commercial reasons. It would be surprising if they were given the lack of prospective commercial return. The evidence suggests, however, that large and small companies will undertake some R&D into neglected diseases for a variety of reasons. The issue we address in section 6 is whether appropriate IP and non-IP related incentives will encourage them to invest additional resources in R&D for global health and whether it is efficient for the international community to encourage such developments.
6 Incentive mechanisms for the private sector to engage in neglected diseases R&D

6.1 What will work?

We consider in this section how the private sector might be more effectively engaged in R&D for neglected diseases. We have set out in section 5.7 the historic role of the private sector in bringing products for neglected diseases to market and the role of the PPPs in expanding the development pipeline by harnessing public and private sector resources through subcontracting, and co-development or licensing agreements. We have concluded that commercial incentives have a potential role to play in leveraging greater private sector involvement. This could manifest itself either through greater participation in PPPs or through companies’ own in-house R&D programmes. Thus, additional incentives can be seen as useful either for facilitating the engagement of private sector resources which PPPs need or to encourage independent commercially-based approaches to R&D.

The criteria we propose should be used to assess incentive mechanisms are that they:

- be credible to commercial companies, so that they are likely to respond;
- provide value for money, by which we mean that:
  - the expected social value in terms of global health and related economic benefits generated from the innovation will exceed the (private) price paid to the companies, including the value of the incentive;
  - they are efficient as compared to other mechanisms to achieve the same results;
- can be combined with other measures that are likely to ensure that new products arising from R&D get delivered to patients in the target countries.

We draw on the experience of two existing incentive mechanisms – orphan drug legislation and the paediatric initiative – and the experience of tax incentives. These are discussed in Appendix 3. Appendix 4 presents a discussion of proposed incentive mechanisms. The discussion in this section takes these Appendices as read.

The critical issue is to find measures that create market demand, either as a result of a transferable IP right (whereby undertaking R&D into neglected diseases can give access to a developed country market for a different product which has sales that will provide a return on the R&D expenditure incurred on the neglected disease) or from a purchase (or buy-out) fund specifically created to pay for products arising from R&D into diseases of poverty9. The evidence from the orphan drug and pediatric schemes is that IP (in the form of market exclusivity or patent extensions) where there is market demand does stimulate R&D investment. Public sector procurement of medicines is the norm for much health care in the developed world and clearly stimulates pharmaceutical R&D. However, credibility is a crucial issue and for this reason we do not favour “buy-out” based proposals. We do not think that valuation

9 There is good evidence on the importance of market size for stimulating new drug and vaccine (Finkelstein A, 2003; Lichtenberg FR, Walsfogel J, 2003; Acemoglu D, Linn J, 2003.)
formulae and funding can be established in such a way that companies will regard them as likely to bind donors to provide a commercial return on successful innovation. We therefore conclude that the following “pull” incentives have the greatest potential to generate the innovation needed:

- transferable/roaming intellectual property rights (TIPR), whereby a company is awarded additional IP on a product of its choice in exchange for developing a given neglected disease product. This is likely to attract companies, providing the period of transferable patent extension is set at a level to provide a return on R&D and the rules are clear ex ante, i.e. governments do not retain discretion over how much patent extension to provide. It will achieve value for money if the patent extension is only made available for needed products. This may require more than one tier for length of patent extension depending on the qualifying disease or indication. It will deliver products if the reward is linked to the successful licensing of a product with arrangements to ensure use. This could involve obligations on the company to ensure manufacture (or to provide a license to enable others to organise this) combined with a purchase fund to cover manufacturing and distribution costs. It would in theory be possible to link the patent extension to delivery of the product to patients in developing country markets but this would require a significant increase in any patent extension and separate arrangements make more sense;

- transferable fast track/priority review/accelerated approval (TFT) whereby a company receives more rapid regulatory review for a product of its choice in exchange for developing a neglected disease product (effectively lengthening the period of patent protection for the chosen product). We discuss a version of this approach that is also called Priority Review Voucher (PRV). The performance of this incentive against our three criteria is similar to TIPR. There are two important differences, however. Firstly, each month of the effective patent extension is more valuable because it comes earlier in the life of the product. Secondly there is much greater uncertainty about the length of effective patent life to be obtained. This is because it depends on the difference between fast track and “normal” approval times, which is likely to vary over time;

- advance purchase commitments (APCs) provided through a guaranteed purchase fund. This can be selected for diseases and indications where social value will be high, helping to provide value for money. The reward can be triggered by the delivery of product to developing countries, helping to ensure use. The challenge is to ensure an APC is regarded as a credible commitment by companies. This can be achieved via the use of confidence building measures.

In addition there are two other “push” measures (as well as investment in PPPs) which can be effective in stimulating R&D but which are not sufficient in isolation because they do not create market demand. These are:

- tax credits to subsidise the costs of R&D into neglected diseases;
- grants i.e. public/philanthropic funds to support R&D (outside of the monies given to fund PPPs).

Tax credits are a useful support for those companies with tax liabilities (and so may not be useful to biotechnology companies) but provide little incentive to bring an R&D project to completion when the prospects of being able to cover even the product’s manufacturing costs through sales are limited.

In Appendix 4 we also discuss the TFT proposal from the PRPP. However, this is not strictly a proposal to stimulate private sector R&D into neglected diseases.
The ability to *trade* IP rights within a TIPR or TFT or to trade rights to participate in the APC (if there is some form of pre-qualification) will be important. We have set out in section 5 the dynamic network of actors that comprise the R&D environment. In all three cases it should be possible, for example, for a small biotech company involved in early stage development to sell its product to a larger company after (say) completion of Phase I or Phase II trials. This helps to ensure that the reward is used efficiently, with a range of companies able to undertake R&D in the knowledge that as they make progress they are creating a marketable asset.

It is also important to note that these mechanisms can be used for diagnostics, vaccines and pharmaceuticals. For example, a TIPR for a pharmaceutical could be given for the development of a diagnostic kit meeting relevant regulatory requirements in a target disease area.

Thus our view is that there are three credible options for incentivising the private sector. They are not mutually exclusive and could be regarded as complementary both to each other and to “push” investment in PPPs. They will provide incentives for big and small companies and can be used for pharmaceuticals, vaccines and diagnostics. However, there are differences between them and we now consider:

- some detailed design issues;
- the value for money question;
- their applicability to the types of innovation we have identified in our three case study diseases.

### 6.2 Design Issues

We identified the main elements of the three incentive mechanisms. In doing so we drew on the typology of five design issues identified in Towse and Kettler (2005). Two of these (credibility and ability to ensure delivery) directly map onto two of the three assessment criteria we set out in section 6.1. The other three (setting the price, setting the quality specification, and handling subsequent entrants) relate to the third criterion – does the incentive deliver value for money?

The five criteria and our comparative analysis of how the three incentive mechanisms meet the criteria are set out in Table 6.1 below. Our findings can be summarised as follows:

- **Credibility**: All three deal effectively with the concern of opportunism or time inconsistency. APCs have no track record in delivery yet, whereas extensions of IP are understood by companies. However, TFTs / PRVs have more uncertainty attached to them than TIPR for two reasons. Firstly, their value depends on the difference between fast track and normal review times and on the criteria for fast track. These may change over time. Secondly, TFTs / PRVs offer benefits on drugs which have not yet been launched, as compared to TIPR which rewards products with a proven track record of revenue generation;
• Price: All three only reward success, but all three may reward innovation that companies would have undertaken anyway because they found a compound serendipitously that worked for a neglected disease or because they want a philanthropic element to their portfolio to meet their corporate goals. For an APC the price can be set very specifically. This, however, could give rise to a “ratchet effect” whereby asymmetry of information about the scientific challenge and about the effort committed by the companies could lead to the donors being put under pressure to increase the price. For a TIPR the price is set by the length of the extension, which could be differentiated by the type of innovation, but would need to be specified in advance in the legislation. For a TFT/PRV the extension is determined by the gap between fast track and normal review. A problem for the TIPR is that in delaying generic entry it generates a “deadweight” efficiency loss and an equity issue. However, in most health care systems, where drug costs are met by third party payers and prescribers are not price sensitive, these effects will be minimal;

• Quality specification: All three would require marketing authorisation. The APC would set very specific targets above this. For TFT/PRV and TIPR then the legislation would need to set out the eligible diseases and indications;

• Subsequent entrants: In all three cases better products get used. The APC needs to set rules which balance the need to encourage competition with the need not to undermine the benefits of being first to the market. For the TIPR and TFT/PRV any product meeting the legal criteria gets the reward. This raises the danger of overpaying for some innovation as follow-on products may vary in the additional benefits they bring, but the rewards will not vary;

• Ensuring use: In the case of the APC the company has to deliver the product to recipient countries, not just get it licensed. For a TIPR or a TFT/PRV the company has to assist, for example by offering a free licence, but is not under an obligation to supply as part of the price. Thus a separate fund is required to buy the product at manufacturing cost. In all three cases a health care delivery system is required to get the product to the patients.

The key issues in distinguishing between the three incentives are probably the following:

• The credibility problem for APCs and, to a lesser extent, TFT/PRVs;
• The ability to “fine tune” APCs with respect to price and specification, as compared to TIPR and TFT/PRVs where the levers are cruder;
• The equity and efficiency issues for the TIPR which may make it hard to implement politically, even though they are probably small in impact in practice;
• The danger of an upwards “ratchet effect” on price for the APC. The risk of this will be greater the earlier in the R&D process;
• The need for separate arrangements to ensure manufacture and delivery in the case of the TIPR and TFT/PRV.
Table 6.1. **Design characteristics of the three schemes**

<table>
<thead>
<tr>
<th>Design issue</th>
<th>Advance Purchase Commitment</th>
<th>Transferable Fast Track (PRV)</th>
<th>Transferable IPR</th>
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<tbody>
<tr>
<td><strong>Credibility</strong></td>
<td>· overcomes time inconsistency</td>
<td>· overcomes time inconsistency</td>
<td>· overcomes time inconsistency</td>
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<td></td>
<td>· no track record on delivery</td>
<td>· uncertain value of potential blockbuster</td>
<td>· little uncertainty for manufacturers of potential benefits</td>
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<td></td>
<td></td>
<td>· uncertainty about future regulatory environment</td>
<td>· track record on additional IPR</td>
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<tr>
<td><strong>Setting the price</strong></td>
<td>· only rewards success</td>
<td>· only rewards success</td>
<td>· only rewards success</td>
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<td></td>
<td>· donors set the price</td>
<td>· legislation sets the price/reward</td>
<td>· legislation sets the price/reward</td>
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<td></td>
<td>· rewards serendipitous/philanthropic innovation that may have occurred anyway</td>
<td>· rewards serendipitous/philanthropic innovation that may have occurred anyway</td>
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<tr>
<td></td>
<td>· potential for a “ratchet effect” on price</td>
<td>· additional value of speeding potential blockbuster to market</td>
<td>· deadweight loss due to delayed generic entry</td>
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<td></td>
<td></td>
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<td>· equity issue in terms of who pays</td>
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</table>
### Specification
- Marketing authorization required
- Specification set by donors
- Legislation to set eligible diseases and indications

### Subsequent entrants
- Rules for subsequent entrants
- Difficulty of getting incentives right
- Any product meeting legal criteria
- Better products are used

### Ensuring use
- Company has to deliver product
- May be co-payment
- Need health system to deliver
- Company has to offer free licence
- Fund needed to buy at manufacturing cost
- Need health system to deliver

- Marketing authorization required
- Legislation to set eligible diseases and indications
- Legislation to set eligible diseases and indications
- Marketing authorization required
- Legislation to set eligible diseases and indications
- Legislation to set eligible diseases and indications
6.3 Value for money

All three incentives make similar assumptions about underlying costs and hence the revenues needed to reward companies. They draw on the DiMasi et al. (2003) study of R&D costs and the Grabowski et al. (2002) study on the distribution of returns. These studies suggest that at the time of launch companies need to recover $800m of R&D costs and that revenues with an NPV (discounted back to launch) of some $2.5bn - $3.0bn are needed to provide that R&D recovery. There is nothing to distinguish the three proposals in this respect. All three are subject to challenges that this is too much money. Four main arguments seem to be made as follows:

- Others (such as biotech and emerging market companies) can do the research more cheaply;
- Development costs will be lower because fewer patients will be needed in clinical trials and they will be conducted in developing countries (Towse and Jamison, 2003);
- Others (such as contract manufacturers and emerging market companies) can do the manufacture more cheaply;
- Large companies would have done the R&D anyway for philanthropic (or global citizenship) reasons.

If any or all of these were to be the case then the rewards set under any of the three incentives could be adjusted downwards to reflect this. Providing rewards are transferable, companies will have an incentive to find the most cost-effective ways of undertaking the work.

We do not address directly the question of the value for money of these proposals compared with direct funding of research by means of PPPs or some other “public” route of undertaking research. This is not part of our terms of reference. We would note however, that in any comparison of cost it is important to recognize that:

- the known costs of undertaking successful commercial development are often being compared to an estimate of the costs of using alternative routes which are as yet unproven;
- much of the differences in drug development cost estimates reflect assumptions about the numbers of patients in clinical trials and the location of trials rather than who is doing the trials;
- commercial “pull” incentives provide ex post rewards where the outputs of R&D meet the criteria of the incentive, i.e. these can be set only to reward the development or delivery of usable products. “Push” incentives fund or reward ex ante R&D effort. There is no guarantee that any usable product will emerge from the funding process and the public sector does not have a track record of developing successful pharmaceutical products;

We see incentivising the private sector as a complementary strategy to supporting PPPs.
6.4 Characteristics of innovation needed for neglected diseases

Table 6.2 lists the range of innovations needed in the three diseases we have considered, pneumonia, malaria and visceral leishmaniasis. The features we have chosen to characterize these innovations help us to understand the place of enhanced incentive mechanisms to encourage R&D, are as follows.

- The existence of a global market indicates the extent to which the private sector already has an incentive to invest;
- Science knowledge indicates the extent to which R&D is supported by a good scientific understanding of the disease and of potential targets and promising leads;
- R&D progress indicates the stage of the R&D process at which innovation is required (early or late), and hence the corresponding degree of investment required, which may have a bearing on the appropriate incentive mechanism;
- Private sector capacity indicates whether the private sector is currently investing and therefore the extent to which it already has the skills to respond to incentives;
- PPP involvement indicates whether there is currently expertise which can be drawn on to assist the private sector and whether there is a PPP to act as a potential partner;
- The strength of the access pathway indicates the extent to which there are established mechanisms which can be used for new products, so ensuring they are used.

Thus, for example, in the case of a pneumococcal vaccine there is a developed country market; for a multivalent vaccine the scientific risk is relatively low as one addressing strains of the disease found in developed markets already exists, and the R&D timeline is therefore relatively short; private sector R&D capacity in this area is high, but although there is an ADIP (see section 4.3) there is no PPP to assist in the R&D process. Ease of access is relatively high providing the vaccine can be inserted into the existing regimen of childhood vaccinations in the target countries. A relatively low incentive will be required to get private sector engagement in this area.

By way of contrast, there is no global market for new chemical entities for visceral leishmaniasis; extensive R&D investment will be required to take a product through the development pipeline from early stages, although the underlying scientific challenge is moderate rather than substantial; PPPs exist to assist the process, but existing private sector capability in this area is small; and ensuring access to patients is more difficult. A relatively high incentive will be needed to stimulate private sector involvement in this area.

Our view is that different types of incentives will be suitable for stimulating R&D in different diseases depending on the type of innovation required.
Table 6.2 Characteristics of innovation needed for neglected diseases

<table>
<thead>
<tr>
<th>Health technology</th>
<th>Disease</th>
<th>Global Market</th>
<th>Scientific knowledge</th>
<th>R&amp;D progress</th>
<th>Private sector capacity</th>
<th>PPP involvement</th>
<th>Access pathway</th>
</tr>
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<tbody>
<tr>
<td>Vaccine</td>
<td>Multivalent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>●</td>
<td>●</td>
<td></td>
<td>●</td>
<td>●</td>
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<tr>
<td></td>
<td>Malaria</td>
<td>○</td>
<td>●</td>
<td>○</td>
<td></td>
<td>○</td>
<td>●</td>
</tr>
<tr>
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<td>Pneumonia</td>
<td>●</td>
<td>●</td>
<td>○</td>
<td></td>
<td>○</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td>Malaria</td>
<td>●</td>
<td>●</td>
<td>○</td>
<td></td>
<td>○</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td>VL</td>
<td>○</td>
<td>●</td>
<td>○</td>
<td></td>
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<td>○</td>
</tr>
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<td>Drug</td>
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<td>●</td>
<td>●</td>
<td></td>
<td>●</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Formulations to use in infancy and pregnancy</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
<td>●</td>
<td></td>
</tr>
<tr>
<td></td>
<td>New chemical entities</td>
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<td>●</td>
<td>●</td>
<td></td>
<td>●</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Malaria</td>
<td>○</td>
<td>●</td>
<td>○</td>
<td></td>
<td>●</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VL</td>
<td>○</td>
<td>●</td>
<td>○</td>
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<td>●</td>
<td></td>
</tr>
</tbody>
</table>

● = substantial/significant  ○ = small/limited  ■ = moderate

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6.4 Matching incentives to the challenges

TIPR has an advantage over TFT of providing a more flexible reward than TFT (as the effective additional period of market exclusivity is not limited by existing approval times) and a more predictable reward, given the uncertainty over the length of time by which a fast track process will shorten regulatory approval in future. Therefore, TFT may be better suited to providing an incentive to bringing an R&D project to fruition over the short or medium term, such as – in our case studies – new formulations for malaria and visceral leishmaniasis treatments, working alongside PPPs.

TIPR could be tiered with a short additional patent life option for some types of development and a longer patent extension for others. Such a structure could provide an effective incentive for late stage involvement but might, in addition, provide an incentive to initiate an early stage R&D programme, for example – using our case studies – for malaria or visceral leishmaniasis, where new chemical entities are needed. In principle, this could be an in-house project which a large pharmaceutical company takes from discovery through to regulatory approval, or it could be initiated by a small biotech company in the expectation that as the project progresses it will have a saleable asset, i.e. a large pharmaceutical company will be increasingly prepared to pay to have rights to the product as the probability of it triggering a TIPR increases.

From the policy maker’s point of view, the difficulty is in devising an incentive which is sufficient to incentivise companies to undertake R&D but, at the same time, does not offer an excessive reward. However, it is possible that an incentive of this kind could encourage large pharmaceutical companies to increase their engagement with PPPs, perhaps being more proactive in helping to initiate early stage projects but subsequently handing over to the PPP and possibly re-engaging at the final stages of bringing the project to fruition. Depending on the stage at which the private sector becomes involved, the risks and rewards associated with TIPR could be adjusted accordingly – providing that the rules were spelt out in advance. For example, taking the risk of initiating the discovery stage could be rewarded with a longer period of exclusivity than if the company had taken the project from phase II to completion.

APCs could provide an incentive for the private sector to become engaged at a late or early stage of development. A late stage APC has been suggested for a multivalent pneumococcal vaccine, and has also been proposed in the context of a malaria vaccine. Credibility issues suggest that APCs may initially be most useful at the later stages of development, until the industry has gained confidence in the measure. They may also be useful in incentivising developments of diagnostic tools, where the R&D process is shorter and less expensive. A diagnostic test for malaria that was useable in the field could bring substantial health and cost benefits.

APCs might have greater flexibility compared with TIPR or TFT, with policy makers having greater control over the rewards offered to the private sector, although the risk
6.5 Conclusions

For neglected diseases, there is a spectrum of new innovations we can identify as desirable. There is a need for various types of technology (drugs, vaccines, diagnostics) and for types of research (improving on current technologies, developing new technologies). Given the nature of the R&D process and its uncertainties, the overall message is that not only are there many tools/changes to tools that would be useful but even within a single category of innovation (such as vaccines), our ultimate objective of a safe and highly effective product is likely to be reached through a number of intermediate steps. For example, a vaccine with relatively low effectiveness may have an important contribution to make to controlling a disease as an intermediate step to developing a vaccine with all the characteristics we would ideally want. Therefore, there needs to be an environment which encourages further improvements once an initial technology has been developed.

Designing an effective system of incentives requires us to consider not only the types of innovation needed but also the types of organizations involved in R&D. In pharmaceuticals, innovation is supplied by a dynamic process involving public and private organizations. In general, we have interfaces between research institutions, public laboratories, and large and small companies, each with strengths in one or more aspects of the R&D process. Most of the research in neglected diseases is currently conducted by a range of players through the vehicle of public private partnerships (PPPs) which, on the basis of funding from philanthropic sources, are able to harness the skills of different organisations at different stages of the R&D process. Experience with PPPs to date is that smaller companies have become engaged on commercial terms, either through partnering or sub-contracting, while multinational companies have been involved on a semi-commercial basis, with any payments or prospective rewards unlikely to cover their costs.

To engage companies in undertaking more R&D into diseases of poverty, via collaboration with PPPs or through in-house activity and partnerships with other public and commercial bodies replicating the “dynamic network” approach to R&D that is replacing the traditional model, mechanisms to provide companies with a return for undertaking R&D are needed. Proposed incentives include advance purchase commitments (APCs); transferable intellectual property rights (TIPR); and transferable fast track (TFT).

These proposals have advantages and disadvantages and, since they are so far untried, are of unknown effectiveness. However, experience with orphan drug legislation and the paediatric incentive suggest that IP regimes can incentivise required types of research. To some extent, the ability of the proposed incentive mechanisms will depend on how they are designed. The earlier in the R&D process they are intended to operate, the greater is the risk from the company’s point of view and the greater the difficulty of providing a sufficient but not excessive incentive from the policy maker’s
point of view. A number of issues would need to be resolved before a proposal such as transferable IP could be implemented, such as the period for which an extension of IP is to be granted, and there are important design issues to be resolved in preparing an APC. However, we think there could be major benefits from seeking to implement these incentives.
References


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Wirth D (2001). A harvest not yet repead: genomics to new drugs in Leishmaniasis and trypanosomes. MSF/DNDi Working group

## Appendix 1: list of those interviewed

<table>
<thead>
<tr>
<th>Name</th>
<th>Organisation/Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boris Azais</td>
<td>International Federation of Pharmaceutical Manufacturers’ Associations</td>
</tr>
<tr>
<td>May Chu</td>
<td>World Health Organisation</td>
</tr>
<tr>
<td>Renu Dayal-Drager</td>
<td>World Health Organisation</td>
</tr>
<tr>
<td>Marcos Espinal</td>
<td>World Health Organisation</td>
</tr>
<tr>
<td>Andrew Farlow</td>
<td>Oriel College, University of Oxford</td>
</tr>
<tr>
<td>Henry Grabowski</td>
<td>Duke University</td>
</tr>
<tr>
<td>Janis Lazdins</td>
<td>WHO Special Programme for Research and Training in Tropical Diseases</td>
</tr>
<tr>
<td>Mary Moran</td>
<td>Pharmaceutical R&amp;D Policy Project</td>
</tr>
<tr>
<td>Fatoumata Nafo-Traore</td>
<td>World Health Organisation</td>
</tr>
<tr>
<td>Bernard Pécoul</td>
<td>Drugs for Neglected Diseases Initiative</td>
</tr>
<tr>
<td>Lembit Rägo</td>
<td>World Health Organisation</td>
</tr>
<tr>
<td>Rob Ridley</td>
<td>WHO Special Programme for Research and Training in Tropical Diseases</td>
</tr>
<tr>
<td>Cathy Roth</td>
<td>World Health Organisation</td>
</tr>
<tr>
<td>Shamim Qazi</td>
<td>World Health Organisation</td>
</tr>
</tbody>
</table>
Appendix 2: drugs developed for neglected diseases

Table A2.1 *FDA approved orphan drugs for neglected diseases*

<table>
<thead>
<tr>
<th>Disease</th>
<th>Drug</th>
<th>Sponsor</th>
<th>Designation Date</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>Halofentrine</td>
<td>SKB</td>
<td>November 1991</td>
<td>July 1992</td>
</tr>
<tr>
<td></td>
<td>Mefloquine HCL</td>
<td>HL Roche</td>
<td>April 1988</td>
<td>May 1989</td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td>Liposomal Amphotericin B</td>
<td>Fujisawa</td>
<td>December 1996</td>
<td>August 1997</td>
</tr>
<tr>
<td>Meningitis</td>
<td>Cytarabine liposomal Amphotericin B</td>
<td>DepoTech</td>
<td>June 1993</td>
<td>April 1999</td>
</tr>
<tr>
<td></td>
<td>Liposomal Amphotericin B</td>
<td>Fujisawa</td>
<td>December 1996</td>
<td>August 1997</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Aminosalicylic acid</td>
<td>Jacobsus Pharm Co</td>
<td>February 1992</td>
<td>June 1994</td>
</tr>
<tr>
<td></td>
<td>Rifampin</td>
<td>HMR</td>
<td>December 1985</td>
<td>May 1989</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HMR</td>
<td>June 1995</td>
<td>June 1998</td>
</tr>
<tr>
<td>Trypanosoma</td>
<td>Eflornithine HCL</td>
<td>HMR</td>
<td>April 1986</td>
<td>November 1990</td>
</tr>
<tr>
<td>Leprosy</td>
<td>Clofazimine</td>
<td>Novartis</td>
<td>June 1984</td>
<td>December 1986</td>
</tr>
</tbody>
</table>

Source: Kettler H (2002).

Table A2.2 *Orphan products for TB, malaria and African Sleeping Sickness*

<table>
<thead>
<tr>
<th>Orphan Designation Year</th>
<th>Generic Name</th>
<th>Company</th>
<th>Orphan Approval</th>
<th>Orphan Designated Disease</th>
<th>Disease Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1985</td>
<td>Rifampicin (Rifadin IV)</td>
<td>Marion Merrell Dow; HMR, Aventis</td>
<td>Y (1989)</td>
<td>Tuberculosis treatment where oral form is unfeasible</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rifampicin, isoniazid, prazinamide (Rifater)</td>
<td>Marion Merrell Dow; HMR, Aventis</td>
<td>Y (1984)</td>
<td>Tuberculosis short course treatment</td>
<td></td>
</tr>
<tr>
<td>1986</td>
<td>Eflornithine HCL/DFM (Ornidyl)</td>
<td>Marion Merrell Dow; HMR, Aventis</td>
<td>Y (1990)</td>
<td>Trypanosoma brucei gambiense infection (sleeping sickness)</td>
<td></td>
</tr>
<tr>
<td>1987</td>
<td>Mefloquine HCL (Mephaquin)</td>
<td>Mepha AG (Switz)</td>
<td>Prevention: malaria falciparum chloroquine-resistant</td>
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<td></td>
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<td></td>
<td>Mefloquine HCL (Mephaquin)</td>
<td>Mepha AG (Switz)</td>
<td>Treatment: chloroquine-resistant falciparium malaria</td>
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<td></td>
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<tr>
<td>1988</td>
<td>Aconiazide</td>
<td>Lincoln Diagnostics</td>
<td>Tuberculosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year</td>
<td>Drug Name</td>
<td>Manufacturer</td>
<td>Year</td>
<td>Use Description</td>
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<td>------</td>
<td>-------------------</td>
<td>--------------------------------</td>
<td>------</td>
<td>----------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>1988</td>
<td>Mefloquine HCL</td>
<td>Hoffman-La Roche (USA)</td>
<td>Y (1989)</td>
<td>Prevention: Plasmodium falciparum malaria resistant to other drugs</td>
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<td>1988</td>
<td>Mefloquine HCL</td>
<td>Hoffman-La Roche (USA)</td>
<td>Y (1989)</td>
<td>Treatment: Acute malaria due to Plasmodium falciparum &amp; Vivax</td>
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<td>1991</td>
<td>Halofantrine</td>
<td>SmithKline Beecham (USA); GSK</td>
<td>Y (1992)</td>
<td>Malaria acute mild to mod due p. falciparum/p.vivax</td>
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<td>1992</td>
<td>Aminosalicylic acid</td>
<td>Jacobus Pharmaceutical (USA)</td>
<td>Y (1994)</td>
<td>Tuberculosis infections</td>
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<tr>
<td>1993</td>
<td>Aminosidine</td>
<td>Dr. Thomas Kanyok</td>
<td></td>
<td>Tuberculosis</td>
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<td>1993</td>
<td>Thalidomide</td>
<td>Celgene Corporation (USA)</td>
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<td>Mycobacterial infections due to mycobacterium TB &amp; non-tuberculous mycobacterium</td>
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<td>1994</td>
<td>Sodium dichloroacetate</td>
<td>University of Florida (USA)</td>
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<td>Malaria caused lactic acidosis</td>
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<td>1995</td>
<td>Rifapentine</td>
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<td>Y(1998)</td>
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<td>Artesunate</td>
<td>World Health Organization (Switz)</td>
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<td>1999</td>
<td>Rifalazil</td>
<td>Pathogenesis Corp. (USA)</td>
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<td>Pulmonary tuberculosis</td>
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Source: Milne et al. (2001)
Table A2.3 Tropical disease drug development output 1975-1997

<table>
<thead>
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<th>Drug</th>
<th>Year of registration</th>
<th>Indication</th>
<th>Partners</th>
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<tbody>
<tr>
<td>Praziquantel</td>
<td>1980</td>
<td>Schistosomiasis</td>
<td>Bayer</td>
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<tr>
<td>Mefloquine</td>
<td>1984</td>
<td>Malaria</td>
<td>Hoffman La Roche, WRAIR</td>
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<tr>
<td>Ivermectin</td>
<td>1987</td>
<td>Onchocerciasis</td>
<td>Merck</td>
</tr>
<tr>
<td>Ivermectin</td>
<td>1987</td>
<td>Onchocerciasis</td>
<td>Merck</td>
</tr>
<tr>
<td>Halofantrine</td>
<td>1988</td>
<td>Malaria</td>
<td>Smith Kline Beecham, WRAIR</td>
</tr>
<tr>
<td>Eflornithine</td>
<td>1991</td>
<td>African Tryp.</td>
<td>Marion Merrel Dow</td>
</tr>
<tr>
<td>Liposomal amphotericin B</td>
<td>1994</td>
<td>Leishmaniasis (Kala azar)</td>
<td>NeXstar</td>
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<tr>
<td>Artemether</td>
<td>1997</td>
<td>Malaria</td>
<td>Rhone Poulenc Rorer, Kunming</td>
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<td>Artecest</td>
<td>1999</td>
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<td>Novartis</td>
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<td>Artemether-umefantrine</td>
<td>2000</td>
<td>Malaria</td>
<td>Arteceef, WRAIR, Dutch Min. Dev.</td>
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<tr>
<td>Miltefosine</td>
<td>2002</td>
<td>Leishmaniasis (Kala azar)</td>
<td>Zentaris, Indian CMR</td>
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<td>Chlorproguanil-dapsone</td>
<td>2003</td>
<td>Malaria</td>
<td>Glaxo Smith Kline, DFID</td>
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Source: [www.who.int/tdr/about/products/registration.htm](http://www.who.int/tdr/about/products/registration.htm), adapted from Pécout et al. (1999)
Appendix 3: Evidence on established incentives

A3.1 Orphan drugs

Orphan drug legislation works primarily through the provision of extended market exclusivity for the orphan indication. In the USA, the “most sought after incentive” of the 1983 Orphan Drug Act, according to the FDA, is its seven year market exclusivity period (Grabowski, 2003). In Europe, the market exclusivity component of the orphan drug regulations adopted in 2000 is similarly regarded as “by far the most important” of the incentives on offer (de Varax et al., 2004).

The provisions of the US Orphan Drug Act mean that the FDA “cannot approve a marketing application for the same orphan drug that treats the same orphan condition for seven years from the date of approval of the first orphan application, even in the absence of a patent” (Milne et al. 2001). In Europe, a ten year period of market exclusivity is awarded. The 1993 Japanese orphan drug scheme also provides a market exclusivity incentive. Details of all three systems are presented in Kettler (2000).

Grabowski (2003) argues that the seven year period of exclusivity has been an important market incentive for biopharmaceutical companies, some of whose products are not eligible for a patent on the molecule as they are natural substances. It has also been important for some older chemical entities which were found to be useful for orphan indications. He reports that, as of May 2003, the FDA had granted 1238 orphan drug designations, of which 238 had received marketing approval. This is a 10 fold increase on the pre-ODA rate of development of orphan drugs.

However, of these 238, only 5% (12 approvals) were targeted at tropical diseases (Kettler, 2002). Nevertheless, Milne et al. (2001) consider that the US ODA “has contributed significantly to the current medical armamentarium for the neglected diseases”. They refer to 16 orphan designations for malaria, tuberculosis and sleeping sickness, with eight product approvals, the off-label use of another five orphan drugs in malaria and sleeping sickness, and 20 orphan approvals for AIDS treatment.

As Milne et al. (2001) point out, market-based incentives may work well in some neglected diseases such as malaria, for which a market in prophylaxis for travelers in the developed world exists, while others, such as HAT, are less attractive to the private sector. They therefore propose a number of modifications to orphan drug legislation in the US and Europe, including “transferable market exclusivity for the development of new molecular entities, and expanded market exclusivity for new indications of existing products”. Emphasis is placed on creating a more favourable environment for the private sector to engage in R&D for neglected diseases, given its importance in health R&D generally. They envisage this incentive forming part of a package of measures, some of which are viewed as attractive to larger companies (pull and regulatory measures) while others are needed by small companies (push measures).

Overall, the evidence is that orphan drug incentives do result in new products for orphan diseases. A number of products for neglected diseases have been given orphan
designations and, in some cases, approvals. These are listed in Appendix 2. However they have not been developed in response to the orphan incentive (Kettler, 2002). As Milne et al. note, orphan status is not sufficient to stimulate effort for neglected diseases. The market in the developed world will not provide a commercial return. They recommend transferability, so that those developing a drug or vaccine for an orphan disease can obtain market exclusivity or a related IP reward on a product for which there is a developed world market. We return to this in Appendix 4.

A3.2 The paediatric incentive

To date, market exclusivity in relation to developments in paediatrics is provided only in the US, although draft legislation is currently being considered in the European Union. Under the paediatric exclusivity incentive, enshrined in the FDA Modernisation Act (FDAMA) of 1997, testing of patented drugs in children is rewarded by the granting of a period of six months compound specific market exclusivity on all approved indications for the compound from the date of patent expiry. The scheme therefore provides an additional period of exclusivity in adult uses and applies even if no benefit is demonstrated in children. In other words the reward is for doing the work, i.e. for finding out if the treatment works for children, not for finding a drug that does work in children.

As an indication of the impact of the paediatric exclusivity incentive, Milne (2001) estimates a potential trebling in the number of ongoing paediatric clinical trials compared with the situation prior to the introduction of the incentive. The incentive has been effective in stimulating research into the effectiveness of treatments for children. Whilst companies have an incentive to develop new formulations specifically for children where the trial results are positive, we note that the market exclusivity incentive applies to all indications for the product and not simply for any new paediatric indication. Indeed the number of new paediatric indications is more limited than the number of extensions. This illustrates the potential effectiveness of exclusivity which is transferable beyond the new indication being sought. In effect the prospect of an IP extension on the adult indication is incentivising companies to do the clinical and related research necessary to explore the potential benefit of the product for children.

A3.3 R&D tax credits

For a comprehensive review of the evidence on fiscal incentives for R&D in all industries in OECD countries see Hall and Van Reenen (2000). They find that they are effective – with a $ of tax credit leading to a $ of extra R&D. However, this is in a context in which there is a market for the products of the R&D.

The US Orphan Drug Act provides an example of an R&D tax credit, a 50% tax credit being available on clinical trials for orphan drug indications undertaken in the US. However, as we noted above, the prevailing view is that pull incentives are crucial. R&D tax credits are likely to have an impact but there has to be a market.
Appendix 4: Other incentive mechanisms

A4.1 Transferable/roaming exclusivity

As we noted above, enhanced market exclusivity on a product developed for a neglected disease is likely to provide a weak incentive in developing countries given the lack of purchasing power in countries where these diseases are prevalent. A much stronger incentive would be provided if companies were able to transfer patent rights from the neglected disease product to a developed world product. Kremer (2000a, 2001) attributes this idea to Jonathan Mann, the founding director of the WHO Global Program on AIDS, who suggested compensating the developer of an HIV vaccine with a ten year patent extension on another drug. Milne et al. (2001) noted in their work for the WHO Commission on Macroeconomics and Health that the UK government’s Performance and Innovation Unit (PIU, 2001) had proposed an international roaming exclusivity.

Roaming or transferable patent exclusivity as discussed by Grabowski (2003) and Towse and Renowden (2004) would allow companies to benefit from an extended period of patent life for a product of their choice for a specified period in high income markets in exchange for developing and obtaining market approval for a neglected disease in poor countries. A list of qualifying disease categories would be prepared by a group of experts, which would also approve applications from companies for special neglected disease designations. Once designation had been achieved, the reward would automatically follow once the success criteria had been met. Thus, upon approval of the product by a regulatory body (or whatever trigger was set) the firm would receive the transfer of exclusivity rights in the participating developed country’s market.

Towse and Renowden (2004), exploring the feasibility of an EU incentive noted that transferable intellectual property rights (TIPR) could, in theory, be triggered by reaching different stages of the R&D process short of distributing the product (e.g. development work or by obtaining a licence from the regulatory authority or by distributing the product in a developing country.) In addition, they identify three types of non-patent intellectual property protection which could be used in the EU as the basis for transferable exclusivity:

- data exclusivity – in the EU there is an eight year period of data exclusivity from receiving the marketing authorisation for the first indication for a product. During this time, others cannot use the innovator’s data to make an abridged application for a generic version of the product;
- market exclusivity – compound specific market exclusivity can be given following the period of data exclusivity, in effect the licensing authorities are not able to licence a generic;
- supplementary protection certificates – currently the EU provides up to five years compound specific market exclusivity to compensate for the loss of effective patent life caused by a long development and authorisation process.
With a TIPR triggered by licensing, there is little contractual reason for the company to consider how the product is actually utilized. Assuming that an additional purchase mechanism is required to buy the manufactured product and so make the product accessible, care needs to be taken to ensure that R&D is not being rewarded twice, once through the extended IP rights and once through payments for the product itself. One option would be for property rights for the new product, or at least for the developing country indication, to be relinquished (transferred rather than simply transferable property rights). To provide a sufficient incentive, TIPR could be organized in such a way that not all the reward is at the end, that is, there could be interim rewards (analogous to research prizes) for making progress towards a goal. However, this removes any obligation on the company to assist in ensuring the product is manufactured and does reach target patient groups.

**How much TIPR is needed?**

Towse and Renowden (2004) look at the Di Masi et al. (2003) numbers on the costs of undertaking R&D for new drugs which suggest that the average pre-tax cost of new drug development was around $800m (in year 2000 dollars) for a cohort of drugs coming to the US market around 1997. This figure included the costs of failures, and an opportunity cost of capital of 11%. In other words, the out-of-pocket costs were around $400m and a further $400m represented the required return for having capital tied up in drug development for a period of up to 12 years.

They note that the cost of developing a drug or vaccine for use in less developed countries may be lower than that if failure rates were lower or trial costs were lower. It is not obvious why failure rates will be lower. However, trial costs might be. An analysis of estimates by two PPPs (Towse and Jamison) notes their assumptions that patient numbers might be substantially lower (below 2,000 patients as compared to over 5,000 patients in the Di Masi et al. numbers) and also that trial costs per patient in less developed countries may be much lower, though this might not take account of the infrastructure costs of developing capabilities for undertaking clinical trials in developing countries. On the basis of these patient numbers and costs per patient, the cost of drug development would be around $400m, taking account of failures, with the out-of-pocket share of this being around $200m.

Towse and Renowden (2004) note that R&D costs may now be higher than the Di Masi et al. figures. Di Masi et al. found R&D costs rising in real terms (i.e. above the rate of inflation) by approximately 7% per annum. This would mean that the $800m cost would be $1,285m in 2004 (in year 2000 dollars). Thus they conclude that average R&D costs including the opportunity cost of capital for achieving an EMEA licence could therefore range between $400m – $1,285m (in year 2000 dollars).

The opportunity cost of R&D effort may be higher (or lower) than the opportunity cost of capital number of 11% used by Di Masi et al. and reflected in the numbers above. This may be because the cost of funds has changed from the Di Masi et al.
calculation or because there is a constraint on R&D investment which means that there is a higher hurdle rate for R&D investment within the company than the cost of capital. Some R&D investment may also offer higher returns because it offers synergies with other programmes. An “isolated” or self standing poverty related or neglected disease R&D programme may offer fewer potential spillover benefits into other company programmes. Towse and Renownden do not explore these issues further, but note that there is a great deal of uncertainty about the cost of R&D.

To answer the question “how big an incentive is needed?” Towse and Renownden (2004) compare the opportunity cost of developing a new drug with the profit stream from a “blockbuster” drug that might be given the TIPR. There are three elements to the profit stream calculation:

(i) sales revenue per annum. They use the IMS figures for the top 10 selling drugs in the EU in 2002. These show only 2 drugs with sales over €1bn, 4 with sales between €400m and €1bn, and four with sales below €400m. Returns are highly skewed;

(ii) the gross margin, i.e. the proportion of sales revenue that is available to cover the fixed costs of the business and provide a return to shareholders. This will vary by drug depending on manufacturing cost and they did not have a basis for making estimates at this stage;

(iii) what happens to the product after patent expiry. Generic entry is variable in its speed and effect in different European markets. In many countries generic entry is swift and significant for major products. However, if patent expiry makes little difference to the value of sales in some European markets, then the value of a TIPR is reduced and a longer period is needed to provide a significant incentive.

Towse and Renownden set out in Box 1 some indicative calculations for the length of IP extension that would be required using the figures of $400m, $800m and $1285m for R&D cost set out in section 5.1 above. The figures are adjusted to 2004 dollars and converted to Euros at the exchange rates of 0.80€:1$. They vary gross margin and sales gain from TIPR to give an indication of the potential variability in the estimates of the length of TIPR required.

12 Di Masi et al. used a variant of the conventional capital asset pricing model approach to arrive at a risk premium to add to the risk free rate of return.
13 Strictly, companies are assuming a shadow price for R&D resources which is above the cost of capital. Logically they would exploit all opportunities for which expected returns exceeded the cost of capital, but this may not happen in practice because of a scarcity of resource.
14 Grabowski and Vernon (2000) have numbers for the US market that also show highly skewed returns by product.
Box 1: Illustrative estimates of the required length of additional Exclusivity

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimate of cost</td>
<td>€350m</td>
<td>€700m</td>
<td>€1130m</td>
</tr>
<tr>
<td>Estimate of gross margin</td>
<td>60%</td>
<td>55%</td>
<td>50%</td>
</tr>
<tr>
<td>Estimate of TIPR annual sales gain</td>
<td>€600m</td>
<td>€500m</td>
<td>€400m</td>
</tr>
<tr>
<td>Years of TIPR required</td>
<td>1.0</td>
<td>2.5</td>
<td>5.7</td>
</tr>
</tbody>
</table>

The indicative results suggest a potential sixfold difference in the period of exclusivity required depending on the assumptions made. Clearly, were discussions on the TIPR to progress then work would be required to obtain much more robust estimates of these and other key variables.

Different types of drugs and vaccines or different diseases may require different levels of R&D effort and have different success rates, related to scientific complexity. For example, a combination product or reformulated product may require much less effort than a breakthrough “first in class” product. Should they get the same length of transferable exclusivity?

Thus it may be appropriate to differentiate rewards according to either the degree of innovativeness or the type of disease. For example, with two disease lists, and two degrees of innovativeness (e.g. combination / reformulation versus any other type of innovation), then four possible TIPR lengths would be available.

Again there is a trade-off. It is important to keep the incentive clear and simple to understand. This suggests having one benefit triggered by achieving one hurdle. If there were to be any differentiation, Towse and Renowden (2004) argue strongly that there would have to be transparency in the reward available before companies committed R&D effort. Creating uncertainty by having a committee vet the value of the innovation or the effort expended by the company once the product had been submitted for an EMEA licence would significantly reduce the incentive value of any TIPR.

Towse and Renowden conclude that:

- TIPR is a powerful “pull” incentive to undertake R&D into neglected diseases;
- It can be implemented in the EU via an extension of data exclusivity, market exclusivity, or SPCs;

15 Of course in some cases, combination products may generate enormous social value.
16 It would probably not be sensible to include in the degree of innovativeness any reference to the number of therapies already available in a class as, ex ante, companies undertaking R&D will generally not know whether they will be first in class or a follower product. Evidence suggests that follower products usually have substantial therapeutic value, and in some cases supplant the first entrant as the product most valued by prescribers.
Access to the TIPR is probably most effectively triggered by obtaining an EMEA licence for a qualifying neglected disease;

Indicative calculations suggest additional IP protection of between 1 year and 6 years may be required, depending on assumptions about R&D and opportunity costs, margins and sales revenues. More work is needed to clarify these assumptions;

It may make sense to have different lengths of exclusivity depending whether the medicine is a product line extension or a new molecular entity, and perhaps also on the nature of the disease. However there is a case for simplicity and so having one single period;

Full tradability of the TIPR is essential if the R&D benefits are to be maximized;

EU pharmaceutical markets are already distorted by Member State measures. Introducing a TIPR will not add to the overall distortions;

TIPR cannot be funded from development rather than health care budgets, although Member States could make offsetting adjustments to health care programmes or as between tax and social insurance rates;

Any sunset clause in the legislation (providing for a review point) would need to be accompanied by a guarantee that R&D programmes already underway would continue to attract a TIPR on the terms in force when the programme began.

Although Towse and Renowden (2004) look at the EU, there is no reason in principle why a TIPR could not also operate in the US and Japanese markets. If the same product was able to trigger a TIPR in each of the EU, US and Japan then a much shorter period of additional IP would be needed in each individual market than the Towse and Renowden estimates of 1–6 years for the EU alone.

Kremer (2001) has argued against TIPR on the basis that the cost of innovation is inequitably borne by patients in need of the treatment for which the period of market exclusivity has been extended. This hits at the political feasibility of introducing such a measure. This point is also made by Ridley et al. (2005) who point out that the TIPR would delay access to generic drugs and thus raise average drug prices and insurance or tax premiums compared to what they would otherwise have been. As well as the transfer of income there will also be a “deadweight loss” at the margin, as patients change behaviour as a consequence of the prices being higher than would otherwise have been the case. However, they note that deadweight loss would be mitigated by pharmaceutical insurance. In reality most drug costs are met by third party payers who are less likely to change behaviour and moreover who could in principle be compensated from the relevant government aid budget.
Critics of TIPR have also pointed out that it breaks the link between the quality of the innovation and the size of the compensation. There is a danger that companies undertake the minimal R&D necessary in order to cross the threshold and trigger the reward. This makes it important to ensure that relevant diseases and indications are specified in detail in such a way that products that trigger the reward are those for which social value exceeds the cost of the incentive. It may also make sense to provide different periods of TIPR for different categories of innovation. However, it will be necessary to specify qualifying products and periods of exclusivity ex ante so that companies do not face uncertainty as to the likely period of exclusivity they will receive if they are successful in getting a product to registration. This may be difficult to do in the case of “follow on” products. For example, the first malaria vaccine to get an EMEA licence might trigger a full TIPR, but subsequent vaccines should only do so if they are better than the incumbent vaccine in some way and so offer additional health gain. Critics argue that it is all too difficult. At the point where they are simple enough to be feasible and workable, TIPRs risk incentivising relatively low-innovation, relatively high-cost products. On the other hand, they argue, a TIPR designed to incentivise high-innovation products in priority health areas – the desired goal – is likely to be so complex as to be unworkable for stakeholders, and for industry in particular. This is in part an empirical issue where work could be done to define disease and cost categories and to draw up rules to tackle rewards for “follow on” products.

This problem is related to another – which is that the earning of a TIPR involves developing but not manufacturing the product. There is no guarantee that the product will be made and distributed to patients. A separate fund is required to purchase and distribute the manufactured product. The company could be required to make a licence available so that it could be made by generic companies, but these companies would still need to be paid. Of course, one option would be to require companies to manufacture a number of doses. However, this would require a longer period of additional IP protection which would be difficult to set as the required number of doses would vary depending on the product, indication and disease. There is a related problem that cumulative IP extensions become progressively less valuable to companies because the market place may have changed and the product to which the longer TIPR is being transferred may no longer be so successful.

TIPR is also criticised as a measure for big companies. However, providing the TIPR is tradable this criticism is misplaced – small companies can undertake R&D in the knowledge that TIPR has created a market for their products. The ability to trade the TIPR in the market is important from an efficiency point of view because those who stand to gain most (have the most commercially valuable pharmaceuticals) are not necessarily the best placed to engage in the development of needed vaccines or drugs.

A4.2 Transferable Fast Track and Priority Review Vouchers

Ridley et al (2005) observe that many orphan drugs are eligible for priority review, accelerated approval and fast track status by the FDA. Priority review, the objective of which is to review new drug and biologics applications in six months or less, is
reserved for new drugs which provide a significant improvement in safety or effectiveness, and most orphan drugs qualify. It does not entail lower standards for safety and efficacy, simply that the FDA commits the resources to analyse the data in six months. Accelerated approval is intended to speed the approval of new treatments for serious or life-threatening diseases and allows approval to be granted at the earliest phase of development at which safety and efficacy can reasonably be established. Fast track designation for drugs with the potential to address unmet medical needs for serious or life-threatening conditions can take advantage of accelerated approval based on surrogate endpoints, rolling submissions of applications for marketing approval and priority review.

A transferable fast track would provide an option for the firm of electing for a priority review for a product designated for standard review. The average time to review a non-priority application by the FDA is 18 months compared with six months for priority drugs.

Ridley et al. (2005) propose a “Priority Review Voucher” (PRV). Companies that developed a treatment for a neglected disease would get a transferable voucher for priority review at the FDA for a different drug. The voucher would be triggered by getting FDA approval for a product for an indication linked to a neglected disease. The company would be required to freely license the product so that it could be made by a generic manufacturer. As in the case of the TIPR discussed above, a separate fund would be needed to purchase and distribute the product to patients in poor countries.

Ridley et al. estimate that the cost to the FDA of priority review is $1million and this cost would be levied as a charge on the voucher holder. It speeds up review time by a year Berndt et al. (2004). Research by Grabowski et al. (2002) showed the NPV of a top decile drug was $2.7 billion (in 2002 $) which the authors equate to $3.2 billion in 2004 $. The potential value of getting to market 12 months earlier is therefore $357m in 2004 dollars\(^\text{17}\). This calculation is based on the assumption that patent life does not change (because of the Waxman Hatch extension) so the benefit is getting sales a year earlier at each point in the life cycle.

They assume that the costs of drug development are below the $802m of the Di Masi et al. (2003) calculation because:

- the manufacturer qualifies for tax credits on clinical development;
- the manufacturer gets goodwill from R&D spending on neglected diseases;
- only one pivotal Phase III trial might be needed (or combined Phase II / III trial), rather than the two Phase III trials normally required;
- R&D into infectious diseases has a higher probability of success and shorter development time than other therapeutic indications, because of the greater

\(^{17}\) The additional expected producer surplus from changing from standard to priority review status is as follows: \(pp - ps = \frac{(1+r)\left((ts-tp)/12\right)-1}{r}\) where \(r\) is the discount rate, \(ts\) is the median approval time for standard drugs, \(tp\) is the median approval time for priority drugs, and \(V\) is the expected net present value of the product in 2004 dollars.
understanding of the molecular basis of the pathogens as a result of scientific advance;

- of the possible ability to exploit benefits from BioShield initiatives (which can be thought of as externalities or economies of scope depending on whether these are internal or external to the firm).

However, if necessary multiples of PRVs could be awarded depending on whether 12 months is regarded as too much or too little reward. The authors note that the PRV could be combined with other incentive mechanisms.

An important issue in the TFT is the efficiency of allowing transferable fast track to products that would not automatically have received fast track status. There is a strong incentive on companies to seek to transfer a PRV to a potential blockbuster drug. This is efficient. If pharmaceutical markets are working then the best selling medicines are the ones that bring the most value to patients. This does of course raise the issue as to why such a medicine is not given priority review status in its own right? It may lay outside of the criteria because lack of resources forces the FDA to have a narrow definition, or because the company has a (correct) view of its high value that is not reflected in the FDA definition which is based on perceived scientific importance.

There is an issue of uncertainty around the potential value of the reward because:

- companies do not know how the regime may change over time (in terms of what qualifies for fast track status) and how many months expedited review is worth (i.e. what is happening to the timelines on normal, unexpedited, review;
- companies do not know how successful their products are going to be when they are launched.

The PRPP (2005b) propose a variant of this (a Fast Track Option or FTO) whereby fast track is auctioned and so used to raise revenues from the private sector. However, whilst this has powerful revenue raising potential it does not provide an incentive for the private sector to engage in R&D for neglected diseases and so is strictly outside of our terms of reference. It is making implicit assumptions about the efficiency of a “push” approach. It is however, helpful to set out the basic elements and assumptions of the proposed approach, which is as follows:

- the PRPP argues that it is more efficient to target incentives at lower cost R&D models, including PD-PPPs and SMEs with “modest commercial aims.” Thus an FTO should not be aimed at offering rewards to incentivise large companies. We discuss this element of the PRPPs findings, based on its analysis of current R&D projects for neglected diseases, in chapter 5 of our paper;
- TFT or FTO is therefore a revenue raising exercise. It would provide the regulatory benefits the FDA currently offers under fast track (including scientific advice on trial design) but not the “R&D short cuts” of “unproven surrogate end points or smaller trials to establish efficacy and safety”;
- because it included regulatory advice it had the potential to cut clinical development time by 2 years as well as cutting approval time by 1 year, giving a total time of 3 years;
the EMEA could offer FTO as well as the FDA;
FTOs could be auctioned at 1-2 per year to raise money;
it can be used at any point by companies. They don’t have to have (or have rights to) a product for a neglected disease;
it delivers new drugs for developed country patients more quickly, so producing health benefits.

It is worth making a comment on the auctioning element of the proposal because parallels can be drawn with the assumption that is often made in each of TIPR, APC and TFT proposals that big companies will buy products for neglected diseases at various stages of clinical development from smaller companies. The state of the market for these “intermediate research outcomes” will depend on supply and demand. In the case of a predictable annual auction of FTOs there is a possibility that the market will be less than perfect because of the small number of companies involved.

A4.3 Advance Purchase Commitments

A purchase guarantee (Towse and Kettler, 2005; Grabowski, 2003) would entail the establishment of a fund to purchase a pre-determined amount of a new product meeting a given therapeutic profile for a neglected disease. The commitment would allow for a reasonable return on expected R&D outlays. This proposal has been extensively discussed in the context of vaccines by Kremer (2000b) and recently the UK government has proposed the advance purchase of a malaria vaccine via the establishment of an International Finance Facility (IFF) to help alleviate global poverty. The issues around putting a commitment into practice are summarised in Towse and Kettler (2005) who conclude that advance purchase commitments are, in principle, high-powered incentives to develop drugs and vaccines for diseases of poverty and should be tried, although design issues have to be addressed. A report by Barder et al. from the Center for Global Development (2005) has set out a prototype scheme.

Defining what we mean by “advance purchase”

There are two senses in which purchase commitments could be made in “advance”:

- Firstly, as an “advance contract” in terms of a multi-year commitment to purchase;
- Secondly, as an “advance contract” in terms of a commitment to purchase a product which does not yet exist.

The first could involve the use of agents such as the Global Fund for AIDS, Tuberculosis and Malaria or the Global Alliance for Vaccines and Immunisation (GAVI) to make longer term commitments to purchase current treatments. This would

18 The remainder of the discussion of APCs in this Appendix draws on both work for DfID undertaken by one of the authors and on the Towse and Kettler (2005) analysis.
enable investments in manufacturing capacity to be more readily justified by companies competing for contracts. Increasing the use of “advance” multi-year commitments to purchase existing products would be very valuable in expanding access to existing products. As this is not part of our brief we do not consider this element of advance purchase further.

If companies saw these purchases as a signal that future (new) products would also be purchased, then there would be an incentive to invest in additional R&D. Companies would still want to be sure that they would achieve a return on their investment comparable to that achievable on their marketed drugs, and would be concerned that once the product had been developed the fund would be concerned with purchasing at as low a price as possible. This is known as the “time inconsistency” problem, because decisions on the part of companies and purchasers are made at different times and there is significant sunk investment, giving rise to the potential for opportunistic behaviour. Once pharmaceutical companies have made the R&D investments necessary to develop health technologies, governments and aid institutions often use their powers as dominant purchasers and arbiters of intellectual property rights to keep prices close to marginal cost in the interest of increasing access to life-saving products from limited budgets. Because, however, the largest part of the industry’s expenditures lies in the initial R&D cost, prices that cover the (typically modest) variable costs of production will not enable companies to recover their R&D investment, thereby deterring industry from investing in such R&D in the first place. Contracting mechanisms that overcome this problem are required if private sector investment is sought.

The second way of using purchase guarantees is therefore as a form of purchase commitment that is made specifically to incentivise the development of new technologies. Commitments must be credible enough to spur substantial R&D over long periods of time to generate candidate products which may or may not survive the product development pipeline and eventually make it to market. As we will discuss, care needs to be taken in how to construct contracts which are legally binding, yet only pay for useful products and pay in proportion to how useful the product is.

In advance purchase commitments, sponsors commit – in advance of product development and licensure – to fully or partially finance purchases of health technologies for poor countries at a pre-specified price. A financially (and otherwise) credible programme sponsor or coalition of sponsors would sign a contract underwriting a guaranteed price for the supplier. Poor countries would decide whether to buy a product at a low and affordable price (say, $1 per treatment), and sponsors would guarantee to top-up to a guaranteed price (say, $15 per treatment) – thus providing market returns for the developer which are comparable to other products. Once the full number of treatments has been purchased at the guaranteed price, the supplier would, in return, be committed to selling further treatments at an affordable price in the long term. The sponsors could retain the right to seek alternative suppliers at the end of the guaranteed price contract period. Although not part of the contract, there would be nothing to stop the original sponsors or other donors from covering the $1 price on behalf of poor countries at the time of purchase.
The advance purchase commitment structure as recommended in the CGD report is presented in Figure A4.1.

**Figure A4.1 Example structure of an advance purchase commitment**

<table>
<thead>
<tr>
<th><strong>Advance market commitment</strong></th>
<th><strong>Example for malaria vaccine</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Legally binding contracts, enforceable by law</td>
<td>Offer made by a group of sponsors</td>
</tr>
<tr>
<td>Total market value approximately equal to sales revenues earned by average new medicines</td>
<td>Total market size of $3 billion (net present value, 2004 dollars)</td>
</tr>
<tr>
<td>Sponsors under-write a specific price</td>
<td>$15 per treatment (e.g. $5 per dose for 3 doses)</td>
</tr>
<tr>
<td>Price guarantee applies to a maximum number of treatments</td>
<td>Guarantee for first 200 million treatments</td>
</tr>
<tr>
<td>Treatments sold in eligible countries</td>
<td>Vaccine Fund eligible countries</td>
</tr>
<tr>
<td>In return, the developer guarantees to sell subsequent treatments at a low price</td>
<td>$1 per treatment</td>
</tr>
<tr>
<td>Recipient country makes a co-payment for the products they buy (or asks a donor to do so)</td>
<td>$1.00 paid by recipient, $14.00 paid by sponsors</td>
</tr>
<tr>
<td>Successful developers receive $15 per treatment sold.</td>
<td></td>
</tr>
<tr>
<td>Subsequent products are also eligible for the guaranteed price, if superior to existing</td>
<td></td>
</tr>
<tr>
<td>products – as developing countries can switch their demand to these subsequent, superior</td>
<td></td>
</tr>
<tr>
<td>products.</td>
<td></td>
</tr>
</tbody>
</table>

An Independent Adjudication Committee oversees the arrangement.

Source: Barder et al (2005)

For firms, this type of advance purchase arrangement would reduce economic uncertainty and give investors confidence about the returns they can expect if the relevant scientific challenges are overcome. Advance purchase commitments would not eliminate all risk to developers – the scientific challenge and risks, as in markets for diseases in rich countries, would be considerable and the risk of failure high - but advance purchase commitments would greatly reduce the risks specific to markets for diseases concentrated in poor countries (such as the time-inconsistency problem, and the lack of purchasing power).

In the short-term, access is facilitated through donor purchasers at the higher, pre-specified purchase price. In the long-term, financially sustainable access to these technologies is facilitated through the contract provision which requires developers to commit to drop the price to a low level (close to marginal cost) after all high-price purchases have been made.

Several design issues are critical for advance purchase commitments. Towse and Kettler (2005) set out five design issues that need to be addressed in developing an advance purchase commitment:
• Establishing credibility;
• Setting the price;
• The quality specification;
• Dealing with improved follow-on products;
• Ensuring the products get used.

_Credibility_

A key issue with advance purchase commitments is that the contracts must be credible. Legal precedents suggest that such contracts are enforceable by contract law and existing legal institutions. The sponsors must have credible financial backing – such as developed country governments and well-endowed foundations.

_Setting the price_

Perhaps the most difficult challenge is that of setting price and volume in advance. Too high a price would result in a waste of public finances, but too low a price may result in no company response at all.

Drugs are a risky business and sales are highly skewed. Seventy per cent of drugs do not recover the average cost of R&D; the 30% that do gain significant profit margins for the company (Grabowski et al., 2002). In the case of an APC, the price must provide an expectation of revenues that cover the expected costs, including those of failures, and provide a return on R&D investment should the company succeed. Expected revenues will depend, in turn, on expected volumes, the price offered and the probability of winning the APC. To set the price, the agent must have some understanding of the state of the science and the regulatory process faced by participating companies (hence of expected costs and failure rates), and take a position on the number of entrants it wishes to see undertake the R&D.

For the case of a malaria vaccine, the CDG report estimates that a purchase commitment of $3.1 billion (comparable to the average revenue for existing commercial products) would cost an estimated $15 per life-year saved – very cost effective compared to other health or development expenditures. It uses the Berndt et al. (2005) estimate of a cost close to $3 billion in 2004 $. They take as a benchmark the need to earn the NPV achieved by the 70th – 80th percentile of recently launched products, adjusting for lower marketing costs (by 10%). This is above the average product (which has an NPV adjusted for lower marketing costs of $2.56bn), which they regard as a conservative estimate. The higher figure is preferred because a malaria vaccine may be harder to develop than a typical NCE. These figures are pre-tax and gross of production and distribution cost.

_The quality specification_

The APC must clearly specify what kind of product it will pay for and what milestones the company producing the product must achieve to win the contract.
For a drug or vaccine against a disease of poverty, given that the focus on health impact is delivered and used products, not just approved ones, the product specifications may go beyond efficacy and safety to include characteristics specific to particular regions such as cost, treatment regime (duration and number of doses) and delivery mechanisms.

The agent could offer a range of prices, depending on what the company develops and delivers, effectively awarding a bonus for products that exceed specifications.

**Dealing with improved follow-on products**

Given the scientific challenges and the low likelihood that the first product to market will meet all of the needs of the targeted patients, even if it meets the product specifications, the APC should be designed to encourage competition in R&D and to reward subsequent products, while recognizing the impact that this approach will have on incentives. This approach means that advance purchase commitments could potentially lead to duplication of R&D activities if companies are competing for the contract and it is possible to construct theoretical examples in which advance purchase commitments could lead to excessive duplication of research. However, it is often appropriate to pursue many different leads simultaneously in searching for solutions to important problems. It is not clear therefore that this is a problem.

Commitments will therefore need to cover the case in which more than one vaccine is developed. The rules should be set with several objectives in mind: first, fashioning incentives to appropriately reward development of the initial vaccine; second, creating incentives to improve on the original vaccine; and third, delivering the best available vaccines to patients. For example, from the standpoint of society as a whole, it is not a good use of resources to encourage development of second products that are different but not superior for use. We can note that the US Orphan Drug Act allows market exclusivity for “follow on” products if they can demonstrate superior efficacy or safety.

The terms of eligibility to win the APC could require that companies provide upfront disclosure of their intent to undertake research. With this information, the agent and the other companies will know which and how many companies are in the field.

**Ensuring delivery**

A focused effort is required that includes the agent, the company and other global and local stakeholders, working with countries in advance of product approval to ensure that the countries are prepared to take up products approved for purchase.

The CGD proposal uses a co-payment to incentivise manufacturers and countries to get the product to patients. The company has a price guarantee and only gets revenue if the product is bought by the recipient countries. It has a strong incentive to work with countries to ensure take up of the product. If countries pay the co-payment, they then have a strong incentive to ensure the product gets used.
A purchase commitment should ideally only pay for a product if there is demand for that product. This requires manufacturers, sponsors and recipient countries to work together to take the steps necessary to ensure that the product is be delivered to those who need it – thus ensuring that sponsors do not find themselves legally obliged to purchase a product that nobody wants. However, companies are unlikely to want to bear the burden of marketing these products in regions and through systems they know little about. So linking their reward to what they are able to sell is likely to dramatically weaken the incentive. That said, the agent cannot be seen to be paying a company for products that sit on a shelf or in a warehouse.

An advance purchase commitment could use a revenue (or price and quantity) guarantee. That is, rather than simply committing to a guaranteed minimum price for a desired product, sponsors could commit to how many treatments would be bought from each supplier at this price.

In a revenue guarantee scheme, manufacturers of qualifying products would be guaranteed all – or, if there are multiple qualifying products, a portion – of the sponsor’s financial commitment, regardless of whether the products are actually used. This has the benefit of reducing the demand risk for manufacturers, which is an important benefit for pharmaceutical companies in light of the existing deficiencies in the forecasting and procurement systems in many poor countries.

The critical issue is who bears risk. Credibility in commitment is necessary given the time consistency problem. That is, the contract cannot allow sponsors to renege. On the other hand, companies have to deliver high-quality products that countries want to use. We can note that a “front loaded” pricing structure (whereby the price guarantee starts very high and comes down slowly so earlier volume sales generate higher profits) can provide some insulation against quantity risk.

Should incentives be announced early or late in the R&D process?

Some critics argue advance purchase commitments are more well-suited for late-stage products (such as a rotavirus vaccine, which is very close to market) than for early-stage products (such as a malaria vaccine, for which extensive R&D is still required). This is because of the scientific uncertainty involved at early stages which may make it harder to set the guaranteed price and risk a “ratchet effect”, whereby companies complain if the price is too low given the scientific challenges and the specification of the product required, but not if it is high. On the other hand, there are strong arguments that advance purchase commitments would be useful for early-stage products. For any given size of commitment (in terms of the amount of money and end product purchases), announcing earlier rather than later will align incentives earlier, and accelerate R&D efforts towards the end goal of a useable product which is suitable for use in poor countries. If the price is seen as “high” then greater R&D effort will be stimulated. This should bring forward the launch of a new product and/or increase the likelihood of follow-on products with better performance being available soon after the launch of the first product. Both of these effects would increase the health gain generated by the contract commitment.
Towse and Kettler argue for establishing a purchase commitment for diseases with products already at a late stage of development for which the science and economics (i.e. costs and probability of success) are well understood and the time to market (or failure) is relatively short. This will provide an opportunity for the donors to commit to purchase, recipients to commit to use and companies to respond with the desired product.

What products – vaccine, drugs, diagnostics?

To date, most work on advance purchase commitments has been applied to vaccines – in part due to a number of other challenges which arise in thinking about their application to drug treatments. Because of this, it is likely that the critical design issues involved with advance purchase commitments can most easily be dealt with for the case of vaccines.

Advance purchase commitments may well be able to be applied to diagnostics, but this would require additional analysis. Applying advance purchase commitments to drug treatments would require additional consideration of issues such as:

- The degree of out-of-pocket purchase of the drug, which will reduce the size of the price guarantee needed;
- How the emergence of any side-effects will be dealt with. These may not be known for several years after the launch of the drug;
- As some drugs already exist for most diseases, the specification of any commitment for a drug would need to be very carefully defined to avoid the risk of creating an incentive to develop new therapies that are only slightly better than existing ones and so not worth the price guarantee. For example, advance purchase commitments for artemisinin-based combination therapies (ACTs) may well create inefficient incentives to develop new ACTs that are only slightly better than existing products;
- Because drug resistance is more likely to develop than vaccine resistance, it may make sense for new drugs (for malaria or tuberculosis, for example) to be initially restricted to patients who have strains of diseases resistant to mainstream treatment. Thus, a program providing a price guarantee but requiring use to give the company a return could potentially cause a counterproductive shift toward widespread early use.

It seems likely that these problems could be addressed through careful programme design, but these issues would have to be carefully thought through.

Which firms would be expected to respond to advance purchase commitments?

In general, market incentives such as those provided by advance-purchase commitments allow biotechs, pharmaceutical firms, and emerging market suppliers to create whatever R&D structures they believe will be most effective. Rather than having sponsors dictate which R&D set-ups (or divisions of labor) between pharmaceutical firms, biotechs, and emerging market suppliers would be most
effective, this open structure allows the firms (which have much more information) to make these decisions and arrangements themselves.

The only way to know for certain how firms would react is to implement an advance-purchase commitment and observe what happens. The CGD working group conducted structured consultations for the case of vaccines. These suggest that for products at an early stage, for example, an advance-purchase commitment may initially motivate biotechs and potentially the venture capitalists which provide their funding, while some larger multinational pharmaceutical firms may get involved only after further advances in the science, perhaps led by biotech firms. This theme is also supported by anecdotal evidence that biotechs responded more enthusiastically than big pharmaceutical companies to orphan drug incentives and the BioShield incentives in the US. BIO Ventures for Global Health (a Bill and Melinda Gates Foundation-funded agency designed to get biotech companies involved in neglected disease research) is a strong supporter of advance-purchase commitments.

The expected response to an advance-purchase commitment from either biotechs or pharmaceutical firms may depend on whether the commitment is for an early- or late-stage product, but the general picture is that an advance-purchase commitment is likely to generate a response from biotechs and other early-stage researchers by creating a market sufficient to stimulate investment. Biotechs would be more willing to invest because they would be more confident that they would attract interest from pharmaceutical companies for the products they develop. There is considerable evidence that firms do, in fact, respond to market signals by adjusting their R&D to reflect the size of the potential market (see Acemoglu and Linn 2004).

The emerging market vaccine supplier consulted by CGD particularly welcomed the proposal. Although they lack the financial backing of large pharmaceutical companies, emerging market suppliers bring considerable expertise in developing country diseases, and might have a comparative advantage, for example, in managing clinical trials in developing countries. Unlike some incentives which would primarily benefit large and profitable pharmaceutical companies (e.g. US tax credits, transferable patents), all firms would be in a position to compete for the market offered by the commitment. One advantage of the open framework of an advance-purchase commitment is that any firm capable of producing innovations can benefit, and it might well be that the developing country innovators are among the primary beneficiaries.

Criticisms of Advance Purchase Commitments

Farlow (2005) makes a number of criticisms of APCs. Many of his detailed points relate to the specifics of the Barder et al (2005) proposal and to analysis by Kremer, (http://www.pm.gov.uk/files/pdf/Appendix%203.pdf) and Kremer and Glennerster (2004). However, a number of his concerns have more general application. The main concern he expresses is that “early stage” APCs involve too much risk. This is because of the:
- Degree of uncertainty about the underlying science;
- Complexity of patents on upstream technologies, leading to secrecy, lack of information sharing, and difficulties in getting access to necessary technologies;
- Intractibility of the “time inconsistency” problem. The degree of scientific uncertainty requires ex post discretion, hence reintroduces the chance for donors to behave opportunistically;
- Difficulty of setting an efficient price and quality level.

We have set out these concerns in our discussion of setting price above. The consequence he foresees is of a ratcheting up of price.

His other main concern are:

- The length of the commitment period. Farlow implies that the commitment is “forever”. Strictly, however, the APC could be set up with a sunset clause. If progress was not made, then the offer would expire;
- Use of the private sector involves a high cost of capital. This means that much of the contract funding is going to reward “capital costs”. Farlow calculates that with a long enough development period and a high enough cost of capital then a $6.25bn APC could go to a company that had invested as little as $200m in out-of-pocket R&D expenditure. The basic point here is that the cost of capital faced by the private sector is higher than that faced by the public sector. Engaging the private sector involves paying this higher cost. Two points need to be made. The first is that the reason the public sector has a lower cost of capital is because of its tax raising power (or ownership of monopolies where prices can be raised). High risk projects can be funded using low borrowing rates because if the projects fail the agency undertaking them is subsidised by the rest of the public sector. The risk is still there, and is borne by tax payers, but it is pooled and so hidden. The second point is that the private sector may have a better success rate which more than compensates for the higher cost of capital;
- Biotech companies will find it hard to compete for an APC because they do not have the resources to sustain a full development programme. However, as we discuss in section 5 of the paper, there is a market for deals between big and small companies at each stage of the R&D process. The existence of the APC means there is a de facto market for intermediate research outcomes. A small company can sell promising leads in a neglected disease covered by an APC in the same way that they would sell leads in a major developed country therapy area such as cancer or heart disease;
- Development costs may be lower than the $800m for drugs in developed countries. This is true and price will need to take account of likely efficient development costs;
- In practice there will be few competitors and this will raise the likely cost because of their ability to bargain. This may be more likely with a late stage APC. If the social value relative to cost is not positive then the APC should not be initiated by donors;
• The problem of “crowding out.” In other words how does the APC interact with other initiatives such as PPP “push” funding? If a PPP is working in a disease area then companies not working with the PPP will view it as a competitor. Those working with the PPP will in effect have some of their R&D costs met via PPP “push” funding. In both cases the genuinely new R&D stimulated by the APC is less than might be expected – in the one case because the incentive properties of the APC are reduced due to fears that the PPP will win the race, in the other because the “push” measure was funding some of the R&D anyway. Our view is that no exact offset formula can be found to eliminate all crowding out. This is an inevitable problem in any public policy area where more than one policy instrument is used to achieve the same objective. However, mechanisms can be found to minimise it. For example, a successful company can be required to compensate a PPP or donors where “push” funding has assisted development, or the APC value may take account of expected “push” funding. Where the PPP is competing for the APC the reduced private sector R&D impact should be offset by the potential saving if the PPP wins the APC (assuming the donors have a “clawback” clause that covers public as well as private bodies that win using other sources of donor finance).

• Crowding out may also occur in the sense that companies may reduce philanthropic investment elsewhere in order to focus on APCs or donors may reduce funding for R&D into other diseases. However, this in part reflects the essence of priority setting. If the APCs are not in key priority areas there is a problem. The whole point of priority setting is to “crowd out” less important areas of activity.

• It is not sensible for companies to bear the demand risk, as they are not well equipped to do this. We are inclined to agree with this and have argued above for a revenue commitment, i.e. the donors take on the volume risk.

• It is difficult to get the right quality, in particular to reward follow-on products that offer higher quality products. Our view is that it should be possible to set an effective quality threshold, and that the terms of the APC must allow for superior quality follow-on products to be used. Farlow makes the important point that there may not be enough money left in the initial APC to reward the R&D involved in developing some of the superior follow-on products. This is quite possible, as the commitment is only designed to generate at least one product that meets the quality threshold. Clearly a view would have to be taken by the donors as to whether they wished to finance follow-on products with additional money. This would be a separate investment decision from the original APC.

Many of Farlow’s concerns are around the asymmetry of information between the donors and the companies working on the project and the IP / commercial incentives to keep information secret. It is important to recognise that many of these problems are present in the two alternative models Farlow implicitly has in mind:

• A “normal” market. Here prices tend to reflect potential value rather than cost. (They may be above or below an average cost including R&D – Di Masi et al found that 70% of NCEs had revenues that did not cover R&D costs.)
Companies are not, however, able to keep research ideas private to themselves. As we discuss in Section 5 of the main paper, there are spillover effects and also evidence that the most successful companies encourage their scientists to publish. Patenting itself reveals information to competitors. It is intended to – that is the trade off, the knowledge is put in the public domain in exchange for proprietorial rights to use it;

- Public sector “push” funding of R&D. Here institutions compete for R&D funding, presumably on the relative progress they are able to make. There is a real danger of institutions hanging on to projects rather than killing them and “hypping up” results in order to attract more funding. There is still an assymetry of information – this time between the donors and the research institutions. This is a problem faced by donors in relation to PPPs. Here it makes sense for donors to use a portfolio approach (Towse et al, 2004) and manage PPPs on pipeline results. Where donors fund research institutions individually it becomes much harder. The analogy is with venture capitalists who have to develop milestone setting approaches. If these are not met then no more funding is supplied. Information disclosure for peer review scrutiny will help of course, but it may be selective. Farlow’s preferred model is the Global HIV Vaccine Enterprise with its “open source” logic of sharing out tasks and sharing results. He also cites the discovery of the Human Genome as a collaborative effort, but the reality of that exercise was that competition from the private sector seeking commercial uses for genes stimulated the public/foundation financed activity to work much harder and more quickly. However, whilst Farlow critiques the potential failings of APCs he does not apply the same rigour in looking at the potential weaknesses of public sector “push” funding and non-IP based forms of collaboration such as “open source”.

Farlow’s overall conclusions are that more work needs to be done on APCs to understand the costs, benefits and risk, and that late stage APCs will involve less risk than early stage ones. We agree with these overall conclusions, but, as we set out above, only with some of his specific points.

Conclusions

The work done to date suggests that advance purchase commitments offer an opportunity to funnel the energy of the private sector into developing products needed by the world’s poorest countries. If no products are development, no donor funds would be spent. If successful, millions of lives would be saved at a very low cost. For the case of a malaria vaccine, the CDG report estimates that a purchase commitment of $3.1 billion (comparable to the average revenue for existing commercial products) would cost an estimated $15 per life-year saved. Such a figure is very cost effective compared to many other health or development expenditures.

There are several critical issues that need to be considered when thinking about whether and how to move ahead with advance purchase commitments. Further and more targeted analytic work by governments, industry and public health experts is needed on several key topics.
Priorities for further work include:

- Developing long-term advance market commitments with producers of products that will be available in the near future, using the commitment to negotiate on price, timing of supply, and characteristics of the products and their presentation;
- For products that are at an early stage:
  - Considering the specific issues with respect to individual diseases (such as the likely demand from high-income and middle-income markets)
  - Validating estimates of the market size needed to induce private sector investment in R&D, using alternative datasets for market revenues;
  - Working closely with industry and the public health community to develop the contractual framework, including addressing the various design concerns highlighted here;
  - Developing technical specifications for products, in collaboration with developing country health specialists and the scientific community;
  - Considering how an APC in a particular disease area will interact with PPP R&D in that area.
- More carefully considering the issues involved with whether this approach could be applied to drug treatments, including microbicides, and diagnostic tests as well as vaccines.

**A4.4 Non-IP pull proposals**

**A4.4.1 Patent buyouts**

As Kremer (2001) points out, patent buyouts are similar to purchase commitments but instead of a commitment to make a stream of purchase over time, governments offer to pay the present discounted value of this stream of payments, less the manufacturing cost, and receive the patent rights in return. The patent would be placed in the public domain and free competition allowed in manufacturing.

However, he argues, in the context of vaccines, that purchase commitments are superior. A number of reasons are given for this. Firstly, he argues that the difficulty of producing biologicals might leave the innovator whose patent is purchased with an effective monopoly due to trade secrets even in the absence of the patent. Secondly, he argues that purchase commitments maintain a closer link between payments and vaccine quality. If, for example, a drug is found to have unexpected side-effects, purchases can be suspended, whereas it might be difficult to recover the money from a patent purchase made at the time of regulatory approval. Thirdly, making a stream of purchases over time is argued to be politically acceptable (and therefore more credible) than the provision of a substantial windfall gain to a pharmaceutical company.

Kremer (1996, 1997) proposed an auction mechanism by which patent buyouts could operate. The big problem with patent buyouts is avoiding the ex post expropriation of the rights of inventors. Kremer seeks to avoid this by giving patent holders the option
of not participating in the buy-out process and of not accepting the offer. The government is also required to give a mark up to reflect the social value over and above the private value. However, it is not clear how such a process can be applied to a patent for a product for a neglected disease where the private value of the patent is low and the main purpose of the R&D effort would be to obtain the buy-out value. If the purchase price is not set in advance (or the rules by which it will be established) it is unlikely to stimulate new R&D from the private sector.

A4.4.2 DEFEND

A proposal having some similarities with patent buyouts is the recommendation made by Ganslandt et al. (2001) to establish a Developing Economies’ Fund for Essential New Drugs (DEFEND). This envisages an international fund managed by UNAIDS or WHO purchasing licences to produce and sell patented essential drugs in the least developed nations which choose to be part of the programme. Licence fees should cover “all or a substantial portion of fixed R&D costs, thereby establishing a strong incentive for pharmaceutical and vaccine firms to product new treatments.” The products are then made available at low prices, reflecting manufacturing costs, to developing countries.

Ganslandt et al. propose that payments to patent holders should be “in the form of a fixed, annual, lump-sum transfer that would feature three characteristics”:

1. “a net present value over the life of the program that should equal expected R&D costs”;  
2. “positively related to the social value (associated with reduced mortality, morbidity, and spillovers) of the drug in the licensed areas in order to tie R&D incentives to underlying needs”;  
3. “given that there may be broader markets . . . positively related to the global share of patients in the licensed areas.”

Such an approach to reward seems well designed, providing more detailed rules as to how these elements were to be calculated was set out, but the paper does not explain how such an approach could be structured to provide signals in advance to companies. Participants would need to know ex ante whether or not successful R&D in a particular disease area would be rewarded under this scheme. Nor do the authors set out how such a programme would be financed, although they note that the sums required (which they estimate at $8bn - $12bn per annum) would be large relative to current assistance but small relative to the income per capita of OECD countries.

A4.4.3 The Hollis “Efficient Reward System for Pharmaceutical Innovation”

This proposal replaces the existing patent reward (the right to profits obtained through exclusive use of the innovation) with a new type of patent reward (a payment based on the incremental therapeutic benefit of the product).
The key contribution Hollis (2005) seeks to make is by identifying an efficient ex post method of determining the payment to be made to innovators, based on the therapeutic contribution of their product using QALYs. Although rewards would be paid for 4 types of innovation the main one is based on the incremental QALYs gained multiplied by the dollar value of a QALY.

There would be problems in funding the buy-outs although there would be savings in existing drug expenditures in developed countries. Hollis proposes a separate special international fund to act on behalf of less developed countries. Indeed this special fund could be created independently from the adoption of the proposal in developed countries. He argues that “one option would be to designate special funds for diseases of particular interest in developing countries. For example, a malaria fund could be designed to reward only estimated gains in malaria treatment. This would have some advantages over an advance purchase contract (which would have to meet very specific technical criteria), because it would be flexible in rewarding any patented treatment, whether a vaccine or drug, without having to specify any criteria in advance”.

The problem with ex post rewards in this context is their credibility. Companies undertaking R&D have to believe that money will be available in the international fund when their products come to market. They also have to have confidence in the mechanism for calculating incremental QALYs and in the values attributed to a QALY.

**A4.4.4 The foreign filing licence approach**

The foreign filing licence approach (Lanjouw, 2002, 2004) is intended to reconcile the tension between restrictions on access to drugs in poor countries presented by patents and the maintenance of R&D incentives in developed country markets. The scheme proposes that inventors of new products in developed countries make commitments to their own governments that they will not enforce patent rights in particular countries. While companies have historically made voluntary commitments of this kind, the proposal would establish a legally binding rule.

Firstly, countries are ranked in order of income, and sales of drugs for a particular disease are summed country by country starting with the poorest until a figure of 2% of global sales is reached (but with a ceiling on the scheme of US$5,000 real GDP per capita). All the countries in the group making up 2% of sales fall into a “generics region” where firms can manufacture and sell generic products without going through compulsory licensing procedures. In the remaining countries, the normal TRIPS rules apply. For diseases such as cancer where a relatively small proportion of sales is made in poor countries, a large number of countries would fall into the generics group. In comparison, for diseases such as malaria, the 2% limit will be reached much more quickly and fewer countries will fall into the generics group. The reasoning is that some incentive is required from sales in developing countries if products are to be developed. Nevertheless, the poorest countries would have access to generic versions of all pharmaceuticals. Moreover, it is envisaged that sales to the poorer TRIPS countries would be financed at least partly by the international community.
The mechanism by which companies commit themselves not to seek the enforcement of patent rights in the generics group of countries is as follows. When companies seek permission from the government to make overseas patent filings, as they are required by law to do in the US for inventions made in the US, they undertake not to sue for patent infringements in the generic. If a company were subsequently to sue, in contravention of this agreement, then the US patent would be rendered unenforceable and competitors could enter the market.

This mechanism is unlikely to stimulate commercial R&D into neglected diseases. Indeed, the discussion by Lanjouw (2002) of the scheme suggests that it is intended to support other policies in this respect, rather than provide a significant incentive in its own right. Thus although patents for markets are potentially available for (say) malaria products in countries outside of the poorest group who always have access to generics the problem remains that these countries do not have the money to purchase products at prices that create a market that would reward R&D investment.

A4.4.5 BioShield

The US Government approved in 2004 legislation relating to Project BioShield — a package of “push” and “pull” incentives to accelerate the availability of drugs and vaccines to combat bioterrorist threats such as smallpox, anthrax, ebola and plague (Gottron, 2004). The major component of this package is funds appropriated for the purchase of designated products. So in effect an advance purchase commitment is created. The government will establish such contracts with companies to purchase a product for inclusion in the Strategic National Stockpile up to eight years before the product is expected to be delivered. The reaction of the biopharmaceutical industry to this legislation has been mixed and discussion of BioShield II is now underway.

A4.4.6 Prizes

Cash prizes could replace patents to lead to free competition in manufacturing newly invented goods. Like patent buy-outs, prizes would need to be specified in advance. The issues in using prizes would be similar to those faced with designing patent buy-out schemes.

A4.4.7 Tax credits on sales

Grabowski (2003) notes that tax credits have been advocated in the US for sales of vaccines for AIDS, tuberculosis and malaria, to non-profit and international organizations serving developing countries. Each dollar of sales would be matched by a dollar of tax credit. The boost to market value is however limited as sales will be low in the absence of other incentives.
A4.4.8 Tournaments

In a research tournament, the sponsor promises a reward to whoever has progressed the farthest in research by a certain date (Kremer, 2000a). If the final objective, e.g. the production of a vaccine, has not been met by that date, then additional funds would need to be set aside for further rounds of the tournament. The value of such an approach seems limited as it is a “winner takes all” approach and there is no requirement to have reached certain programme goals, only to be ahead of any rivals.