

Product development partnerships on ‘neglected diseases’: How they handle intellectual property and how this may contribute to improving access to pharmaceuticals for HIV/AIDS, TB and Malaria

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Various graphics in this article have been kindly supplied by the Medicines for Malaria Venture.

Major ‘public-private partnerships’ addressing health problems in developing countries

Public-private collaborations in some way directly addressing health problems in low and middle income countries fall into four main categories:

- Product development partnership (PDPs);
- Partnership for improving access to pharmaceuticals;
- Global coordination and financing mechanisms; and
- Partnership for strengthening health systems.

Others, e.g., for advocacy, play a less direct role.

Further general information on such partnerships is available on the website of the Initiative on Public-Private Partnerships for Health (IPPPH) (www.ippph.org), particularly in the IPPPH Partnership Database that is accessible on that site.

PRODUCT DEVELOPMENT PARTNERSHIPS (PDPS)

Recent reviews of product development partnerships include those by Widdus and White (2004)¹, and Kettler and Towse (2002)²

PDPs can be roughly divided into those that seek to develop multiple candidate products, i.e., use a ‘portfolio’, and those that work on only one candidate. Use of a ‘portfolio’ guards against the risk of failure for individual projects.

There are approaching 20 multi-candidate/portfolio-based, not-for-profit ventures developing products to combat a range of diseases. To varying degrees they all collaborate with pharmaceutical and biotech companies, using the latter’s skills and/or resources in the interests of reducing health inequities that affect the poor.

They include:

HIV/AIDS

- International AIDS Vaccine Initiative (IAVI)
 - HIV/AIDS vaccines
- South African AIDS Vaccine Initiative (SAAVI)
 - HIV/AIDS vaccines
- International Partnership for Microbicides (IPM)
 - Global Microbicide Project
 - Microbicide Development Project
 - Anti-HIV microbicides

¹ Widdus R and White K 2004 Combating diseases associated with poverty: financing strategies for Product development and the potential role of public-private partnerships (Abridged version) Initiative on Public-Private partnerships for Health, Global Forum for Health Research, Geneva.

² Kettler H and Towse A 2002 Public-private partnerships for research and development: Medicines and vaccines for diseases of poverty. Office of Health Economics, London.

Malaria

- Medicines for Malaria Venture (MMV)
 - Malaria drugs
- Malaria Vaccine Initiative (MVI)
 - Malaria vaccines
- European Malaria Vaccine Initiative (EMVI)
 - Malaria vaccines

Tuberculosis (TB)

- Global Alliance for Tuberculosis Drug Development (TB Alliance)
 - TB drugs
- Aeras Global Tuberculosis Vaccine Foundation³ (Aeras)
 - TB vaccines
- Foundation for Innovative New Diagnostics (FIND)
 - TB and (later) other diagnostics

Other diseases

- Drugs for Neglected Diseases *initiative* (DNDi)
 - Trypanosomiasis, Leishmaniasis
- Institute for OneWorld Health (IOWH)
 - Trypanosomiasis, Leishmaniasis, other
- Pediatric Dengue Vaccine Initiative
- Human Hookworm Vaccine Initiative
- Rotavirus vaccine Accelerated Development and Introduction Plan
- Pneumococcal Vaccine Accelerated Development and Introduction Plan

Other health problems

- Consortium for Industrial Collaboration in Contraceptive Research (of CONRAD)
 - Contraceptives

Product development partnership using a portfolio approach vary on a range of features:

- Choice of product/disease focus, which determines:
 - Scientific difficulty
 - Availability of partners
 - Downstream delivery system
- Legal status
- Operations:
 - They may decide to manage most of the product development activities in-house, through contracts (with Contract Research Organizations, CROs), or in collaboration with pharmaceutical and biotech companies;
- Breadth and depth of financing, which is mostly from foundations and bilateral aid agencies
- Philosophy: degree of collaboration with big pharma

Product development partnerships using a multi-candidate/portfolio approach have the greatest experience with intellectual property management. However, single candidate product development ventures generally manage IP in similar ways. The manner in which they structure collaborations with commercial partners and handle intellectual property issues is discussed below.

³ Formerly Sequella Foundation

Partnership for improving access to pharmaceuticals

Collaborations addressing access to pharmaceuticals in low and middle income countries are usually based around long term agreements to donate or provide products at a discounted price. Less commonly they involve agreements for technology transfer (see Table1).

Recently, the UK Department for International Development has supported extensive in-country study of the operations of donation and discounted price access partnerships in four countries (Botswana⁴, Sri Lanka⁵, Uganda⁶ and Zambia⁷) and a ‘Synthesis Report’⁸ with general conclusions and recommendations. In general the studies found programs for control of tropical diseases were generally highly beneficial with few problems. With programs for HIV/AIDS the situation was more complex: the programs were welcomed and beneficial, but countries generally did not have sufficient support from international agencies to make judgements on the most cost-effective ways to assure a sustainable supply of affordable medications and treatment for HIV/AIDS patients in general.

Access partnerships are most often based around single source products, some of which are under patent in some jurisdictions but often not in the poorer countries.

Where there appears to be a profitable market low cost suppliers will sometimes attempt to supply a comparable ‘generic’ product at a competitive price, as with the case of anti-retrovirals, where ‘generics’ compete with discounted innovator products.

Where branded products are discounted (as through the Accelerating Access Initiative) or donated (e.g., Diflucan®/fluconazole) there sometimes appears to be the perception on the part of officials in recipient countries (e.g., Botswana) that generic products cannot/should not be registered. No instances where this perceived conditionality was in fact a policy of the innovator company supplier were actually identified. Hence, the situation needs to be clarified among the various parties involved in the collaboration(s).

Suppliers of donated or discounted pharmaceuticals are sometimes criticized that their actions are a deliberate strategy to deter ‘local’ production in recipient countries. For some products which are difficult to manufacture, e.g., eflornithine, and/or where a viable human commercial market does not exist (e.g., MDT for Leprosy, Mectizan®/ivermectin) the validity of this criticism is questionable. In other cases, the potential viability of local production would need to be very carefully examined.

⁴ Impact of Public-Private Partnerships Addressing Access to Pharmaceuticals in Low and Middle Income Countries: Botswana

⁵ Impact Public-Private Partnerships Addressing Access to Pharmaceuticals in Low and Middle Income Countries: Sri Lanka

⁶ Impact Public-Private Partnerships Addressing Access to Pharmaceuticals in Low and Middle Income Countries: Uganda

⁷ Impact Public-Private Partnerships Addressing Access to Pharmaceuticals in Low and Middle Income Countries: Zambia

⁸ Impact of Public-Private Partnerships Addressing Access to Pharmaceuticals in Selected Low and Middle Income Countries: A Synthesis Report from Studies in Botswana, Sri Lanka, Uganda and Zambia

Table 1. Partnerships for improving access to pharmaceuticals

	HIV/AIDS	TB	Malaria	Other
Donation	Diflucan® (Pfizer) Viramune® (Boehringer Ingelheim) Merck drugs in Botswana within ACHAP			MDT Leprosy (Novartis) Albendazole for LF/GAELF (GSK) Mectizan®/Onchocerciasis (Merck) Eflornithine etc for Trypanosomiasis (Aventis)
Discounted pricing	Accelerating Access Initiative (AAI)		Coartem® (Novartis)	
Manufacture		MDRTB drug production technology transfer (Lilly)		
Other licensing	Various			Concept Foundation/contraceptives

Global coordination and financing mechanisms

As the name implies, these are umbrella coordination mechanisms:

- Stop TB Partnership
- Roll Back Malaria Partnership
- Global Alliance for Vaccines and Immunization (GAVI)
- 3 by 5 Initiative

Or sources of funding:

- Global Fund to fight AIDS, Tuberculosis and Malaria
- Vaccine Fund

They are mostly for coordination or financing of delivery of products but they may also cover R&D, e.g., the GAVI oversees two Accelerated Development and Introduction Plans (ADIPs) for vaccines against pneumococcal pneumonia and rotavirus diarrhoea. If they cover R&D, that component will probably handle IP in a similar fashion to PDPs.

Such mechanisms may be able to link R&D with access and expedite introduction, especially if they finance product procurement directly as is the case with GAVI through its companion Vaccine Fund.

Partnerships for strengthening health systems

All access partnerships to some degree strengthen health systems but others have it as their main objective. The principal example is the African Comprehensive HIV/AIDS Partnership in Botswana supported by the Gates Foundation and Merck, Inc.

Where IP management fits into the overall strategy of product development partnerships

The following description includes a number of generalizations to which there are often specific exceptions. These generalizations are necessary to convey a picture of the manner in which not-for-profit product development partnerships generally operate. However it should be recognised that the intellectual property situation surrounding each candidate product and the negotiations undertaken by each PDP to reach an agreement with collaborators is different.

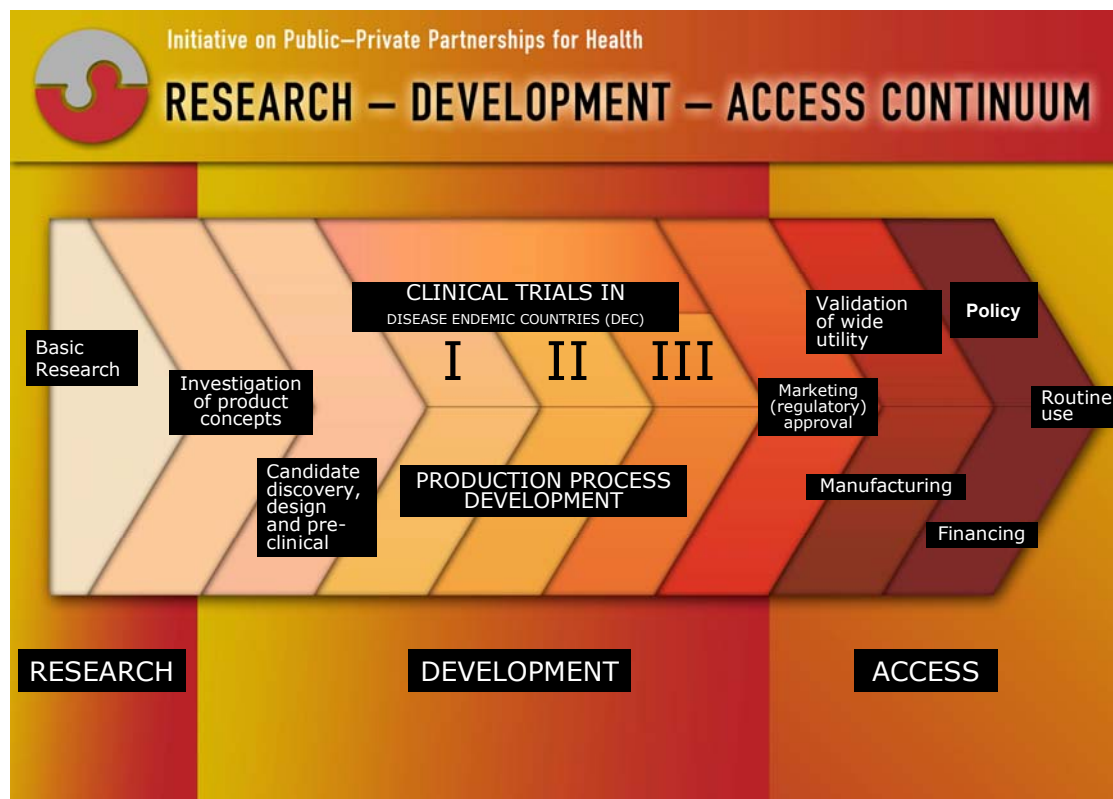
Types of intellectual property (IP) relevant to product development partnership

- Patents
 - Product patents (important for drugs).
 - Process patents on research techniques and manufacturing processes. These are important for vaccines (where product patents do not exist on the vaccines themselves, but may do so on the delivery vehicle, such as single use syringes).
 - Use patents, where the ‘inventive step’ is to identify a particular application for a known molecule, such as using it in a new way, e.g., in a combination (as for Coartem®).
 - The term ‘background IP’ is used to denote existing IP, that one or more of the collaborating parties brings to negotiations. This can relate to the candidate product itself, or to the research or production methods necessary for its further development).
 - Applications for patents are sometimes refused and sometimes successfully challenged. Many patents do not prove to be useful or commercially valuable, but the system overall protects those that do prove to be particularly valuable. Without further investment in product development, there is no reliable way to predict which patents will be useful.
- Trade secrets
 - ‘Propriety’ data (toxicology, efficacy pharmaco-kinetics, etc.)
 - For application for regulatory/marketing approval
 - If developed by a public interest entity, this may be made available to others in an effort to pursue their goals, e.g., WHO data provided to the Concept Foundation
 - Industrial know-how
 - Manufacturing knowledge, etc.
- Trademark rights
 - Relating to trade/brand names

These different types of intellectual property are typically generated at different points in the **Research-Development-Access continuum** shown in Figure 1, and pose different management challenges for PDPs.

Most PDPs currently operate at the pre-clinical and early clinical development stages of the Research-Development-Access continuum. Generally they do not support basic research or the translation of basic research into product concepts. However, there are some exceptions).

Figure 1: Research-Development-Access continuum



Product patents (on drugs) are usually taken out at the very early stages based on basic or product concept research.

- In many cases patents on candidate products will not be held by PDPs, rather they are held by an academic institution or company. The PDPs will need to license these patents from the patent holder in order to have the right to develop the candidate product further.
- In some circumstances PDPs will fund work that generates important patents. The Medicines for Malaria Venture (MMV), funded work at the University of Nebraska on synthetic peroxides as potential antimalarials. University investigators filed a patent as inventors, assigning the rights to MMV, which licenses these to Ranbaxy in India, as part of further development work.

Process patents emerge at the early to middle stage of product development, typically/historically from industry investment. Some process patents however, cover research tools and are held by academic institutions.

‘Propriety’ data are generated in the early to middle stages of product development.

Know-how in manufacturing, emerges in the early to late stages of product development, historically from industry investment.

R&D supported by PDPs may lead to patentable innovations, ‘proprietary’ data, and to technical know-how, all of which the PDP needs to manage in its agreements with collaborators.

How product development partnerships manage agreements and intellectual property issues to pursue their objectives⁹

Irrespective of the current activities that PDPs are now focused on they have two interconnected long-term objectives:

- Creating a new product;
- Ensuring it is widely and affordably available, to the extent possible.

The second objective is always kept in mind even at the earliest stage of their activities.

PDPs pursue their goals through support of projects on candidate products, typically in collaboration with academic and a commercial partners. These collaborations require management of a range of activities and partners and are often called ‘virtual R&D’ (see Figure 2 on page 9), to distinguish it from the typical mode of operations of larger pharmaceutical companies where most activities were historically in-house. These collaborations are based on written agreements that specify obligations and expectations of the different parties.

Rarely does the not-for-profit PDP itself have control over a candidate product at the outset. Control of the candidate products/concepts usually rest with an academic or commercial group and part of the early project negotiation entails the PDP securing the option to pursue its development. The incentive to the candidate product’s ‘owner’ is the prospect the PDP will invest in the candidate’s development, for which adequate commercial funds would most likely not be forthcoming.

Kettler and White (2003) reviewed a number of these agreements between PDPs and commercial partners and found that the nature of the industry contribution varied with the type of company involved.¹⁰ Larger companies were generally in a position to provide more in-kind value to the collaboration.

While they vary considerably, the essence of collaborative product development agreements is that different parties bring different contributions (candidate products, intellectual property, relevant data, skills, expertise equipment and money) and want to get out certain benefits (a proven product, profits in selected markets, public relations benefits, human resources benefits within companies, access for target populations in selected countries.

This is illustrated schematically in Figure 3 (on page 9), but each arrangement is somewhat different.

The term ‘access conditions’ has been used to cover the ways in which the not-for-profit partner (a PDP in this discussion) has attempted to secure its public health goals in these agreements.

Agreements, including ‘access conditions’, can thus cover:

- Access to existing ‘background’ intellectual property related to the candidate product (often specifically obtaining the right to develop the candidate product for particular uses and markets, or to continue to develop it if the commercial partner loses interest).
- Obligations regarding the provision of funding to support product development activities by the commercial or academic partner.
- Ownership of rights to IP generated by the research funded by the not-for-profit partner.

⁹ This discussion draws heavily on a report prepared for the Initiative on Public-Private Partnerships for Health: Taubman A 2004 Public-private management of intellectual property for public health outcomes in the developing world: The lessons of access conditions in research and development agreements

¹⁰ Kettler H, White K. 2003. Valuing Industry Contributions to Public-Private Partnerships for Health Product Development

- Obligations regarding provision of the product, or access to IP, know-how, and/or transfer of technologies developed from the funded research:
 - These can include provisions for supply of the product at cost of production or with a low 'margin' (cost-plus).
- Provisions regarding the licensing of such IP rights to other parties.

Figure 2: Virtual R&D is essentially project and portfolio management through relationships and contracts

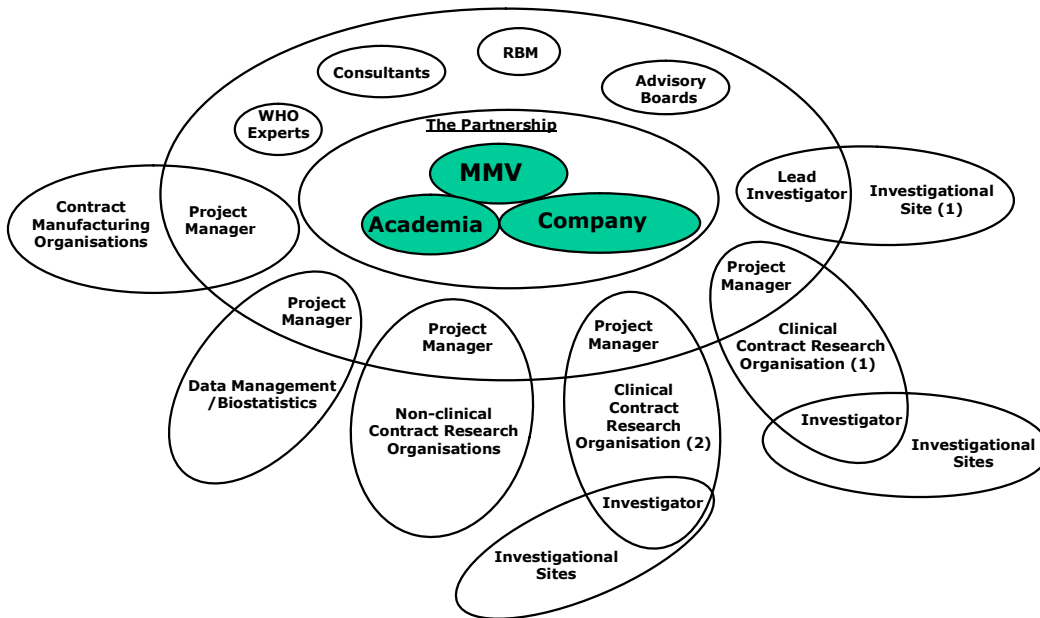
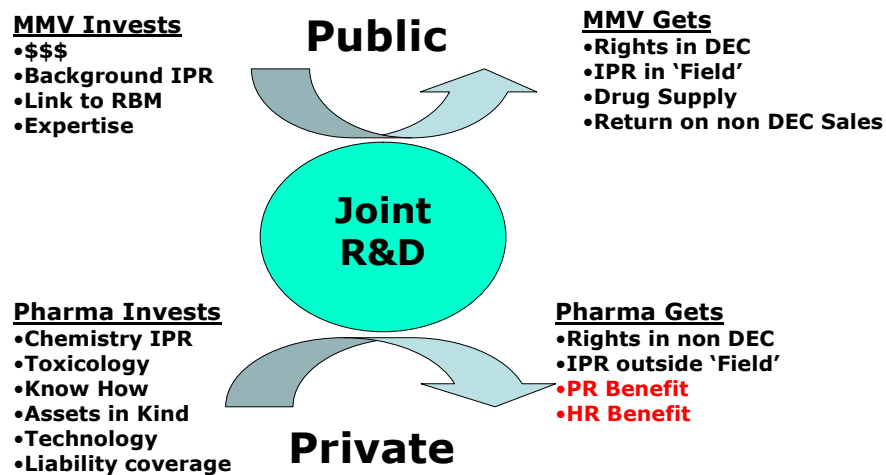


Figure 3: The win/win proposition



The 'deal' is sustained by balancing incentives/costs for each partner

Taubman found that access provisions in agreements generally fell into two general areas corresponding to the development and downstream (or distribution) phases:

- *“Technology development and access obligations: such provisions concern research and creation of new technology per se, or the availability of necessary technology and associated data – this may establish obligations on the research/industry partner to undertake research and development, and to make available background IP, know-how and associated data (including technical know-how or skills and resources required for product development, clinical trials and regulatory approval know-how, as well as the data on safety and efficacy produced by clinical trials). Such provisions may amount to a positive undertaking – such as an agreement to undertake research or to provide technology, or an obligation to license or transfer IP rights in the event the research/industry partner fails to, or has insufficient interest to, develop and disseminate covered technology in a particular market.*
- *Downstream technology dissemination provisions: provisions which set conditions for how the covered technology (typically a pharmaceutical or vaccine) is to be distributed or marketed by the research/industry partner – these may set a price or criteria (such as ‘reasonable price’ or ‘public sector price’) for determining the price for distribution in a certain market); conditions may stipulate more generally that the pharmaceutical will be ‘reasonably available’ or otherwise comply with similar criteria; and conditions may also provide distinct requirements for how the pharmaceutical is to be distributed in distinct markets, such as an undertaking to cross-subsidize developing country or public sector distribution on the basis of preferential pricing, and other conditions defining how access to the covered pharmaceutical should be granted on the basis of market or non-market mechanisms.”*

Taubman’s review¹¹ of PDP agreements also identified that there is wide variations of approach among product development partnerships. It must be emphasized that each agreement will entail a different initial IP environment, different partners, and possibly different downstream considerations (e.g., depending on who may be the chosen manufacturer, who is the likely purchaser and the target disease distribution).

Some examples of these arrangements are included in Annex A to illustrate this variation. Readers should also refer to Kettler and White (2002) and Taubman (2004) to see the manner in which other agreements have been structured. Another somewhat broader set of examples drawing on other public interest activities has been developed by the Center for Management of Intellectual Property in Health Research (MIHR).¹²

Access conditions used by PDPs are commonly defined in terms of guarantees for a preferential sales price in developing countries or in a specified target market. This is generally offset by leaving the commercial parties free to commercialize the product in more lucrative markets without constraints as to price or performance guarantees. Access conditions may also be defined in terms of performance standards, such as conditions setting agreed volume and delivery term commitments for the manufacture and distribution of drugs or vaccines. Other conditions provide for access to the developed technology in the event that the research/industry partner abandons the project or elects not to service a particular market or sector: this can be achieved through an agreement to assign or license IP and to provide know-how and regulatory approval data.

¹¹ Taubman, A. 2004 Public-private management of intellectual property for public health outcomes in the developing world: The lessons of access conditions in research and development agreements

¹² Mahoney, R. 2003 Handbook of Best Practices for Management of Intellectual Property in Health Research and Development, Center for management of Intellectual Property in Health Research, Oxford, UK

Taubman sought lessons from the experiences he documented and attempted to draw practical conclusions or guidelines for these new product development ventures. He cautions however that it is always necessary to interpret access conditions in the overall context of the agreement.

“There is no single template for PPPs that will apply in all cases – each case should be considered unique and planned strategically its own terms given the diversity of inputs (financially, technological, product development know-how) that are brought by the project and industry partners and the differing external factors (including the epidemiological pattern of the target disease, the regulatory environment and the health infrastructure needed to deliver and administer the product”).

Trends

If any trend is evident over the last 5 – 10 years, as these product development partnerships have expanded and matured, it is that they are taking intellectual property management more seriously. They are tackling it with more input from professionals, and moving towards more specific provisions that secure their options and interests. General language simply hoping for ‘reasonable pricing’ for developing country markets is becoming less common.

To what degree are product development partnerships able to influence ‘access’

Product development partnerships, as currently constituted, have a limited capacity to ensure access by individuals in poor populations to any products that may emerge from their efforts. Most attempt to assure future access through interactions with various partners ‘downstream’ to product development itself, as shown in the schematic from the Medicines for Malaria Venture (Figure 4 on page 13). Typically PDPs concentrate on ‘Core R&D’ although they may have secondary activities in other areas.

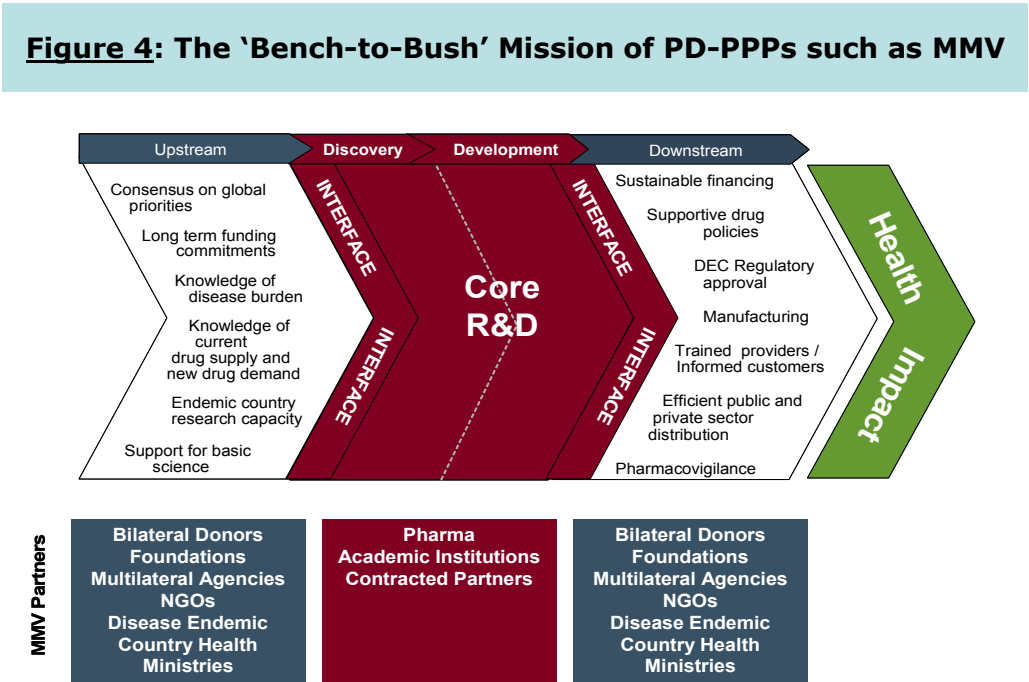


Figure 5 shows the various factors identified over the years by the WHO Department of Essential Drugs and Medicines Policy as contributing to proper access to medicines. Recently more emphasis has been placed on “affordable prices”. However, the broader term of ‘economic factors’ is probably preferable since it includes import tariffs, procurement efficiency, and distributor mark ups, and avoids the perception that the price consumers pay is solely determined by the ex-manufacturer price.

Figure 5: Determinants of Access to Pharmaceuticals

Availability, i.e., whether a satisfactory product has been developed

**Basic research
Discovery
Development**

Accessibility, including:

**Ensuring quality, rational selection, appropriate prescribing and use
Distribution system effectiveness and efficiency
Economic factors, inc. cost, pricing, procurement and financing
Knowledge and ‘health-seeking’ behaviour of ‘consumers’**

Many of these factors are outside the control of the product development partnerships and are likely to remain so. Responsibility for assuring most of these rests with governments. To put in perspective the extent to which PDPs can influence access to their anticipated products, including the potential contribution of active IP management to this goal, it is worth identifying what aspects of access are under PDP influence and which not.

What aspects of access to medicines are under control of product development partnerships

- The choice of which candidate products to develop, that
 - Can influence manufacturing costs, to some extent, and
 - Can also influence stability/storage shelf life, distribution difficulty, ease of administration and likely compliance, which are factors in access.
- The choice of development partners
 - These vary in policy and philosophy on addressing the needs of poorer developing countries
- Manufacturing costs (to some degree)
 - Can retain the right to ensure low cost manufacture, but cannot basically alter cost of goods if difficult to manufacture
- Whether to seek regulatory approval as a product sponsor, or to leave this to the chosen manufacturer
- Within access conditions

- Populations targeted for preferential supply, i.e., countries, markets
- Cost of manufacture (to some degree by choice of manufacturer)
- Price charged (to some degree, to some degree through ‘cost-plus’ conditions)

- Specifying ownership of IP (all types) generated during the agreement (i.e., leveraging its investments)

- Anticipating and investigating questions regarding the candidate product’s broad public health utility, in low and middle income countries.
 - This includes studies that go beyond the minimum required for the claims made in licensure applications for efficacy and safety, but may include studies of co-administration and safety in malnourished groups, efficacy in pregnancy, etc.
 - If conducted sequentially to licensure, conduct of these studies may delay wide introduction and potential public health impact. However, conducting them early on all candidate products is financially unrealistic.

What aspects of access to medicines are not under PDP control?

- Health systems issues
 - Reach of health services
 - Staffing of health services
 - Competence of health personnel
 - Efficiency of health services/product distribution
 - Public/private mix in health services, which can affect quality of care
 - Procurement practices and efficiency
 - Allocation of resources for health systems
 - Allocation of government resources for product purchase
 - Purchasing power of consumers
 - National policies regarding product choice and drug policy, and the speed of their formulation
 - Policy recommendations of international agencies and the speed of their formulation
- Regulatory approvals sought, if it does not choose to itself be a sponsor for regulatory approval
 - Where and with what timing approvals are sought will be at the option of the manufacturer.
- Manufacturing costs and pricing, if the PDP calculates it is not advisable to attempt to control manufacturing

Illustrations of recent ‘access’ failures”

Experience shows that even where certain products were designed for developing country use and with attention to affordability, the policy formulation and introduction process has been disappointingly slow.

- Low cost production of praziquantel in Korea, did not result in wide uptake to control schistosomiasis;
- Development of the anti-malarial drug LAPDAP needed to be ‘restarted’ with an artemisinin component when policy shifted;
- The combination anti-malarial Coartem® was offered at a discounted price, but a new policy for its use was resisted by some bilateral agencies and uptake is slow because of cost even though cheaper treatments are losing effectiveness because of resistance.

A host of products initially developed for industrialized country markets have seen slow policy formulation at international and developing country levels and delayed uptake. These include not only anti-retrovirals

but products like Hepatitis B and Hib vaccines where relatively low prices after a few years would have meant high cost-effectiveness.

Some PDPs are more active in addressing ‘access’ issues

Each product development partnership needs to consider the nature of the downstream delivery systems relevant to its anticipated products. These vary considerably among products and countries. In some cases (e.g., vaccines and TB drugs) the purchaser and distributor is usually the government. In other cases products are mostly accessed through private sector distribution and private providers.

Some PDPs have recognised that access to their anticipated products will not occur automatically in a timely fashion due to the lack of an identifiable delivery system (e.g., for vaccines to adolescents, or microbicides to the poorest women). They have therefore identified advocacy and activities for access as significant parts of their missions. These PDPS include the International AIDS Vaccine Initiative and the International Partnership for Microbicides, each of which has documented actions necessary to ensure ‘access’.¹³¹⁴¹⁵ IAVI has supported development of demand estimates to assist in estimating necessary production capacity.

Others such as the Medicines for Malaria Venture are recognising that existing policy formulation and distribution systems will not necessarily expedite uptake and wide use of their anticipated products and are considering what actions are realistic for them to undertake.

Ghosh (2004)¹⁶ has summarized the case for addressing access issues in parallel with product development activities for vaccines and the case is equally strong for drugs and other products.

¹³ IAVI 2000 AIDS Vaccines for the World:Preparing now to Assure Access, IAVI, New York.

¹⁴.IAVI 2001 A New Access Paradigm :Public Sector Actionsto Assure Swift Global Access to AIDS Vaccines

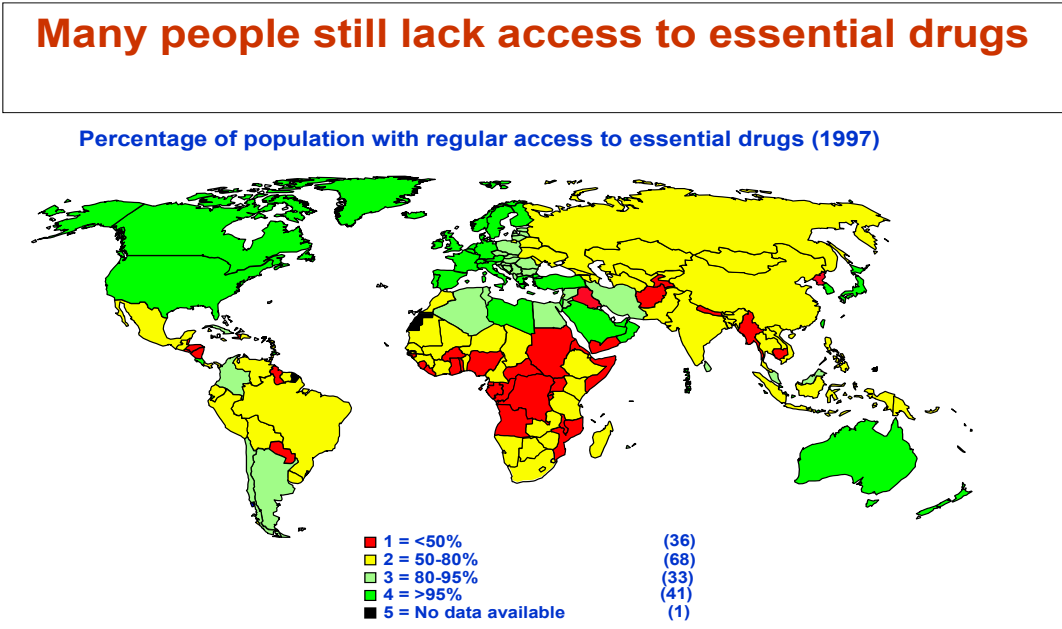
¹⁵ IPM2004 Preparing for future access: country preparedness Available at www.ipm-microbicides.org/preparing_future.cfm

¹⁶ Ghosh, G 2004 Emerging lessons in preparing for uptake of new vaccines, in Combating diseases Associated with Poverty:Finanacing Strategies for Product Development and the Potential Role of Public-Private Partnerships, Widdus R and White K Initiative on public-Private Partnerships for Health, Global Forum for Health Research, Geneva.

Barriers to access to medicines from the consumer perspective

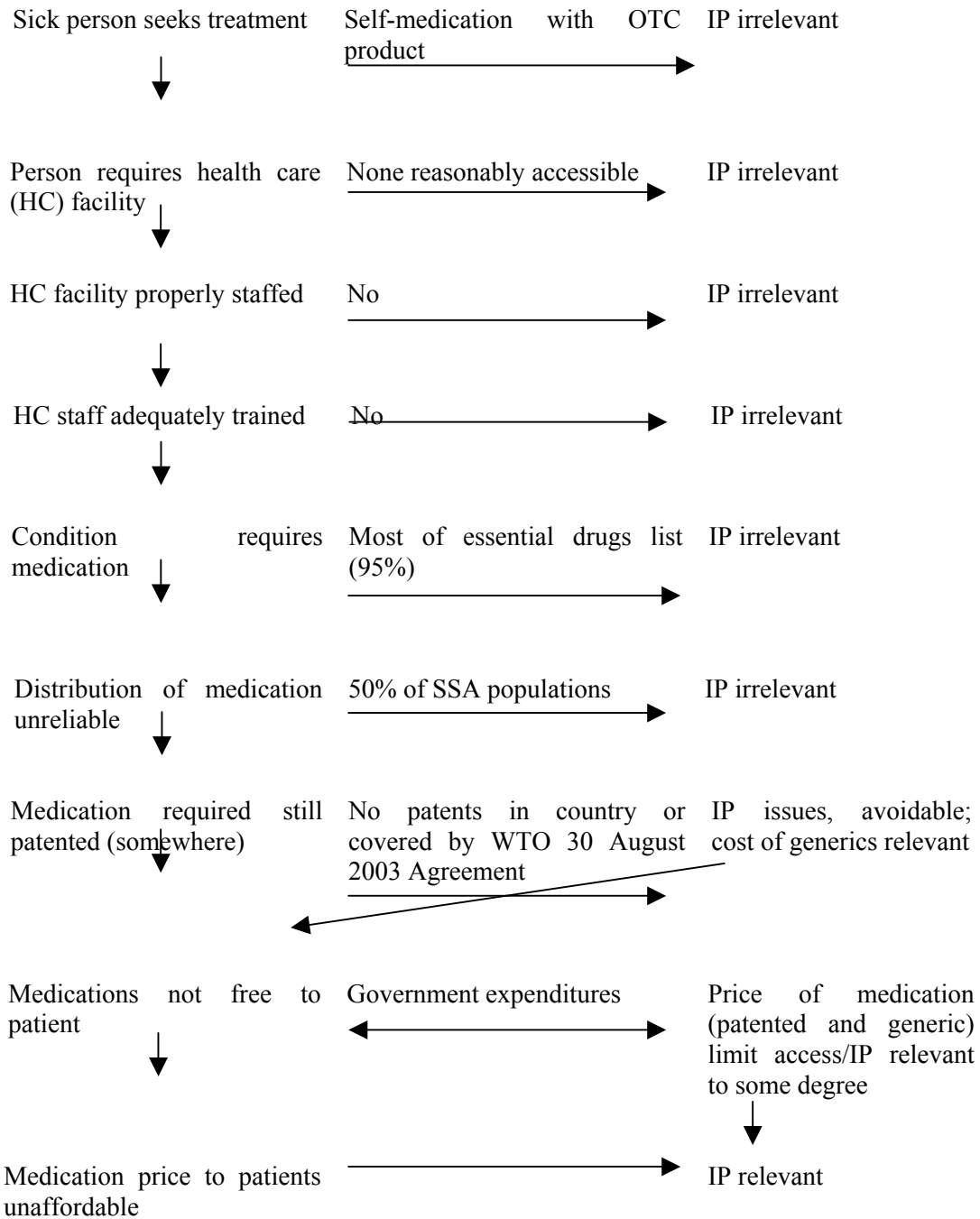
Figure 6 shows the level of access to ‘essential’, i.e., basic medicines, as of 1997. In general one-third of poor populations and half of populations in Africa do not have access to the most basic of medicines.

Figure 6:



If one looks at the question of access to (any) medicines from the point of view of a poor person, especially one in a rural area, the impact of intellectual property in the big picture can be better put into a balanced context.

IP and access to medicines: A consumer perspective



Thus putting in place systems for basic health services would have enormous impact and improving access to basic essential drugs is the most cost-effective approach.

However, price to consumer or other purchaser does have an effect on access in some circumstances so it is worth looking at how patents and other IP contribute to price.

The price to consumer consists of

- Distribution cost/distributor mark-up;
- Import tariffs (in some cases);
- Shipping costs (in some cases;)
- Ex-manufacturer price in which IP costs are included

Which leads to the question, “What are the components of ex-manufacturer price”? These are basically the ‘cost of goods’, within which is included the cost of royalties for acquiring IP if not held within a company; the margin needed to support ongoing R&D (for innovator/R&D based companies); plant depreciation; costs of company administrative overheads, costs of marketing to consumers and health care providers in some situations; and contribution to dividends to shareholders. Marketing costs are proportionally less if sales are to those that procure in large quantities.

Where prices include all the above components, the cost of goods is a relatively small component (say less than 20%¹⁷) but the overall price is what is needed for the company to stay in business. Many R&D based companies will differentially price products for poor countries and in doing so forgo contributions to R&D (recouped from richer markets) getting closer to the cost of production. Even in highly competitive markets such as that for HB vaccine to UNICEF with low cost suppliers actual production costs may still only amount to 60% of price.

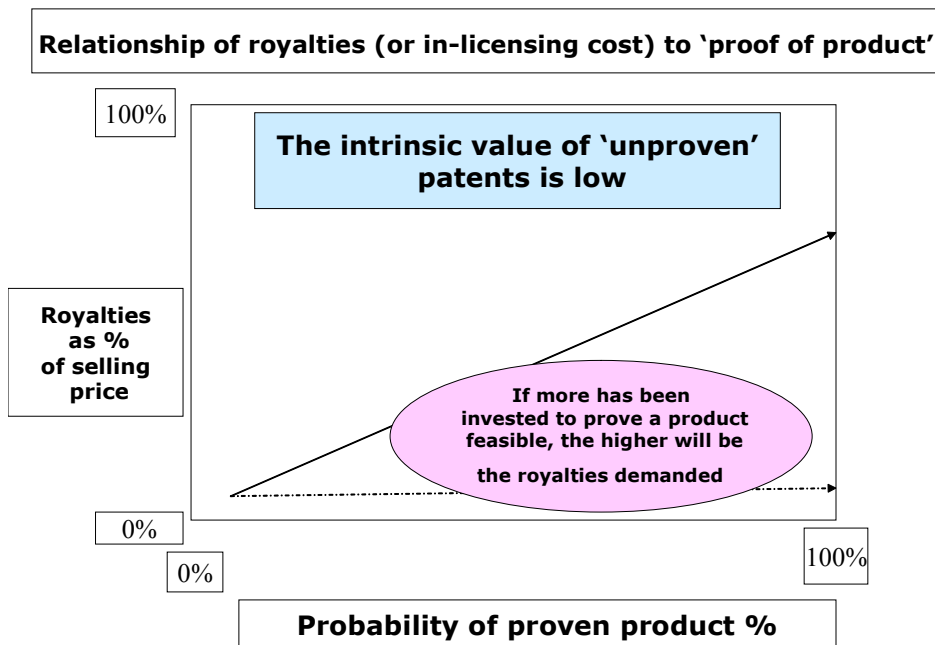
There is considerable disagreement on how to gauge the true costs of production. Some producers do operate in lower cost environments, such as India, but all commercial manufacturers, *including so-called generic producers*, will price their products according to market dynamics, i.e., what the market will bear and will not bother competing where the market does not allow some profit.. Usually all manufacturers will have an incentive for keeping production costs as low as possible consistent with necessary quality. Most manufacturers source their active pharmaceutical ingredients from low cost producers anyway. It is probably misleading to make sweeping generalizations about production costs in developing countries being “a fraction of those in industrialized countries”. There are probably some cost advantages for some products but estimates for vaccines have not shown this to be a major difference especially for new, complex technologies, either for establishing a production plant or for unit cost of product.¹⁸

What are the real costs of patents and other IP within royalties?

The rise in royalties (or in-licensing costs) that can be achieved in commercial negotiations as products are acquired at later stages of development represents the investment made in proving a product is feasible. If a patent is commercially acquired/in-licensed early in the development process from an outside patent holder it commands royalties of only a few percent of selling price and/or a relatively small payment. For example, all the various patents ultimately required for production of rDNA Hepatitis B vaccine were acquired early by two companies, and only commanded royalties of a few percent each, to an aggregate of about 13% - and this is regarded as a powerful patent in the vaccines field.

¹⁷ Mercer 1995 Comparison of drugs and vaccines price structures in a study of the US vaccine industry

¹⁸ GAVI 2002 Accelerated introduction of priority new vaccines in developing countries, McKinsey and Co.



The inherent value of a patent not yet proven to be critical to a prospective product is relatively low. As far as is known, PDPs for drugs and vaccines has so far been able to access desired candidates for further development for the target disease and poor populations without payments of in-licensing fees .

Conclusions on IP as a component of or barrier to access to medicines

The intellectual property protection system is not in itself an incentive to innovate or manufacture products. The incentive for commercial investment in innovation (or manufacturing) stems from the existence of some market.

Product development expertise resides overwhelmingly in commercial pharmaceutical and biotech companies. For most products, even those that are needed to combat diseases that primarily affect poor populations, there are some markets in which these companies are interested even if only slightly and/or which they will not wish to cede to potential future competitors at their expense, e.g., the private market in poor but large countries. Engaging the expertise and resources of companies in product development for 'neglected' diseases makes sense. In many cases they hold patents (on molecules), licenses, data, and know-how that are needed for developing the desired products. If they are to be engaged then they will expect professional management of IP issues to protect their commercial interests just as they expect professionalism in the scientific aspects.

PDPs should actively manage negotiations involving the IP they need to access and leverage the best terms for their financial and other contributions to product development. This should contribute to some extent to facilitating access for the populations they wish to benefit. However, many factors limit access to medicines that are not at all related to intellectual property and many of these will remain outside the control of PDPs.

Improving North-South collaborations on diseases associated with poverty

In identifying problems with North-South collaboration it is useful to differentiate among so-called developing countries. The range of these includes, according to World Bank classifications, low income countries, and upper and lower middle income countries. Of the middle income countries, the larger, such as India, China, and Brazil have sizeable populations, relatively well financed research institutions and a developing commercial R&D sector in the pharmaceutical and biotech areas. North-South scientific collaborations with these large advanced developing countries tend to be between partners of closer status with respect to resources and balance of power in negotiations.

The poorest countries, many of which are in sub-Saharan Africa, have nowadays a reasonable cadre of highly trained professional scientists even though many of these use their skills as expatriates in the 'North'. Research institutions in the poorest countries are grossly under-funded and suffer from lack of critical mass generally and deficiencies in selected capacities (e.g., data analysis). They lack support politically and suffer from weak state/governmental infrastructure to facilitate R&D, such as national ethical review committees and regulatory agencies. North-South collaborations which involve the poorest countries thus suffer from a severe imbalance in access to resources and relative power.

Many groups from the 'North' that enter into collaborations with research institutions in the 'South' are focused on their own missions and needs, e.g., academic publications, and rapid results from clinical trials. They do not regard capacity strengthening as part of their mission, or if it is included, it is a secondary aspect.

In these circumstances, it is not surprising that research scientists from the South have voiced dissatisfactions with many North-South collaborations. These dissatisfactions have been voiced many times in the last few decades, recently in a workshop¹⁹ on Clinical Trials Capacity in Low and Middle Income Countries: Experiences, Lessons Learned and Priorities for Strengthening, held in Arusha, Tanzania in November 2002. Other references carry similar complaints: These include:

- Trials design is not always ethical;
- Topics not always selected with adequate input from researchers and policy makers from the "South";
- Researchers from the 'South' have great difficulty in initiating/financing R&D on their priority concerns;
- Local communities not always adequately engaged;
- No consideration to future access by local population/country in which products are tested;
- Samples and data removed to industrialized country;
- South collaborators not involved in data analysis, preparation of articles and presentation of results;
- No plans for sustaining capacities in the "south" when collaboration is over;
- No thought to career development for investigators from the "South".

Obviously not all North-South collaborations suffer from these defects but enough do for it to be a lingering concern. Many groups willing to take a long term view and truer partnering approach have forged collegial and productive collaborations over the years. These can serve as models

In practical terms, there is obviously a need for those from the North to recognize the value of true R&D partnership, and to act with greater sensitivity to the implications of inequality in access to resources and the power balance within collaborations. However, ultimately the situation calls for diminishing the source of power imbalances through more resources – externally and domestic – for building R&D capacity in the

¹⁹ Workshop on Clinical Trials Capacity in Low- and Middle-Income Countries: Experiences, Lessons Learned and Priorities for Strengthening (2002), IPPPH, Geneva

poorest countries. Regrettably providing resources directly to institutions in the poorest countries is not a high priority strategy of most funders, with the exception of the UNICEF/World Bank/UNDP/WHO Special Programme for Research and Training in Tropical Diseases.

What can public authorities do to assist in improving access to pharmaceuticals and the contribution of product development partnership?

Table 2 provides a reasonably comprehensive list of things that could be done to improve access to medicines for poor populations. Part A covers ‘availability’, defined as new product development and Part B covers making products ‘accessible’ Given that many cheap off-patent products are not available to the poorest populations, attention to the activities in Part B is a priority. For some diseases there is a need for new or better tools for prevention, diagnosis, or therapy. Hence new product development is necessary in selected areas, and also to anticipate the threat of resistance.

Selecting among these activities is difficult as certain steps, if ignored, simply become the new barrier, in a chain that needs to be intact and integrated for patients to receive proper care including access to necessary medicines. In 2002, some areas were suggested for public sector, private sector and joint action (shown in Table 3) but these were largely personal suggestions. Some priorities will obviously need to be selected at different levels (international, country) but these need to be based on a careful analysis of what have been the reasons for the apparent lack of sufficient progress in the last two decades.

Product development partnerships have mobilized around an additional US\$ 200 million per year from foundations and bilateral aid agencies. Unfortunately, there does not appear to have been a similar increase specifically targeting strengthening the infrastructures to ensure access to existing and new products. While there has been a substantial increase in funding through the Global Fund to fight AIDS, TB and Malaria, it is not yet clear what effect this is having on the infrastructure for access to medicines. In other cases where there has been activity on tasks that would normally fall to the public sector it has been supported by philanthropic actors rather than governments or international agencies. The GAVI ADIPS represent comprehensive approaches to ensuring access to new products. These include better definition of disease burdens in specific countries to raise awareness and demand. These are funded by the Bill and Melinda Gates Foundation.

Some governments (e.g., UK DFID) have spent considerable effort in analysing and developing new strategies in these areas²⁰. Hopefully these and other efforts will bear fruit in the next decade.

²⁰ Department for International Development, UK Increasing access to essential medicines in the developing world: UK Government policy and plans, DFID, London.

Table 2: Proposed Interventions to Promote Access to Drugs and Vaccines - Part A: Availability

'Push' Interventions		'Pull' interventions
To lower costs and risks of research and development	To remove barriers in the development 'pipeline'	To provide incentives for development and manufacture, by creating a market, providing other economic rewards or removing economic deterrents
<p>Basic research funding (from government or philanthropy)</p> <p>Grants for product development</p> <p>R & D tax credits to companies</p> <p>R & D expense 'write-offs'</p> <p>Tax credits to investors</p> <p>Establishment of R & D capacities in endemic situations, e.g., Phase III trial sites</p> <p>Protocol assistance, as per U.S. Orphan Drug Act</p> <p>Support for R & D to identify new indications for existing entities:</p> <ul style="list-style-type: none"> - Financial - Through mass screening facilities <p>Consortia (Public; private; or public/private)</p> <p>'horizontal' – discovery</p> <p>'vertical' – development/manufacturing</p>	<p>Regulatory harmonization</p> <p>Expediting regulatory/licensing processes</p> <p>Lowering regulatory fees for specified product categories</p> <p>Simplification (not lowering) of standards</p> <p>Protocol assistance</p> <p>Setting ethical guidelines for conduct of research involving human subjects, and or international collaboration</p>	<p>Improved delivery of existing drugs and vaccines</p> <p>Identification of public health priorities for new projects</p> <p>Product specifications/contingent recommendations for use</p> <p>Recommendations for use (earlier)</p> <p>Market assessments</p> <p>Patent extension</p> <p>Patent 'exchange' (extension on another product)</p> <p>Market exclusivity</p> <p>Prizes (for first to meet specified product characteristics)</p> <p>Market 'assurances'</p> <ul style="list-style-type: none"> - Purchase funds (for existing and/or future products) - Contingent loans and credits - Minimum price guarantee 'cost-plus' formulas - Requisition to buy <p>Legislation on product liability litigation</p>
<p>Proposals to manage 'orphan' product R & D:</p> <ul style="list-style-type: none"> ▪ US HHS Secretary's Vaccines Work Group, 1978: National Vaccine Commission ▪ US Institute of Medicine: 1986, National Vaccine Commission; 1993, National Vaccine Authority ▪ Ad Hoc Committee on Health Research and Development, 1996: Health Product Development Facility or Alliance (p.xxxvii) ▪ At GAVI R & D discussion, 1999: Public-private vaccine partnership 'umbrella' for development and/or manufacture ▪ Creation in late 1990s to early 2000 of numerous not-for-profit entities to foster public-private partnerships in product development 		

Interventions addressing product quality, rational selection and appropriate prescription and use	Interventions addressing supply/logistics	Interventions addressing economic factors
<p><i>Assurance of quality</i></p> <p>Strengthening national regulatory agencies and their enforcement capacities</p> <p>Implementation of measures against counterfeit and ineffective medicines</p> <p>Rational selection</p> <p>Designation of national 'essential' drugs lists</p> <p>Identification of optimal formulations/packaging</p> <p>Ethical criteria for drug promotion</p> <p>Consumer education</p> <p>Use</p> <p>Training in appropriate use</p> <ul style="list-style-type: none"> - prescribers - dispensers, drug sellers - patients and community <p>Consumer education</p> <ul style="list-style-type: none"> - compliance/adherence <p>Regulation of drug and vaccine provision through private providers and monitoring of compliance (NB: Private sector distribution in many countries at 50-90% of markets)</p> <p>Monitoring consequences of misuse, e.g., antibiotic resistance, and educating on its dangers</p> <p>Consumer knowledge and health behaviour</p> <p>Consumer education (for appropriate use)</p>	<p><u>Reliable sources of supply</u></p> <p>Preparation of demand/uptake estimates for global needs, to predict and coordinate necessary production capacity requirements</p> <p>Training in preparation of demand estimates at national level</p> <p>Multi-year predictions/contracts</p> <p>Training in procurement procedures (to secure fair prices)</p> <p>Brokering by international organizations between potential suppliers and 'consumers' to ensure reliable supply</p> <p>'Local' manufacturing</p> <p><u>Availability at point of use</u></p> <p>Market consolidation (bulk procurement) to facilitate supply to previously unserved populations (e.g., UNICEF, PAHO procurements)</p> <p>Training in design/management of distribution systems</p> <p>Expand pharmacy services in rural areas</p> <p>Contracting for private sector delivery systems</p> <p>Consumer education (to increase demand)</p>	<p><u>Resources</u></p> <p>Allocation of adequate government financial resources</p> <p>Targeting of public financing to neediest</p> <p>Cost-recovery schemes</p> <p>Cost-sharing schemes/insurance</p> <p>Advocacy to policymakers particularly on 'value' of prevention</p> <p>Social marketing to 'consumers'</p> <p>Debt relief, loan contingencies</p> <p>Market segmentation (for procurement for poorest countries) and price tiering by suppliers</p> <p><u>Cost</u></p> <p>Tax credits to encourage donations by industry</p> <p>Support for new methods to lower production costs</p> <p><i>Pricing policies and controls</i></p> <p>Encourage generic drug use/competition</p> <p>'Compulsory' licensing (Innovation may be inhibited)</p> <p>Parallel importation (Innovation may be inhibited)</p> <p>Government price controls (Innovation may be inhibited)</p> <ul style="list-style-type: none"> - cost-plus - reference pricing - profit/return on capital <p>Tiered/concessionary pricing based on market segmentation</p> <p><u>Price at point of use</u></p> <p>Elimination of import taxes</p> <p>Reduce distribution margins that increase consumer prices (by up to 80% in some cases)</p>

Table 3:

Box 3. Action that could be taken by the public and private sectors

The **public sector** could:

- mobilize new resources for financing health, both within countries and from external sources, to help the poorest people;
- establish public health priorities for drugs, vaccines, diagnostics, and other health products;
- create fair health care financing systems to cover all people;
- assess the disease burden for major pathogens, country by country;
- assess the economic impact of diseases, country by country;
- conduct cost-effectiveness assessments for existing and anticipated products;
- strengthen research capability, including that associated with clinical trial sites in areas where certain diseases are endemic, through increased funding and training;
- support legislation that provides incentives or lowers the costs and risks of developing new or improved products for neglected diseases;
- support market segmentation for the poorest countries and price-tiering policies by industry;
- support market assurance mechanisms not only politically but also with solid financial appropriations.^a

The **for-profit private sector** could:

- increase the use of devices such as licensing, tiered royalties, market segmentation, and tiered pricing to make products more accessible to all in need;
- allow wider access, under appropriate legal conditions, to chemical compound libraries in order to facilitate the search for new indications for old drugs;
- broaden personnel exchanges in order to allow public sector programmes to benefit from private sector skills, e.g. market/demand forecasting;

- create information policies in order to permit easier identification of partners for potential collaboration by interested parties.

The **collaborative efforts between the public and private sectors** could:

- agree on a working definition of the neediest countries and on how to target resources and special attention to them;
- estimate the need, demand, and uptake for existing and new products in developing countries collaboratively, since the public sector has the data and the private sector has the expertise;
- manage the challenges of concessionary supply to the poorer countries, including preventing the diversion of products from intended beneficiaries to markets where prices are higher and the potential erosion of revenue from the richer markets necessary to support continued research and development;
- test and pilot new products earlier in developing countries to establish their potential benefits and reduce the delays that occur before the products become widely available;
- review partnerships engaged in donation/distribution and strengthening of health services, for lessons on distribution systems in poorer countries, and devise ways in which future efforts can apply the lessons within the framework of national plans and priorities;
- create additional partnerships, where necessary, in order to develop the products most needed to meet the health needs of the poor. This work should aim for products suitable for use under the conditions prevailing in poorer countries: simple administration and short-course treatment are desirable characteristics. Given the anticipated increase in the burden of noncommunicable diseases, it is advisable to look now at partnerships that would tackle the requirements of developing countries in this area.

^a In the absence of efforts to make markets function effectively to meet health needs in as many countries as possible, the bilateral development assistance community will be faced with the unmanageable prospect of subsidizing health in many countries for the foreseeable future. In the absence of a prospect of some revenue and effective delivery systems, there is little reason to think that the interest of the pharmaceutical industry in the needs of poorer populations can be markedly increased solely by push interventions for product development.

Annex A: Examples of agreements between product development partnerships and commercial collaborators.

In-licensing of PA-824 by the Global Alliance for Tuberculosis Drug Development (TB Alliance)

The Global Alliance for TB Drug Development (TB Alliance) designs its contractual arrangements to enroll the best scientific partners worldwide and to ensure that the resulting technologies are affordable, accessible and adopted by healthcare workers and patients in countries with the greatest need. The TB Alliance uses ownership or rights to intellectual property (including assignment, inventorship, licensing, sublicensing and other appropriate legal mechanisms) to balance its interests with incentives that make the industrial development, production and commercialization of new drugs economically feasible.

In 2002, the TB Alliance signed a landmark agreement with Chiron Corporation to in-license PA-824 and its analogs. Recognizing PA-824's potential as a tuberculosis (TB) therapeutic, Chiron was keen to license its intellectual property to an organization committed to advancing its development for TB. The TB Alliance received worldwide exclusive rights to PA-824 and its analogs for the treatment of TB and Chiron pledged to make this technology royalty-free in endemic countries. Chiron retained the right to develop and commercialize the compounds for non-TB indications.

The TB Alliance immediately devised and is undertaking a cost-effective development plan for PA-824, which is overseen by a development team with support from the U.S. National Institute of Allergy and Infectious Diseases. In its first two years of development, PA-824 has successfully passed major preclinical milestones and, if progress continues, could enter clinical trials in 2005. The TB Alliance is also pursuing a backup program initially evaluating two analogs of PA-824 that have demonstrated even greater potency in vitro than PA-824.

The PA-824 agreement demonstrates how the public-private partnership model can be leveraged to develop new products for the diseases of poverty and that the economic realities of drug development can co-exist with a social mission.

Royalty-free compound license from Tibotec/Johnson and Johnson to International Partnership for Microbicides enables development/supply for resource for poor countries

Since women are biologically and socially more vulnerable to HIV infection than are men, preventive options that women can use are critically important components of global efforts to stem the HIV/AIDS epidemic. The mission of International Partnership for Microbicides (IPM) is to accelerate the development and delivery of microbicides, products that can be used topically to prevent HIV transmission, for women in resource-poor settings.

The ideal microbicide will kill or inactivate HIV before it can reach its target cell. A product that blocks HIV from attaching to or entering its target cell could be a second line of defense. Should virus escape, a third approach is to inhibit HIV from replicating within cells, thus preventing it from spreading throughout the body.

Currently, there are several classes of HIV therapeutics that are being successfully used to treat HIV-infected patients, and pharmaceutical companies are actively pursuing development of new generations of these compounds. Many of these drugs could be formulated for topical delivery to prevent HIV infection. To address this need, IPM entered into an agreement with Tibotec Pharmaceuticals Ltd, a subsidiary of Johnson & Johnson, to develop the promising compound TMC120 as a microbicide. TMC120 belongs to the class of drugs known as NNRTIs (non-nucleoside

reverse transcriptase inhibitors) which are already widely used therapeutically to treat people living with HIV/AIDS. This agreement marked the first collaboration in the microbicide field between a major healthcare company and a public-private partnership such as IPM.

Tibotec developed TMC120 as an oral AIDS drug in the early 1990s, but has since adapted it into a gel that is currently in Phase I clinical trials. Under the arrangement, Tibotec provides a royalty-free license to IPM to develop, manufacture and distribute TMC120 as a microbicide in resource poor countries. Additionally, IPM will look to develop other formulations with TMC120, both alone and in combination with other active ingredients. Under the agreement, Tibotec will bear the cost of the compound through Phase II testing and will remain active as a scientific advisor.

Agreements such as this one benefit both organizations. Through these arrangements, IPM and other non-profit microbicide developers can significantly expand the pipeline of promising candidates for development. Pharmaceutical companies can minimize the risks (proof-of-concept; regulatory; market size) of developing a new class of products by transferring the development of the drug to another entity. Should the product eventually receive regulatory approval, then both IPM and Tibotec will have achieved their goals.

Concept Foundation facilitates low cost contraceptive supply to public markets in developing countries

The Concept Foundation was established to ensure the supply, to developing country markets and at reasonable cost, of a contraceptive product arising from WHO funded research.

WHO developed the clinical data necessary for regulatory approval of a new contraceptive product through research that it funded. It donated the rights for use of this data to the Concept Foundation. The Foundation in turn licenses manufacturers in various (mostly) developing countries to apply for regulatory approval, manufacture and sell the product to public markets on a 'manufacturing cost plus X% profit margin' basis. The Concept Foundation sets and enforces certain performance milestones and confidentially reviews production cost data from its licensees.