Challenges for Product Development Partnerships in Facilitating Equitable Access to New Health Products in Low Income Countries

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Introduction: Ensuring Access to new products

The core mission of the Product Development Partnerships (PDPs) is the development of appropriate products – acceptable, affordable and available - for use in low income settings. Ensuring access to these products, so that they reach those who need them most, poses a significant challenge for the PDPs and needs to be considered early on in product development.

The challenges of ensuring that end-users will be able to access products are clearly recognized by the PDP community, and both PDPs and donors are actively involved in discussions identifying the key components for the development of effective access strategies.

The meeting described here was convened to advance the discussion in five main areas: access strategies; country decision-making; regulatory; pricing; and economics and financing.

Background

In September 2008, a group of PDP representatives and invited experts met in Geneva to "develop a common understanding and record of PDP experiences, best practices and challenges in the area of access." One outcome was a definition of what access means to PDPs (Brooks et al *Innov. Strat. Today* 3:1-5). The conversations from this meeting continued with further meetings in Seattle in July 2009 and via a PDP Access Steering Committee. This Steering Committee commissioned, with support from the Netherlands Directorate-General for International Cooperation (DGIS), a series of discussion papers on discrete topics relevant to new product access. Preliminary findings from these draft discussion papers were presented at the meeting in July 2010, and formed the basis for information exchange on each of the topics.

The primary goal of this meeting was to develop common strategies using the expertise available across the PDPs, thus improving performance, efficiency and use of resources, with the overall goal of improving public health.

The specific objectives of meeting were as follows:

1. Share preliminary conclusions regarding strategies (and rationales for those strategies) from the draft discussion papers on 5 topics: Overall access strategies; supporting country decision-making; regulatory; pricing; and economics and financing.
2. Determine the implications of the conclusions for PDPs and their access work.
3. Agree on next steps to build upon the shared conclusions and areas for further investigation.

The agenda of the meeting is attached in Appendix A.

The following provides a brief summary of the five main issues considered and discussed by participants and the next steps proposed by the working groups. The complete presentations and discussion papers can be accessed at www.conceptfoundation.org

SESSION 1: Country and Donor Perspectives

Anthony Mbewu, Global forum for Health Research

Access from a country perspective.

Key issues for PDPs to bear in mind:

- The broad definition of access is "a set of coordinated activities needed to ensure that the products developed will ultimately have an equitable public health impact" [Brooks et al., Innov. Strat. Today]
- Definition of success in access is critical, but definitions of success and metrics to track progress are lacking.
- It is for countries to select the appropriate mix of interventions and strategies relevant for their situation
- How are access strategies developed and communicated?
- Research is an important part of achieving health equity: internationally, research is skewed towards the diseases of the wealthy world but PDPs can try to redress this imbalance.
- How do PDPs assess the complexity of a health system that is very fragmented?
- How can health systems afford the products they need now and those that will be developed by PDPs?
- How will these products be accessed in the public and private sectors?

Using South Africa as an example, access issues from the perspective of the consumer were explored. Despite a relatively large GDP, the inequities in South Africa are still huge and the public health sector is straining to provide services in the face of the HIV/AIDS and TB epidemics. Although there has been some progress there are still major inequities in access. Whilst the number of adults receiving anti-retrovirals (ARVs) had grown from 5% of adults in 2004 to 40% by 2008, the target is 80% by 2011. The state is spending $800M on HIV/AIDS but remains $300M short of the finances needed. South Africa is still reliant on importation as only 20-25% of all pharmaceutical products are manufactured locally. For ARVs, the majority are formulated locally but APIs are imported (and APIs are 60-70% of the cost of the products). This creates a negative trade balance (could rise to $600M/annum for ARV APIs alone), so local manufacturing has become a higher priority. There have been benefits in addressing the challenges of costs of HIV/AIDS medicines by interacting with diverse organisations including the Clinton Foundation and the Cuban government.

South Africa's attempts over the past 10 years to increase affordable and sustainable access to ARVs provide useful learning points for access to medicines in general. The following issues need to be addressed:

- Financing – government versus private, sustainability, reliability & stockouts, tiered pricing whether for low income v middle income countries, or within countries (public vs private)
- Pricing – country vs global (external reference price), market power and leverage, transparency, regional tenders (such as within the 9 Southern African Development Community countries)

- Regulatory issues – fast track, early discussions, licensing agreements, harmonisation (e.g. SADC, African Union), WHO prequalification
- Decision-making – political will, cogent arguments, economic case and not just health impact, national security (e.g. pandemic flu vaccines), integration (e.g. National Strategic Plan for HIV/AIDS and the SA National AIDS Council)

Access from a donor perspective

Patricia Atkinson, Bill and Melinda Gates Foundation (BMGF)

There are some common issues that all donors face; these include sustainable funding, identifying the funding gaps, and how to optimise impact. The donor community expects PDPs to develop strategies to mobilise other resources and increase cost effectiveness.

Some pointers for how PDPs can move forward:

- Build access strategies into the Research and Development (R&D) portfolios – not just cost of goods but also of delivery
- Access considerations need to be part of choosing research partners
- Clinical trials planning and regulatory strategy towards building access
- Selection of partners from an access perspective and how they can help with leveraging commitments
- Increase interaction with access partners not just R&D partners, especially those who share our urgency
- Post-registration and launch activities – what is essential as opposed to what is nice to have. If one PDP does a lot of post-launch activities, other PDPs may be held to this. Do not bite off more than we can chew.
- Know the cost of good and the cost of delivery.
- Address what donors want in an access plan – identify a clear pathway and where gaps exist, especially in funding
- Plan; understand where there are gaps that slow the uptake.
- Collaboration – what do we have in common that we can build on to increase access?

PDPs should identify a pathway to rapid uptake, identify the gaps and threats and where there is a need for other partners. In general, PDPs have done less with access partners and need to do more, although the challenge is finding suitable partners with similar urgency.

SESSION 2: Defining and Developing an Appropriate Access Strategy

Reference paper: *PDP Access Strategy Discussion Paper, July 2010.*

Steve Brooks (PATH), Florence Camus-Bablon (DNDI), Elizabeth Gardiner (TB Alliance), Patricia Atkinson (BMGF), don Douglas (PDVI), George Jagoe (MMV)

The goal of a PDP access strategy is to guide both pre- and post-introduction activities for more effective product planning, rapid adoption and relevant use. In this session the goals were to share best practices, identify main shared challenges, offer various perspectives to address these, and agree on access hurdles that may benefit from joint action and coordinated mechanisms.

Access is defined as '*a set of coordinated activities needed to ensure that the products developed will ultimately have an equitable public health impact (Brooks et al., 2010)..* Strategy was defined as the overall goals, priorities, tactics and metrics guiding access work, which are by definition iterative.

The challenges discussed were:

- Defining success and related metrics

- Branded versus generic positioning
- The PDP's role in ensuring access?
- Incorporating access into the R&D strategy.

Defining success on access and metrics to track progress.
Following a review of the approaches of 3 PDPs, the importance of defining success could be summarised as follows:

- Facilitates planning and priority setting
- Orients the strategy around an overarching goal
- Narrows scope of issues = useful focus
- Linked to country adoption = only products wanted by countries
- Broad scope (all related products) = wide disease impact

The group was challenged to consider throughout the meeting measurement of PDP success in access.

- What metrics to use?
- Who will measure, how, and who will pay?
- What are the other PDPs using to define success?

Some Ideas for adoption of success metrics could be:

- Volume of product sold / # of users adopting
- # of countries with product registered
- Time from Stringent Regulatory Authority (SRA) registration to WHO prequalification
- Time to purchase by countries
- Time to first use
- Number of countries with decision to use or not an intervention

Pre-launch access measurements might include: # of countries visited; # of programme managers met to discuss product; # of 'exposures' of decision makers to product information; # of studies of countries' needs and product preferences; # of countries agreeing to adopt, and changes made to TPP, portfolio or clinical trials as a result of access discussions.
A critical measure of access is whether the medical needs been fulfilled and whether the patients and health care system are using the product are not readily measured in the short term.

Branding: advantages and disadvantages, is there an optimal solution?

The case for branding	**The case against…**
Differentiates product and makes it easily identifiable	Is expensive, adds costs to be borne by the consumer or by the donor
Allows users to form opinion on/ preference for the product	Requires long-term support, and donors will not be willing to sustain
Creates real value in the eyes of industry partners, and perceived value in the eyes of product users	If social concerns start competing with commercial firms in marketing, they 'unlevel' the playing field because they are playing with donor money
Creates intellectual property (trademarks) that can increase the value to commercial partners and allows the PDP to retain control of how the product is costed and utilised	If social products knock commercial firms out of the market, what happens when the donor support ends and revenues are not sufficient to maintain the product in the marketplace?

PDPs are well positioned to take advantage of the strengths of their private, commercial partners in product development and marketing. Even products sold in bulk into public sector procurement systems need to have an identity - a brand name of some description - but do not necessarily need to be heavily promoted as would a purely commercial product. Vaccines and drugs sold through private channels must be clearly differentiated and identifiable – two characteristics of branding. PDP-developed products have social value, and this can be conveyed through branding and identification of the PDP and its social goals, including: the promotion of the intended outcome, e.g., protection against disease through vaccination; or the product category, e.g., the routine use of anti-parasite drugs. Since the PDP's goal is greater health rather than market share, support to both the generic and the commercial forms on the marketplace is valid. PDPs should consider whether there is a case for 'overbranding', i.e., a mark to show that it is a PDP product.

A proposed solution:

- Brand to enhance product value to commercial partners, and to impart social value to users
- Support modest packaging and labeling for vaccines and drugs developed with public funds
- Do not invest in extensive brand marketing campaigns - keep the promotional support generic, which will also complement commercial brands of our private-sector partners
- Harness the marketing power and expertise of commercial partners to support both commercial and non-commercial versions of the products.

One approach is for commercial partners to take over responsibility for promoting the product as soon as it nears the regulatory process.
The PDP is a credible brand which triggers expectations and responses and is respected by industrial partners and could this be consciously developed. The idea of a "PDP seal of approval" could be considered, but issues of liability need to be taken into account this way, PDPs could support "category promotion' rather than single product branding.

Branding must be considered in negotiating licensing agreements and insurance. Although for some PDPs the manufacturing partner has complete control of brands, not the PDP. The question of does branding influence adherence came up but with PDP products it is too early to say.

PDP/commercial partnerships: key drivers for optimized success?
This topic was presented from the perspective of PATH, which collaborates with large companies, emerging market companies, and small companies to produce innovative health technologies.

PATH works based on clear and articulated guiding principles (included with the discussion paper) and expects its partners to subscribe to them in joint ventures that are mutually beneficial. These principles include:

- Clear link to Mission of increased availability, affordability and accessibility
- Recognition of private sector needs
- Clear definition of roles, responsibilities and expectations
- Transparent collaboration
- Appropriate selection of collaborators
- Appropriate management of risk
- Dissemination of results
- Awareness of potential conflict of interests

- Ensuring high standards of quality and ethics

Critical terms of partnering agreements include: ensuring product supply; making products affordable; and managing intellectual property. However there are no magic formulas for the right deal with commercial firms, and optimal success is achieved when partners remain interested and invested over the long haul. It was acknowledged that if leadership of commercial partners changes, PDPs may have to re-start the relationship. The terms of the partnership depend on the state of the science, IP, time to market, clarity of market, distribution system readiness, and partnership complexity – all of these drive risk and therefore partnership terms.

PATH supports both the generic and the commercial forms of products on the marketplace since the goal is greater health not greater market share. It is an advantage if a mixed team, in terms of knowledge, roles and responsibilities (e.g., business development, product development, and public health programmatic experience), can remain engaged throughout development of a product.

One way of measuring success is demonstration of how partnerships can lead to impact – accessibility, availability and affordability and whether the products are replicated or further developed by other organizations.

How far should the PDPs extend their reach?
The current role of access within PDPs was defined from three perspectives: access embedded in the work of the organisation; to inform product development; and to facilitate timely uptake. The PDP role in post-licensure activities was discussed. Following interviews with around 20 stakeholders, factors identified which need to be taken into account include expertise within the PDP and availability of partners.

Most PDPs are not implementers but catalysts. For most modalities, there is existing infrastructure and capacity for implementation. In the majority of cases, PDP Access teams don't see themselves as product implementation agencies. In order to enable countries to accelerate their decision to implement, PDP access teams may need to play a role in identifying gaps and solutions as well coordinating the activities related to adoption decisions

PDP Access teams are responsible for providing critical input throughout the R&D process to ensure alignment of products with what is needed to eventual achieve public health impact; they also ensure a smooth transition of products to implementing organizations. Each team is working to establish effective mechanisms to accomplish this within their PDP, in the specific context of their disease and modality.

The exact access role for a PDP needs to be tailored to disease, intervention, and partnership, geographic and product-specific characteristics. We are learning as we go, and mechanisms for shared learning are critical to minimize mistakes and benefit from others' successes.

The roles for Access depend on the stage of development:

- Preclinical up to early clinical: Access input is essential to: define the TPP (target product profile), inform R&D strategies; product formulation, presentation and dosing decisions; and key stage-gate decisions around product progression. For this reason, access groups need a close (within-PDP) relationship with R&D.
- Late clinical development to launch: PDP Access groups need to have the in-country knowledge and relationships so that they can be sure late clinical

development is well tailored to the needs of countries. They also need to facilitate hand-over to entities appropriate to the intervention type that will lead implementation, not necessarily themselves be implementing. MoH staff, multilaterals and NGOs already exist to pick up the work on the ground.

- Phase IV/demonstration projects will be critical and likely require substantial PDP guidance, commitment and/or involvement, such as a bridge between private sector and policy bodies, to be determined on a product by product and partner by partner basis.

Essential elements of the access strategy: lessons learned. The experience of MMV in incorporating access issues into malaria drug R&D was presented and the following aspects were addressed:

- Access strategy needs to be consistent with the discovery and development agenda. MMV's Vision and Mission reflect the need to address both access and delivery.
- Strategy requires iterative development with input from a wide range of key stakeholders and partners, including 'activated' Board members, pharma and implementing partners, WHO Global Malaria Programme and AFRO, and the Roll Back Malaria partnership. Conceptual guidance was received from BCG during development of the 2008-2012 business plan.
- Simplicity of conceptual framework – the 3 pillars of Acceptance, Expansion, Measure/Evaluate/Feedback required to reach Health Impact
- Readily linked to annual access plans for each MMV product
- Firm but not rigid – adaptable over time because the landscape changes and there will be pressure to re-visit access and delivery strategy. Local manufacturing may be an evolving priority. There may be a case for accelerating generics to expand affordable access.

Lessons learned include:

- Education of partners is essential
- Country registration can be addressed on the back of an organisation with the right experience.
- For a paediatric product, align the publicity around child-friendliness and a public health priority.
- It is important to establish some access metrics before launch

SESSION 3: Country level decision making: what is the role of a PDP in helping to build country-based consensus around the adoption of a new technology?

Reference paper: PDP *Country Decision Making Discussion Paper, July 2010.*

Alan Brooks (Path) William Wells (TB Alliance), Philip Anum (MOH, Ghana), Florence Camus-Bablon (DNDI), Lois Privor –Dumm (IVAC)

The landscape now and what is needed. The decision on whether to take up a product is for the country concerned, in the context of many competing priorities. PDPs, WHO, Pharma and others can assist by providing data on interventions. Globally, PDPs can help multilateral agencies to work through the necessary issues in a harmonized manner. Depending on the product and disease, there may be a need for:

- Definition of disease burden
- Establishment of new decision-making bodies
- Support for local advocacy
- Phase IV studies

Certain activities are common to delivery of all products and will be absorbed in the existing healthcare landscape, but other activities are unique to product introduction. For this latter category, an organization or organizations experienced in this process may be needed to support the national programme. Below are the types of organization that could fulfill this role, with their advantages and disadvantages:

Partner	Advantages	Disadvantages
Multilaterals such as WHO	Extensive reach and impartiality	Typically cautious about new interventions; may be overwhelmed by other initiatives and thus lack time and resources to devote to new product introduction
Local academia, researchers and/or professional organizations	Close to in-country processes, needs and data; credible with local policy-makers	May not have a broad view of a problem; may be influenced by personal research interests
NGOs	Some have specific expertise in new product introduction	Require funding specific to the new product to drive their activities
Pharma and/or manufacturing partners	Product-specific expertise, and in some cases extensive sales networks	May be seen as a biased source of decision-making information; may lack experience in the disease and/or in low income settings

It is important to get the country stakeholders involved during the trials stage and establish a partnership. In order to move from engaging one country to adoption by many, regional meetings and WHO's networks can assist.

What PDPs can do to facilitate country-level decision making; a perspective from Ghana

This topic was introduced by reviewing what informs country decision-making on new products. This includes:

- Health system reviews
- Identification of gaps
- Needs appraisal and potential impact
- Local research data
- Political will
- Decisions by global agencies and countries with stronger health systems
- International regulatory procedures in place
- Financial support and requirements

In addition, for each new product the country needs to address quality and post-registration issues, sustaining supplies and distribution, product information and relevance to the disease in the country, and cost issues at all stages. In terms of access, the social environment, communication needs and the availability of distribution partners such as NGOs need to be addressed. Building local research capacity and the transfer of technology are also important considerations. Procedures to obtain important feedback such as on Serious Adverse Events (SAEs) or equivalent must be determined before delivery.

In summary, while PDPs may be concerned about the impact of their product, the country is interested in how it fits into the public health package as a whole, and the strategies adopted reflect this. However the strategies and structures vary from country to country – Africa is a very heterogeneous continent and PDPs need to understand the local realities and country-specific structures.

It is essential to support existing structures within the public health package of the country and not create parallel systems. On metrics, it was cautioned that just asking how many of x product were purchased does not mean that the product was used appropriately.

Case study 1: DNDi and country decision making - a patient and country-needs driven initiative.

The objectives of DNDi are:

- To develop and deliver 6-8 new treatments for neglected tropical diseases (NTD) by 2014, based upon needs identified by endemic country stakeholders.
- With country stakeholders, to support recommendation and implementation of these new treatments to facilitate equitable access.

DNDi 'facilitates' patients' access to treatment, and is driven by goals of equitable access to new treatments and to enable service delivery by the implementing partners. DNDi engages country stakeholders via 5 main mechanisms:

- 7 Founding partners: centers of excellence in NTD research & care, on Board of Directors along with 2 patients representatives [MSF, ICMR, KEMRI, Malaysian MoH, Oswaldo Cruz Foundation, Institut Pasteur, WHO TDR]
- R&D platforms to strengthen clinical research capacity and assist GCP clinical development for specific diseases in endemic areas, i.e., HAT in Central Africa, VL in East Africa, Chagas in LA, FACT.
- Intervention / field trials to demonstrate feasibility and generate data for adoption
- Other international partners, e.g., WHO NTD, MSF logistics
- Pharmas

Through all of these partnerships, there is a transition to "natural implementers", i.e., National Control Programmes, WHO, and NGOs.

Case study 2 : Working with multilaterals as a way to interact with large numbers of countries.

This focused on two key vaccine initiatives which had not been taken up despite proven efficiency. The initiative was developed in partnership with multilateral agencies in order to scale up quickly. This increased the use of the product from 17 countries in 2005 to 72 in 2009.

The important contributions of multilaterals to the Hib Initiative and PneumoADIP, and some limitations, are below:

Important contributions of multilaterals	**Some limitations**
Provide access to key government officials	Role in advocacy limited
Provide important perspective as partners in country, involvement in implementation	May take a conservative approach
Respected by government as technical partner and honest broker	Lacks flexibility due to bureaucratic processes
Convener of other partners	Priorities may not match priorities of PDP
Critical to ensure sustainability	

Introducing two new vaccine products (via the Hib Initiative and Pneumo ADIP) required extensive consultations with 73 countries in 4 regions of the world. The key

was to try to broaden the partnerships and use meetings for consultation and planning. Investments in multiple visits to countries and in the post of vaccine officers in WHO were considered important in developing the programme.

The conclusions were:

- Multilaterals are critical to the success of PDPs
- Dedicated staff are important – located at regional offices, and additional personnel for programme support
- Continuous follow-up needed (in person, retreats, close monitoring of country situations)
- Can help define target product profiles, disease burden
- Can play an important part in financing and procurement
- Important for sustainability – surveillance networks, building capacity

Health systems are designed for templating and consistency, not for change, but if the right structures can be created the right people will be attracted into the conversation.

A moderated panel was asked to consider 3 questions:

1. **Will the number of products being developed by PDPs in the near future overwhelm the capacity for countries to make informed decisions? What can PDPs, countries multilaterals and other actors do to address this potential problem?**

- If the product meets a need, countries will usually want to adopt it but will require support. Setting up parallel systems must be avoided.
- Lack of evidence-generating and decision-making capacity in-country is often a bottleneck. In particular, context-specific pharmaco-economic analysis is a key bottle neck e.g. health technology assessment. The UK's NICE is supporting capacity building at country level through CALYPSO – but the countries have to find the funds for this so it is restricted to middle income countries at present.
- Capacity on the ground is not always adequate to gather data to demonstrate impact, which is a requirement of donor support. Dialogue between stakeholders can go some way to addressing this problem.
- Establishing a decision-making framework can guide stakeholders through the process of introduction of, for example, a new vaccine.
- Products need to be considered in the context of the full range of strategies for the therapeutic area

2. What determines the extent of a PDP's involvement in country level decisions?

- Using specific examples from one country to another can work although it is important to recognise differences.
- Large and complex countries such as India or Nigeria will require a greater time commitment.
- The wider stakeholders beyond the Ministry of Health need to be brought into the process early – particularly the Ministry of Finance.

3. What determines the choice of partner(s) for country engagement (e.g multilaterals, local researchers, NGOs, Pharma)?

- It is important to encourage the creation of an appropriate structure in-country, such as an advisory committee or task force to the Ministry, which will be the forum for technical and programme management discussions.
- There is a need to be flexible in choosing partners – a research institution may be the most important partner at the beginning, but in rolling out the

programme a range of implementers (eg NGOs, district administration etc) will need to be engaged.
- Funding plays a major role in determining partner availability.

SESSION 4: The regulatory challenges in ensuring equitable access to new health products in low income countries. Reference paper: *PDP Regulatory Discussion Paper, July 2010.*
Mike Brennan (AERAS), Margareth Ndomondo Sigonda (NEPAD), Drew Meek (WHO), Javier Guzman (Policy Cures), Siriporn Chawanaon (MOH, Thailand), Wallada Im Amornphong (Concept)

The best regulatory pathway could be defined as the pathway resulting in a timely response without compromising quality. For the purpose of the paper, 10 PDPs were asked to respond to a number of questions to identify their approach to regulation. Below is a table of the regulatory approaches of the PDPs studied.

PDP	Type of products	Approaches used/considered**
DNDi	Medicines for neglected tropical diseases	Twinned, Article 58 for NCEs, local RA for combos of already registered products
IPM	Microbicides	Article 58 for new API/delivery system, FDA to facilitate PEPFAR procurement
MMV	Medicines for malaria	SRA with or without WHO prequalification
TB Alliance	Medicines for TB	SRAs with or without WHO prequalification
Concept	Medicines for human reproduction	ICH-compliant dossiers to local RAs and WHO prequalification
Aeras	TB vaccines	Initial Phase 1 trial in SRA, joint review, WHO prequalification
MVI	Malaria vaccines	Article 58, joint review by AVAREF, WHO prequalification
MVP	Meningitis A conjugate vaccine	Local RA, twinned review, joint review, WHO prequalification
FIND	Diagnostics	Local RA to ensure ISO compliance
IVCC	Pesticides	For reformulated AI, WHOPES; for new AIs, still considering

*** NCE = New chemical entities; API = Active pharmaceutical ingredient;*
PEPFAR = President's Emergency Plan for AIDS Relief; ICH = International Conference on Harmonization;
AVAREF = African Vaccine Regulators Forum; ISO = International Organization for Standardization; AI = Active ingredient

An ideal for both donors and PDPs is regulatory harmonization (including joint review) that leads to sustained regulatory capacity building in low income countries. There should be one global standard of quality (eg.,ICH's-CTD), set and shortened timelines, and a formalized joint/twinned review process. WHO prequalification could be shortened / made more efficient, harmonized between drugs, vaccines, diagnostics and pesticides (where appropriate), and be opened to a wider list of priority products. Information sharing is critical both between regulators, as part of capacity building, and between PDPs.

Case study: NEPAD and the challenges for regulators in emerging countries:
In 2009 the New Partnership for Africa's Development convened a meeting to consult over the harmonisation of regulation in Africa with a view to improving patient access

to medicines and other public health products. This led to the African medicines regulatory harmonization initiative spearheaded by the Consortium: NEPAD/AU, PAP, WHO, BMGF, DFID and Clinton Foundation.

Regulatory challenges in Africa include:

- Pharmaceuticals are inextricably linked to economic factors but are not an ordinary commodity of trade that should be left only to market forces
- Despite differing interests of industry and public health, the target area of safety, efficacy and good outcomes is common for all
- Common purpose implies timeliness, responsiveness, vigilance, innovation and adaptation to a changing environment. This naturally requires cooperation and different types of partnerships to achieve equitable access
- Each NRA has an obligation to ensure that the risk-benefit balance of every medicine is appropriate for that country
- NRAs have an obligation to deliver the right medicine at the right time and in an affordable manner and to assist society to make informed decisions in their choices
- They have an obligation to guide appropriate policy orientations in the pharmaceutical arena
- PDPs and other stakeholders should ask whether the NRAs in developing are countries doing enough? What challenges are they facing in fulfilling their obligation? What can they do differently?
- There are human resource constraints in regulatory affairs in low income countries, although several initiatives have been designed to strengthen capacity.

In Africa, some treaties and protocols for harmonisation exist but there is a problem in implementing agreed regional decisions, thus progress is slow. For an initial phase 2009-2010, individual regional economic communities (RECs) are proposing a project for financing, with the East Africa Community proposal ready for funding this year. For the next 5 years, a comprehensive programme is being developed by NEPAD and WHO in response to the political, technical and financial challenges of medicines regulation harmonisation and strengthening. The primary aim is to reduce the time to place a product in a particular market through improved regulation of medicines across borders. There are expected to be substantial savings for Government budgets.

To deliver real improvements an objective assessment of NRAs in Africa is needed to determine gaps in medicines regulation and harmonisation (capacity, infrastructure and legislation) and develop appropriate interventions. There needs to be a strategy to streamline the existing regulatory pathways and to coordinate at continental level. Centres of regulatory excellence in Africa for each Regional Economic Community need to be identified as well as a sustainable financing mechanism for the harmonisation initiative.

Case study: FDA processes in Thailand.
This presentation described the drug control system in Thailand, including the structure of the drug control division, the regulatory system, and registration procedures. Thailand's involvement in the Association of Southeast Asian Nations (ASEAN) harmonisation project was also described, as well as related regional capacity building initiatives and the safety monitoring programme.

Overview of the WHO Regulatory Capacity Building and Prequalification programmes.

The different processes WHO currently adopts for prequalification (PQ) of pharmaceutical medicines, vaccines, and diagnostics and the pesticide evaluation scheme were outlined The purpose of the PQ programmes is to give guidance on which products meet WHO quality standards and specific purchasers' specifications/requirements. The products may be procured by UN agencies and other large volume procurers (e.g., the Global Drug Facility), as well as by individual countries. WHO prequalification may facilitate the registration and use of the evaluated products by the Member States of the WHO and other stakeholders.

The PQ processes have a good deal in common, including dossier submission, sample and post-approval testing, audit of manufacturers and reporting and complaints and reassessment procedures. Capacity development is a significant activity aimed at strengthening national regulatory authorities. There is a rotating post at WHO which is only filled on attachment.

WHO is open for more in depth dialogue on PQ and offered to organize a targeted meeting for PDPs on the PQ and regulatory pathways.

Recommendations from the 'Registering New Drugs in the African Context' report.

New challenges for African regulators include the number and variety of drugs becoming available and the presence of drugs developed especially for diseases endemic to Africa (and thus not always being subjected to EMA or FDA review). African NRAs still experience lack of capacity - human and financial – and lack of political support. There is a need to explore alternative pathways (as described in the discussion). The following recommendations were made in a joint report by DNDi and the George Institute[1]:

1. Formal twinned review: all regulatory reviews of novel neglected disease drugs by SRAs (including under Article 58) and WHO PQ to formally include regulators from endemic countries targeted for that product
2. Automatic WHO prequalification for novel products approved by stringent regulatory authorities (SRAs)
3. Improve Article 58's attractiveness to product developers by:
    - Automatic WHO prequalification of drugs given positive opinion under Article 58
    - A positive Article 58 opinion to be converted to European Medicines Agency approval with a single European bridging study *OR*
    - A positive Article 58 opinion to provide automatic European Union Orphan approval
4. Select experienced Western NRAs to conduct prequalifications on behalf of, and in addition to, WHO
5. WHO to conduct a strategic review of drug prequalification priorities, along the lines of SAGE reviews for vaccines, including working with African NRAs and Ministries of Health to identify priority diseases or areas to be included in prequalification (and/or outsourced to reference MRAs)
6. Fund Centres of Regulatory Excellence in each of Africa's main sub-regions: West, South, East, Central and North Africa.

The size and range of the workload of an NRA is huge but is it necessary to have a fully functioning RA in every country? There is a national legal requirement to protect citizens but a growing recognition that there is not the capacity to do everything.

[1] Now called "Policy Cures" http://www.dndi.org/images/stories/advocacy/regulatory-report_george-institute-dndi_jan2010.pdf

At what point would WHO PQ not be required? Once NRAs have adequate capacity? Currently reassessment plus new products is posing a good deal of pressure and increasing time delays. PQ requires funding to enable WHO to undertake assessment.

General discussion points from the first 3 sessions

- Many new products are in the pipelines which have important public health potential, as well as presenting challenges for countries to utilize. Do there need to be strategic discussions to focus on priorities?
- What are the systems that need to be put in place or revised to facilitate their introduction?
- It is important to encourage innovation and PDPs have a role in targeted support to countries to take advantage of new products.

SESSION 4 : Pricing as a strategic element of an access strategy[2]

Evan Lee (FIND), Prashant Yadev (MIT/Zaragoza), Lester Chinery (Concept),George Jagoe (MMV), Tom McLean(IVCC), Carla Botting (PATH) Patricia Atkinson (BMGF)

Many factors affect pricing strategy such as whether the product is unique or whether there are substitutes, some which may perform less well. The appropriate pricing strategy may be different in the public vs. private sector, in areas with high vs. low endemic disease burden, or in countries with different income levels or different payers (e.g., major bulk purchasers (e.g. GFATM, PEPFAR) or multiple small purchasers).

Overview of the range of pricing models available and associated challenges.
In the commercial sector, prices are established to maximise revenue. Demand-side price analysis considers disease incidence, payer willingness, patient willingness and ability to pay, and payer architecture analysis. Supply-side price analysis considers COGs, R&D margins/amortizing of R&D, supply side market structure, and competitor pricing.

The aim is either a revenue-maximizing or access-maximizing price. Revenue is often bimodal, with both a lower and higher price resulting in maximal revenue (but the lower price allowing greater access).

Points of leverage in pricing include:

- APIs, raw materials, cost of production (healthier and competitive supply markets; leverage platform approaches)
- Ex-manufacturer price (manufacturing contracting vs market-driven price; optimal procurement structures; tiered pricing)
- Payer's willingness to pay (health effectiveness and cost effectiveness models; use toe-hold and POC studies to reduce payers' uncertainty, advocacy for financing). PDPs have a role in addressing "information blind spots".
- Distribution margins (help create healthier distribution markets, understand distribution margin legislation)
- Patients' willingness to pay (remove information blind spots, create product awareness)

[2] The discussion paper was not finalized in time for the meeting so the summary of findings was used as background.

Some options for PDP ex-manufacturer pricing:

- Cost plus: information asymmetry (producer may know better), but even their knowledge is limited as there is uncertainty about COGs, and COGs depends on sales volume. How to create incentives for dynamic cost reduction?
- Target price: AMCs include this. Requires a lot of demand side studies. A challenge is how to secure a guarantee supply.
- Health outcome based: more important for second entrants – need anticipatory planning to structure the clinical trials so that they demonstrate usable outcomes. Need country-context-specific data, but there may be costs involved in getting this data based on DALYs, QALYs.
- Pure market: may not lead to best access; requires careful monitoring of buying power in different procurement structures; must incentivize competition in production but IP issues may prevent this in the short run.
- Segmented pricing: based on the idea that not all patients and payers have the same sensitivity to price. The 2nd tier is problematic because its members typically have a wide distribution of income and the lowest in this tier will ask for the lowest price, leading to gradual collapse of the entire tier.

The example of a novel pricing scheme for Velcade®[3] was given – the price paid by the NHS (UK) is based on aggregate (improved) health outcomes, and is paid after the health improvement is observed.

Pricing parameters recently outlined by GSK and their implications.

PATH MVI recognised that there need to be incentives for Pharma companies to feel it is worthwhile to continue development. PATH/MVI partnered with GSK in the development of the RTS,S malaria vaccine. Pricing terms were negotiated with GSK early in Phase 2 (2005) when the novel adjuvant and its cost were not well known. So the agreed price was higher to cover this risk. MVI kept working with them on price. In Andrew Witty's January 2010 speech to CFR, he stated that GSK would only have a 5% return on the cost of manufacturing (including labour, materials and facility depreciation, with independent audit), and even that would go back into research. In addition, 12.5m doses are to be provided free.

But the actual price is still unknown, and as second generation vaccines are being investigated, other companies in the same innovation space may be impacted by GSK's pricing commitment. Moreover, the cost of introduction and pharmacovigilance are not yet factored into the price.

Case study: Reproductive health.

This case study is of Medabon® which as a medical abortion drug is by nature highly controversial. The product is applicable in both lower and higher income markets, and has been branded to de-mystify the product. It is being introduced in 26 low and middle income countries. Concept worked closely with WHO and managed the technology transfer, acting as 'guardian' of product quality and access to public sector agencies at an affordable price, through specific agreement with the manufacturer on quality, availability and pricing.

Even when legal obstacles are overcome and acceptance criteria are completed, often the channels of distribution will be low-profile, more covert –it is likely that actors other than Government will play a key role in providing access at country level. This is true even in areas other than abortion, as 60% of RH products in less developed countries are provided through non-public channels. Thus, a second price point for NGOs became a necessary strategy.

[3] A novel, effective myeloma drug

The conclusions were:

- Country driven public sector supply does not necessarily entail traditional public procurement mechanisms
- Significance and importance of pre-determined mechanism for price monitoring at country level
- Upfront detailed definitions of potential customer profiles (in relation to pricing) required

Benchmarking as a pricing model for PDPs

The concept of cost-plus is attractive to manufacturers, but PDPs need to appreciate that it is then impossible to convince them to lower prices via optimization of processes etc. - until there is a competitor, and then reducing costs becomes a major goal. For products entering existing market e.g insecticides, an option is to include in the agreement a process of benchmarking the prices for the new product against the prices for existing (competitor) products. For PDPs, make competition explicit and early – companies understand this competitive approach more than artificial fixed prices.

Pricing parameters for ACTs

PDPs, in establishing cost-plus pricing, should reserve the right to identify whether the price should come down (in response to expanding volume) and the right to inspect the cost structure.

In pricing considerations for ACTs, there is a notional pricing target before phase 3 starts, validated by the Expert Scientific Committee. The economics of production (COG, production efficiency, lower unit costs with volume increase) and economics of demand (public sector ($0.5-1 notional price), private sector (whatever it will bear), non-premium private sector (AmFm)) need to be taken into consideration. MMV will be cost plus for next two products. Contracts allow price to be revisited as volumes increase (e.g., Coartem prices have dropped 3-4-fold as volumes increased). Often the PDP needs to educate the manufacturer about the competition in order to avoid them crashing.

A donor perspective

Donors do not want invest in the development of products which will not become affordable to the target population. PDPs therefore need to understand the cost of development and delivery, and the role of scale. However, donors acknowledge that it is not always possible, during the early stages of development, to understand what pricing ranges will be achievable.

Pricing needs to be sustainable from the point of view of donors, countries and manufacturers. A healthy market will drive prices down. Short term measures which can lower prices: price negotiations and procurement strategies (e.g. Clinton Foundation negotiations for ARVs). Medium term measures: tweak product or do technology transfer to lower cost producers. Longer term measures: move to lower price producers and explore other technologies.

General discussion points

- Issues of risk play an important role, including how much confidence there is in demand forecasts.
- What distribution margin is acceptable in order to incentivise manufacturers?
- PDPs' pricing negations and agreements should not undermine a procurement agency's ability to operate under international procurement

guidelines and to negotiate lower prices (e.g., UNICEF). PDPs should establish price maximums instead of fixed point estimates for prices.
- Is there a way to make price-sensitivity estimates more robust?
- Other factors can disrupt the economic forces: an example is PAHOs lowest price clause which requires PAHP member countries, which are middle income, to receive the lowest price among tiered pricing structures, thereby disrupting the link between income and price.
- Risk can and should drive prices: if there is little confidence in the demand side, the is high risk and the prices go up accordingly.
- For some products, the local distributor may provide sales support which may mean the price is higher that the PDP-negotiated global price.

SESSION 7: Economics and financing

Reference paper: *PDP Economics and Financing Discussion Paper, July 2010*.
Lois Privor-Dumm (IVAC), David Evans (WHO), Tom McLean (IVCC), Alan Brooks (PATH), Tania Cernuschi (GAVI)

Economics and financing are often addressed towards the end of the project and are approached differently by different organisations.
The questions posed for discussion were:

- Economics – what role does economic data play in introduction and access, and should PDPs be engaged in gathering this data?
- Financing – what role do PDPs play in product financing discussions? What challenges do they encounter? What are the implications of R&D financing and product financing coming from the same donor?

Case study: In the face of competing demands a coalition of partners was formed to drive the pneumonia debate, focusing on a child survival message. A World Health Assembly resolution and UK All Party Parliamentary Group action resulted in increased commitments. The coalition allowed partners to:

- Advocate with one voice
- Focus on donors with a disease and child survival message; disease message received better than “vaccine-only” message.
- Bring important donor country voices to the debate.

Economics
The panel then addressed the following questions:

- Should PDPs be responsible for conducting cost effectiveness studies? If so, for what purposes and at what stage?
- What can be done to make them more useful for country decision-making purposes?
- How can cost effectiveness and affordability issues be addressed when multiple interventions are needed?

Cost-effectiveness (CE) analyses are important and should be a focus of PDPs.
The WHO experience of working with countries on health system financing was discussed. Ministers have external pressures to address individual problems but limited funds are available. In deciding on an intervention, cost effectiveness and benefit to the community are important.

Does CE analysis happen in reality? Generally, lower income countries will implicitly consider the issues – if only by comparing cost, burden of disease, and approximate effectiveness gain. They may think about them more than many donors, as governments are faced with hard choices.

What does this mean for PDPs? Commerce thinks about CE in the early stages of development and PDPs should do the same, considering:

- Will it be used to scale?
- What sort of price would make it affordable?
- What type of subsidy and donor support would make it attractive and allow for scaling up?

Emphasis of PDPs should be on affordability.
Cost effectiveness depends upon context and varies with many local socio-economic and acceptance factors. CE for control will be different from CE for elimination or eradication programmes. CE for a country strategy is different from CE for a donor. CE to compare Insecticide treated nets (ITN) vs IRS will be different to CE comparing vector control with a vaccine. A CE study is always a comparison, so what is the comparison? And what are the benefits measured (DALYs? persons protected?) and which costs should be counted? CE is a highly technical driver but may not be seen as being user driven. Users may care more about affordability, acceptance, compliance, and logistics.

- Can PDPs be unbiased in CE studies? Note that Pharma companies do CE studies on their own products, for consideration by the UK NHS. At a country level there are huge capacity implications for undertaking CE studies - not even the UK or US have done CE studies for every intervention.
- Do countries find them useful? Decisions on interventions are complex and not only based on CE.
- CE studies should be designed with a long-term public health strategy, rather than individual products, in mind. CE can be useful to help decide a strategy rather than decide about a product.
- A CE study needs to be done on a specific setting - not possible generally. However, doing the analysis can be an informative process that increases the understanding of drivers of acceptance.

Financing
The following questions were discussed:

- Should PDPs be involved in product financing discussions? If so, what should their role be? If not, why not?
- How could PDPs work together to expand the pie and is this their role? Is it even realistic that this can happen?
- Who should be convincing donors to finance more and that multiple interventions may be needed?
- What happens when the pie is perceived to be running out? Do PDPs continue on the same course developing new technologies?

Should PDPs get involved in product financing discussions with donors?
PDPs cannot deliver on their access mission if they are not involved in financing discussion. PDPs act as a bridge to ensure equitable access and affordability, and also understand issues of supply and demand. A timely flow of information is required so that need is anticipated, funds generated, and potential bottlenecks identified. The public health context for the entire disease area needs to be kept in mind. PDPs can help with business cases for international partner support.

The Global Alliance for Vaccines and Immunisation (GAVI) sees PDPs' role as that of supporting fundraising and attracting industry. Need should be matched to a long term plan, and costs and returns on investment identified. GAVI has had positive

experience of long-term forecasting (5-20 years) in order to plan fundraising and investment. Evidence submitted should be seen as independent as should PDPs. GAVI's view is that PDPs should mainly focus fundraising for R&D.

Should PDPs work together where more than one intervention is required for a particular disease? Joint operations in specific areas of expertise might be feasible, e.g., advocacy to donors and countries, or economic analysis.

What are the challenges ahead for PDPs?
Javier Guzman (Policy Cures)
Data from the George Institute "G-finder" report were presented. These data relate to financing provided for product development, not delivery, but illustrate some related challenges.

The PDPs manage significant sums. Of the US$2.9 billion financing to neglected disease R&D in 2008, US$580 million went to PDPs, although eight main funders are reducing their commitments due to the financial crisis. Sixty percent of the funding comes from the Gates Foundation, and the top five donors to PDPs provide over 90% of funding. Thus PDPs are vulnerable, especially in view of the financial downturn which affects companies as well as bi- and multi-lateral agencies.

More efficient use of recourses is essential; this could include:

- Increased collaboration on areas of mutual benefit e.g., regulation
- Foster synergy such as the royalty-free license agreement between TB Alliance and DNDi
- Joint activities such as pharmacovigilance of ACTs between MMV and DNDi

Summary of conclusions, challenges and next steps
In the final session, participants split into 4 working groups to consider: take home messages/key findings; remaining gaps; collaboration opportunities; role of other participants in supporting and fostering access goals; and concrete next steps.

The groups came up with the wide range of ideas for further consideration by the Steering Committee. A number of these are noted below.

Possible Future Activities for the PDP Access Steering Committee

(a) Analysis of access options
- Prepare case studies of hand-offs for products recently coming to market
- Analyze and develop metrics that could be used for M&E of access work by multiple funders (in collaboration with e.g Developing country representatives)
- Analyze the implications of individual or collective branding by PDPs
- Document timelines for access activities
- Conduct a costing of access activities

(b) Information sharing
- Establish a centralized repository of resources (TPPs, access plans, private sector principles, etc)
- Establish a website with details on clinical trials and late-stage pipelines; updated every 6-12 mos (see http://www.newtbdrugs.org/pipeline.php for an example)
- Establish a consultant roster (and/or collaborator roster) in key access areas

(c) Joint research or implementation projects
- Share implementation of cost of illness studies (for malaria PDPs)

- Conduct cost effectiveness studies that include more than one PDP product
- Research the methods for assessing affordability/willingness to pay
- Coordinate and/or implement joint pharmacovigilance activities

(d) Convening

- Convene a joint conference with countries on country decision making – particularly how countries can make decisions across multiple diseases and modalities.
- Convene smaller meetings to focus on single access topics, single diseases, or single modalities.
- Coordination with the other PDP working groups so that the access work can be focused appropriately.