PDPs AND ACCESS: WHAT WORKS; WHAT DOESN'T
Geneva, Sept 17-18, 2008

Session 1: An overview of Access

Presentation 1: A Bilateral Funder's Strategy & Bilateral Work on Metrics of PDP Success (Saul Walker, DFID)

Access informs:

- Product design and selection
- Partnership agreements

and is a key requirement for donors and country partners.

No single organization can ensure access by itself.

All of the elements – availability, acceptability, accessibility, and affordability – are needed to get an eventual health impact.

But PDPs could easily go too far: donors are already too far down into complex national systems, and if PDPs insert themselves far into national systems that will make an eventual positive impact less likely.

DFID wants: PDPs to come up with products on a needs-based level; ownership at country level; social and operational research; IP so that the product can be made without encumbrances; identified partners for manufacturing; and adaption of programs to changing global and local contexts.

There is a need to make a business case to manufacturing partners, and a public health case to countries and donors, while explaining the rationale for what you as the PDP will do, what you will facilitate, what others will do, and what you will advocate for others to do. "No-one is doing it" does not mean that the PDP should do it – advocacy may instead be the required role.

Presentation 2: Access Planning (Alan Brooks, MVI)

Access work involves building a bridge from those working on R&D to those who need the product. Work on access shouldn't get ahead of R&D but also shouldn't wait for R&D to finish.

The role of Access at MVI is:

- Informing product development
- Informing regulatory strategies
- Assisting in manufacturing planning
- Working with international agencies to plan ahead
- Preparing countries for decision-making

The job of access is to identify the fastest route to impact. For a malaria vaccine this is via large scale use in infants through public sector immunization programs in developing countries.

Target product profiles are needed to inform R&D decisions as early as the preclinical level. As products progress, they must be aligned with health systems via decisions on formulation, presentation, schedule, means of administration, and packaging.

Regulatory strategies can facilitate the time from development into use. For example, MVI has begun discussions about the possibility of parallel review by European and African

regulatory bodies with WHO pre-qualification. If successful this could save years from development to potential use.

Activities to inform manufacturing decisions must be taken years before a product is to be available. Work to estimate demand is one critical aspect aspect.

PDP's have an opportunity to foresee the critical activities by international and country partners from development to use. MVI convened a consultation in Jan 2007 with 13 global level partners to construct a Gantt chart of the hundred plus policy steps from development to use. It includes WHO policy processes, regulatory decisions, international financing decisions, procurement steps, and activities in countries. This allows MVI to identify opportunities to do certain activities in parallel, and to define which activities are on the critical path for a specific product.

To help prepare countries to reach their own decisions about use of future malaria vaccines, MVI and others have constructed a decision-making framework. www.malvacdecision.net . This is a mechanism for bringing together government, researchers, public health, academics, and other stakeholders at country level to identify in advent the information and processes they foresee to eventually decide on the use, or not, of a malaria vaccine. It is structured to reflect steps countries would like to take before phase 3 data is available, through to the post-licensure period.

Session 2: Planning for Introduction and Implementation

Presentation 1: Strategic demand forecasting as a tool for building access commitments (Lois Privor-Dumm, PneumoADIP)

- A strategic demand forecast is a longer term view that can inform investment in development and production capacity as well funding for new vaccines. It differs from supply chain forecasts which take a 1-3 year view and are used for actual procurement.
- Demand forecasting must take into account the resources and demands of:
    - donors
    - industry
    - countries
- It is important not to equate demand and need: demand reflects the effect of the barriers to adoption and implementation. Credible strategic demand forecasts have been consistently cited by industry as a primary barrier to working in the public sector.
- For a good demand forecast, there needs to be integration of the access group with the R&D group. Forecasts should be tied to willingness to pay and assumptions regarding sustainable pricing and financing.
- Forecasts should be expressed based on the needs of various stakeholders (e.g, in terms of revenues and NPVs for suppliers; financing requirements by year and cumulatively return on investment or lives saved for donors and countries)
- Demand forecasting should be used as a roadmap, as a tool for discussion – not as an end unto itself.
- Industry is more likely to believe an increase in demand if that increase is not steep and is tied to specific assumptions regarding demand generation activities.

- Forecasts need to have transparent assumptions, clear methodology and documentation, and should not be revised with every change in data

Presentation 2: Surveying stakeholder needs and introduction pathways in countries with high TB burdens (William Wells, TB Alliance)

- Where there are already drugs for the disease of interest on the market, the question of whether countries will adopt (i.e., switch) is even more challenging.
- Is reducing the drug regimen from 6 months to 4 months enough incentive to make countries switch?
- Doing a forecast forces people to commit to particular choices and make decisions based on how they think things will unfold.

Strengths

- For a demand forecast, TB has the advantage of being able to rely on yearly WHO-produced epidemiology estimates
- Concerns identified in the field as possibly affecting adoption can be incorporated as variables in a demand forecast. The forecast can be improved as we get better information about the country-level concerns.
- In TB, study of past regimen changes can inform the likely speed, trajectory, barriers, and opportunities for future changes.

Challenges

- the concerns between countries vary widely so it is difficult to come up with one prediction for adoption
- central decision-makers in public programs may change their minds or be replaced
- even a simple regimen change may take many years to implement

Presentation 3: Access model for Paromomycin IM injection for visceral leishmaniasis (Rajshankar Ghosh, iOWH)

A Phase 4 study is being carried out in Bihar, India. It contains 3 Modules designed to expand treatment access closer to where patients live:

1) Urban sites for outpatient treatment studying safety and pharmocovigilance;
2) Peri-urban sites for outpatient treatment (expanding access) with safety data;
3) Rural sites for referrals and possibly treatment (using unlicensed rural medical practitioners)

iOWH collects real-time data via cell phone (and subsequent web entry of forms) to look at:

- Geographic expansion of coverage of PMIM treatment (increasing access for patients)
- Access to treatment for women, children, etc.
- Patient Compliance with the regimen
- Capacity of providers to treat on an outpatient basis with PMIM

The balance between clinical trial practices and on the ground public health realities is challenging. Results from the study and study materials will be transferred to the Govt. of India.

Comments from participants

Role of PDPs and other actors in adoption decisions

- Country decisionmakers must be involved in conceptualizing the problem. If there is a local perception of a major threat – as with Meningitis A because of its epidemic nature – then roadblocks tend to fall away. Diseases with a lower attack rate, like visceral leishmaniasis, are a harder sell. Evidence on both epidemiologic and economic impact are needed. There is a need to examine the relative priority of a drug/disease in a country, although it can be difficult for the country to take on this task (and it is not an appropriate role for a PDP).
- PDPs came into existence to address market failures, but we need to distinguish between markets with some potential (e.g., GSK motivated to address meningitis A with a vaccine) and neglected tropical diseases that really have no viable market. The global world must step in with the latter.
- WHO needs to be re-emphasized as a neutral representative of country needs. Working through the partnerships (RBM, Stop TB, etc) and purchasers (GAVI, GFATM, etc) can reduce overload on countries. What role do these organizations have in prioritizing future interventions, doing demand forecasts, and analysing stakeholder needs? Will they do this early enough to meet the planning needs of the PDPs?
- Post-licensure trials are very country-specific, so PDPs may be more qualified than a pharma company to conduct these trials.
- Neglected diseases should not (and do not) fit into the usual market model. But in industry, many of the steps that PDPs call “access issues” are handled by marketing departments.
- Funders need to make a strong statement on the importance of serious access activities so that PDPs have the internal political muscle to get their job done. R&D also understands the importance of access work if access departments point out the possible barriers to their work being completed, e.g., because of regulatory barriers, manufacturing barriers, and product profiles that may not meet country needs.
- Best practices include early consumer input (at phase II if not before) to derive strategic not procurement information. The process becomes iterative in informing R&D and understanding political bottlenecks. Throughout this process, local ownership can and should be increased.

Demand forecasting

- Demand forecasts are a perfect chance to engage stakeholders, and they should be done early and often.
- In industry, the ability to accurately forecast demand is a critical element of (financial) success. But even the most experienced forecasters are overly optimistic. Accurate and credible forecasts can be used to encourage suppliers to enter the space. Even when there is a

wide range of predictions, the discussions about what determines demand can stimulate interest in an area (e.g., TB vaccines).

- Industry also expects demand to be elastic, with demand depending heavily on price. It is challenging, because the real question is where the price is going, not where the price is at a specific point.
- Adoption decisions that determine demand are a political process, not just an educational one. The difficulty of demand forecasting is the binary nature of decisions; it is not a graded response.
- Lesson from GAVI's PneumoADIP/Hib Initiative: 5 years of funding was not sufficient, because countries were still concerned about the potential budget impact at the end of the 5 years of funding.
- Projections for ASAQ FDCs were simpler because of the known size of the existing ASAQ market. Support was built starting from WHO recommendation and then by presenting findings regionally.
- Shared processes are needed. GAVI got together a variety of vaccine PDP, most of whom had used the same consultants to derive the same, overlapping list of candidate early adopter countries. BMGF could play a role in such coordination, and in producing in-depth analyses of best-practice methods in a way that individual PDPs do not have time to do.
- Is there a role for a body that does demand forecasting in a generic form and then distributes it to PDPs? BMGF is looking into demand forecasting, including using Chris Murray's pooled resources model so that the Foundation does not pay for forecasts over and over. This could save resources, increase knowledge sharing, and prevent PDPs from deriving an inflated (or deflated) demand forecast to use as an advocacy tool. Greater coordination is needed between PDPs to avoid the situation where teams develop forecasts in isolation of one another, not taking into account decisions that countries need to make regarding competing priorities. An exercise to look at adoption of multiple vaccines in GAVI countries revealed that although introduction was spaced realistically in many countries, some large countries would experience unrealistic adoption scenarios if uptake assumptions for various vaccines were not reconciled. Note, however, that the closer a product is to market, the more interested the PDP is in having an accurate demand forecast (to allow reliable planning). In this circumstance, distortion resulting from bias is less likely. Finally, demand forecasting will always vary by disease context.

Session Summary

- A statement on why access is important to the global community and to private industry
- A standard reference methodology / best practices on demand forecasting (although see the CGD report).
- Greater coordination between PDPs on demand forecasts to address forecasting in the context of competing priorities.
- To determine the role of PDPs in producing good demand forecasts
- To define the role of donors and international organizations in demand forecasting.

Session 3: Manufacturing Key Issues

Presentation 1: Price Volume guarantee negotiations as part of commercial partnerships (Marc LaForce, PATH Meningitis Vaccine project)

The MVP started by spending time in Africa to find out what the biggest limitation to meningitis vaccine uptake would be. Assuming good quality MVP was told that price was the most important factor and Africans felt that a transfer price of $0.50 per dose (which has been achieved) would result in sustainability.

Large Pharmaceutical companies were engaged but their prices were very sensitive to volume. All wanted volume guarantees, and were concerned about the uncertainties of supplying in Africa. No contracts were reached with large Pharmaceutical companies.

Developing country vaccine companies were engaged and the discussions were very different: Price-Volume uncertainty was not a dealbreaker and the magnitude of the need (i.e., not necessarily the demand) was attractive. Price discussions were tabled for later.

MVP chose to invest in improving surveillance and laboratory diagnosis on the premise that countries already greatly feared meningitis epidemics and that better case data would drive the market. It was important to get WHO buy-in and this was done by using WHO staff and infrastructure for the enhanced surveillance activities. This investment would facilitate roll-out prioritization because an important factor was demonstrable epidemiological burden. The decision-making group for this prioritization includes AFRO and country-level stakeholders. Better epidemiologic data reassured the manufacturer aand led to increased investments on their part (new facility). African vaccine manufacturers were considered during the early phase of the project but none had the infrastructure required. Note: The large pharmaceutical companies may have changed their approach since this project started.

Presentation 2: Manufacturing strategies: What works and what doesn't work (Rita Khanna, Aeras)

It is important to manage IP to control price and access and to ensure adequate supplies of the product. Aeras' basic philosophy is that, if possible, Aeras owns or has a license for distribution of vaccine at the lowest possible affordable price to populations most in need of them in developing countries of the world.

Market research in India has shown that any price much higher than the current price of vaccine would have a negative impact on the uptake of the new vaccine.

Aeras decided to build its own manufacturing CGMP facility for Aeras' internal vaccine candidate, recombinant BCG (rBCG), for development and product licensing. Aeras will manufacture the bulk vaccine at Aeras' facility and transfer it to a manufacturer in India for fill, finish, lyophilising, labeling, packaging and distribution. Manufacture of rBCG for Phase 2 and 3 trials will be done according to FDA and EMEA standards. The intention is to eventually transfer technology to manufacturer in India, China and other countries.

Aeras is working with a partner to set up manufacturing for rBCG in China. There are restrictions on the importation of bulk vaccine into China so the bulk manufacturing will have to be done in China itself.

For vaccine candidates that are being developed in collaboration with partners, the vaccine is expected to be manufactured by the partner. In this case, the partner is committed to

supply sufficient quantities of vaccine at a mutually agreed upon price in developing countries and public markets in the Emerging Economy countries. Our agreement with the partner stipulates that if the partner is not able to supply the vaccine to these markets then it will transfer technology to Aeras or a mutually agreeable third party for the manufacture of vaccine.

Other issues that need to be considered include: Regulatory filing, Liability, Safety and toxicology, Inspection records, Adultery and misbranding, Performance to specifications and pricing.

Presentation 3: Uncommon Partnerships: An access strategy for semi synthetic artemisin (Nina Grove, iOWH)

The volatile botanical supply of artemisin puts risk into the supply chain; semi-synthetic artemisin has the potential to smooth out supply. The cost of semi-synthetic artemisin will be close to that for high quality field production – this is a manufacturing technology solution applied to a global health issue and over time manufacturing cost is likely to come down. The aim will be to supplement botanical supplies of artemisin not to replace them. Note that bednet programs may decrease demand.

The semi-synthetic artemisin will be made available to the derivitizers and ACT manufacturers. One public health issue is how to discourage sales to non-indicated monotherapy manufacturers.

The Manufacturing strategy was as follows: 1. Conducted market evaluation and developed strategy. 2. Developed list of partners and held initial meetings. 3. RFP sent out followed by feedback and clarification. 4. Developed quantitative and qualitative ranking criteria. 5. Received proposals, second round of feedback and clarification. 6. Conducted due diligence visits with selected candidates. 7. Performed technical assessment and made recommendation to steering committee. 8. Negotiation of Agreements. 9. Integration of new commercial partner.

In the access process there was an up-front commitment to no profit, no loss. Proposals were received from 6 high quality players. The University of California, Berkeley, gave a no-cost license for the technology, but the process developer stipulated that the process should not be sub-licensed to manufacturing in countries that can't properly prosecute IP infringement.

There were 2 types of partner from the proposals; Contract Manufacturing Organisations (CMOs) and ACT Producers with spare capacity. Criteria were drawn up for selection including: Technical skills and capacity; Ability to support public health goals; Risk and cost Sharing; Philanthropic commitment; Contribution to registration and distribution etc.

Lesson: you can make a technology at low enough cost in the developed world.

Comments from participants

Getting the most out of the no profit /no loss principle

How has this principle worked in practice and does it discourage suppliers? Suppliers are happy to agree to this principle for the public market when there is a private market where

they can make profit (e.g., DNDi's experience with ASAQ). And we should not underestimate the value of no loss to partners as this equates to no downside risk.

How is the no profit no loss principle verified? So far this has been theoretical with projects in the R&D phase, although third party inspection has been included in some contracts. Another approach would be to define the costs and agree on a margin but it hasn't been possible to find a partner willing to agree to such a contract.

GAVI is working with manufacturers to get an interpretation of what "at cost", "no loss", "fully burdened manufacturing cost" and "cost plus" means to them. Defining standard definitions of these terms could help to create collective bargaining power to get better deals. E.g. Merck includes marketing costs in "at cost". PDPs should be more assertive in sharing generic information about their contracts to strengthen their future negotiating positions. We may not be fully valuing what we offer, particularly the non-monetary value of the relationship. For example, marketing should not be a component of the base price, as we do a lot of the marketing! For the public sector, the marketing is the work with WHO and national programs.

When should a PDP think about manufacturing?

IVCC does this at the deal stage: It is a condition of the grant that either that either IVCC's partner or their partner's partner is committed to manufacturing. For pharmaceutical companies, they think about commercialization at the end of Phase I (production process, packaging, etc). PDPs seem to want to wait for completion of the proof of principle, but it should not be delayed any more. For vaccines, it can be after Phase IIb, but from then on the manufacturers cannot delay without losing rights.

Should manufacture be at EPA or EMEA/FDA standards or at local country standards?

For insecticides, there is one standard (EPA) for Europe, US, and developing countries. For vaccines, WHO prequalification is the standard (as it was set up by WHO for UNICEF procurement of vaccines) for most developing countries and also the minimum for any company planning to export and hoping to provide healthy competition to an established vaccine manufacturer such as GSK. For dengue vaccines, WHO pre qualification is also the aim (possibly with substantial TA from the PDP), but a state-owned company like Butantan in Brazil may concentrate first on the domestic market. The benefit of this relationship is that Butantan discloses everything on price and costs of manufacturing, which is otherwise hard to determine. It was noted, however, that local manufacturers are not always associated with lower prices – they may be protected as part of industrial policy. It is not clear whether PDPs should be building the technical capacity of local manufacturers, or whether building local regulatory capacity is the more pressing need.

Management of IP

If IVCC's manufacturers stay on track, they retain all IP. But if they drop out or fail to provide to endemic countries they have to make available the license for both the disease and agricultural parts – this ensures that the project is interesting to a third party. Aeras is the same: the defaulting partner would lose both public and private markets. Similarly, PATH generally gives the companies freedom in the private sector as long as they provide the product to the public sector at an affordable price, but manufacturer default would result in them losing both sectors, which are then subject to non-exclusive licensing.

PDVI take the PATH process a further step. The manufacturer is required to sell at a specified price in the public sector. To ensure that the product is sold in the smaller markets PDVI specifies the list of countries in which the manufacturer must market, though this kind of specification has not worked for others.

Different groups define the developing world in different ways, e.g., the World Bank's Low Income category, GAVI-eligible countries, Global Fund recipients, etc. A company may be obligated to supply to the low-income countries, with the rest wide open. The problem is that countries can suddenly change status by moving between these groups, so it can be simpler to define country by country. These categories can also subject middle income countries (including their public sectors) to high market prices. If private markets are also excluded from the agreement they may also have high prices, even in low income countries, although leakage from the public market can sometimes minimize this.

What if a company defaults?

Technology transfer upon default must be included in any agreement. But it is difficult to enforce, even if there are stipulated penalties. At a minimum, it should be the PDP that will pay for the transfer costs, otherwise it will never happen (endless spurious scheduling delays, etc). Also, if the technology reverts to the PDP, it will take several years for the PDP to get going on manufacturing again.

So it is important to make deals that are viable for both the PDP AND the company. Early contracts were often poorly negotiated by both PDPs and companies because of lack of experience. One key element: The manufacturer has to access both the profitable and non-profitable part of the market otherwise there is no incentive. The costs associated with manufacturing make small segments non viable. [Side note: The APIs for DNDi's FDCs had no associated IP, making the process easier for DNDi.]

Session Summary

1. PDPs need to start thinking about manufacturing early (at the latest, by proof-of-principle).
2. Contracts are getting better, but they need to be win/win. At the same time, no-loss contracts do reduce risk, and PDPs should not underestimate their value to partners (5 years ago we might have done so).
3. PDPs should share with each other the structures of deals, without going into the specifics, including a better understanding of how individual companies define terms such as "Fully Burdened Manufacturing cost."

Session 4: Pricing, Finance and Procurement

Presentation 1: AMCs and processes for demand aggregation (Tania Cernuschi, GAVI)

- GAVI's bulk purchasing of vaccines has led to a decline in vaccine prices and a greater diversity of vaccine sources including an increasing percentage of vaccines coming from developing country manufacturers (40% in 2008).
- GAVI's AMC mechanism covers half of the initial $7 price (for 2 years) before conversion to the tail (longer term) price of $3.50 per dose.
- There are guaranteed procurements of a portion of the demand estimates: 20% for the first year, 15% for the second, and 10% for the third. Demand forecasts are updated twice a year.
- Country demand will determine which products are ultimately purchased, including if a superior product enters the market and is demanded by countries
- For pneumococcal vaccine, the key intended outcome of the AMC is to expand production.of products so that demand in developing countries is met.

Presentation 2: Affordable Medicines Facility for Malaria (AMFm) (Renia Coghlan, MMV)

- The Affordable Medicines Facility, Malaria, is an alternative funding mechanism designed to subsidise inherently expensive drugs by putting in money at the top (at the manufacturing level). Unlike an AMC there is no market commitment, but a pot of money available if the demand is there. The proposal goes to the GFATM board in November for an early rollout phase based on disease burden and likelihood of success. The board of Unitaid is still deciding.
- This is a market distortion, so it will be monitored carefully. E.g.,
    - local manufacturers who are not WHO prequalified and thus not eligible may be forced out of the market.
    - this is mainly tackling the private market, so it may prop up a poorly functioning private sector.
    - If the scale-up of funding is too rapid, it may exceed the global supply of botanical arteminisin.
- The level of support is not yet settled, but a 95% subsidy may maintain the incentive to produce at lower prices.

Presentation 3: Estimating the Return on Investment for an Intervention - Lessons from a Malaria Vaccine (Vicky Cardenas, MVI)

- A return on investment analysis can combine: an understanding of demand; social returns to the public sector in terms of lives saved, DALY's averted, etc; and financial returns that an industrial partner could anticipate in terms of net present value, cash flows, etc. Building this model requires 4 pieces of information:
    - Demand projections
    - A means of translating efficacy seen in trials into effectiveness in real life in the context of other interventions
    - Assumptions about R&D costs and rates of attrition for products under development

    - Resources required to deliver an intervention
- The results can inform R&D strategies as well as access planning. For example, for MVI, the results helped to inform decisions of whether or not to go forward with a partially efficacious vaccine. They have also helped with designing an AMC in terms of pricing, tradeoffs, and avoiding overcompensation of industry.

Presentation 4: Pharma's "lessons learned" in pricing, distribution and regulation while making HIV medicines accessible in LICs (Thomas Mertenskoetter, IPM)

- Industry has an extensive history of engaging with access issues, but it has not been made available in a systematic fashion to PDPs. An ongoing survey of 7 large pharma companies working on HIV-related products is finding that:
- Pharma approaches in the developing world have ranged from utilizing entirely the pharma company's own internal networks from manufacturer to direct marketing to local pharmacies, to complete outsourcing including offering licenses to generic manufacturers. Note that generic manufacturers often have the distribution knowledge in Africa, especially in the public sector.
- The resources needed for swift and broad regulatory approval have routinely been vastly underestimated.

Comments from participants

Pharmacovigilance

- Whoever holds market authorization is responsible for pharmacovigilance, but some pharma seem to expect PDPs to do Phase IV and pharmacovigilance in addition to managing the relationship with WHO and providing local knowledge.
- DNDi, MMV and Sanofi are collaborating on a large pharmacovigilance study for ACTs. It would be a good idea to have pharmacovigilance in the original contract, but the original idea was just to develop a product, so it was necessary to renegotiate a rollout contract.
- Rotashield provides an example of how the product can be lost if there is not proper and complete interpretation of pharmacovigilance in the context of developing countries.

Pricing negotiations

- Experience of pricing negotiations between PDPs and manufacturers showed a wide range of agreements including terms with firm prices, cost plus, differential pricing or benchmarking exercises.
- DNDi's approach on pricing for ASAQ (with Sanofi) was to have no exclusivity and at-cost delivery, with a target price of $1 per treatment for the public sector and flexibility for some profit in the private sector.
- Cost of goods is the only rational place to start with pricing discussions, even though stakeholders may want a price closer to that of other, existing and very cheap medicines (e.g., chloroquine).

- MMV kills a lot of projects early based on cost issues, and is also careful in reviewing tenders to make sure companies can really respond at the promised price.
- The HepB vaccine resulted in a paper documenting every penny of the production cost, which was sent for verification to both companies before being published. This gave a firm basis for price negotiations. Companies are used to pricing that is designed to recover all R&D costs, often very fast, but PDPs may have covered all or most of the R&D costs.
- JE and MVI came to firm price-volume agreements – typically for products in Phase II.

Cost-effectiveness

- Do countries look at cost-effectiveness or just at price? JE used cost-effectiveness studies to make the case in India. And they were very influential for HPV.
- For HPV, no price was known, so it was determined that price would have be below a certain level to be cost-effective. But this cost-effective price might be unaffordable – the cost effectiveness study could push prices up. This is also a concern with AMCs.
- WHO has established cost-effectivness standards based on GDP.
- Pure cost-effectiveness comparison arguments can block more technological solutions, e.g., ARVs kept from Africa, based on the greater cost-effectiveness of other interventions such as diarrheal therapies.

Role of PDPs

- If price and delivery negotiations are part of development contracts, as we seem to agree that they must be, then there may be a tailing off of PDP access work, but not necessarily a clear endpoint.
- Danger: if PDPs define their role all the way to the end, others may be put off from entering.
- One role of PDPs is to help guide governments in choosing between several different funding sources for a new technology.
- Medical education must be planned well in advance.

Session Summary

Opportunities

- Investments are being made in innovative financing mechanisms for new interventions (e.g. AMCs; Affordable Medicines Facility for Malaria). PDPs have a critical role to play in informing the design and implementation of these mechanisms, such as pricing structures.
- Demand forecasts can be extended to make estimates of the potential public health returns for the public sector (i.e. “investment cases”) and the potential financial returns to the private sector.
- PDPs have an opportunity for more systematic learning from industry about their marketing practices, not necessarily for comprehensive replication by PDPs but in order to define key strategies that PDPs may use in the transition from product development to use.

Challenges

- Tailoring innovative financing and bulk procurement mechanisms to ensure that there are the right incentives and that new mechanisms do not create disincentives.
- Estimating, and in some cases making publicly available, accurate R&D and manufacturing costs for use in pricing strategies.

Session 5: Global Regulatory Pathways for Introducing New Products

Presentation 1: Two different paths to regulatory approval for two registered products, ASAQ and ASMQ (Jean-Rene Keichel, DNDi)

Overview

- In 2002, WHO recommended Artemisinin-based combination treatments (ACTs), but no co-formulations were available.
- Now ASAQ (combination of artesunate and amodiaquine) is licensed in 20 countries and ASMQ (artesunate and mefloquine) is registered in Brazil.

Registration strategy

- All products involved had well-established use, which makes registration of a combination easier.
- DNDi wanted a partner with a track record in product registration.

ASAQ:

- Product targeted to African countries
- Consulted first with UK regulators, who advised against going through them.
- Chose to register first in Morocco, where the product would be manufactured by Sanofi, and to follow up with either an EMEA Article 58 opinion or WHO prequalification.
- Registration in Morocco took about 14 months (slower than hoped).
- Chose to pursue WHO prequalification, which has not yet been obtained but is expected.

ASMQ

- Product intended for South America and Asia.
- Manufactured by Farmanguinhos, public sector in Brazil.
- Worked closely with ANVISA, Brazilian regulatory agency.
- Registered in 2008, took one year.
- Next step will be PAHO prequalification (some discussion of this: WHO people argue this should not be considered distinct from WHO prequalification; vaccine people note that there's no separate PAHO process for vaccines)
- For Asia, will transfer technology to an Asian manufacturer, register there, and seek WHO prequalification.

Lessons

- API sourcing can be a bottleneck and leave the PDP vulnerable to shortages.
- Critical contribution of licensing partner: DNDi benefited greatly from Sanofi's experience.
- Processes in Brazil were slow despite extensive preparatory work.
- Ultimately want user countries to be able to do regulatory evaluation themselves: need to build capacity. DNDi has had discussions with African regulators using the ASAQ dossier as an example, and suggests this as a useful approach.
- The PDP must identify the fastest regulatory pathway to patients but maintain the same standard of quality as expected for the developed world. For a totally new drug, the expected route would start with the FDA or EMEA. But for neglected diseases (e.g., sleeping sickness), would they have the competency to evaluate?

Presentation 2: Regulatory considerations for a vaccine for use predominantly in developing countries (Rich Mahoney, PDVI)

PDVI portfolio

- The two highest priority projects are with Sanofi-Pasteur and GSK, both involving live-attenuated vaccines.
- Five other projects are with Butantan (Brazilian public-sector manufacturer), Panacea, Biological E, and others.
- Phase 2B trials start soon for the two most advanced projects, followed by Phase 3. Licensure may be possible as soon as 2012-13, with others perhaps 2 years behind.

Regulatory strategy

- Working with WHO on criteria for evaluating dengue vaccines. Have agreed that trial endpoints will be dengue fever rather than more severe manifestations. This allows for smaller trials, since severe manifestations are rare.
- Also working with network of developing country regulators (DCVRN).
- Have created regional Dengue Prevention Boards that will issue recommendations.
- The roles of FDA and EMEA are not yet clear. One company might apply to the FDA, which would rule out an EMEA opinion.
- FDA has said it might license with efficacy data against only one of the four dengue strains, although the vaccines are designed to protect against all four.
- NRAs in DCVRN have expressed interest in joint review, but the mechanism is unclear.

Presentation 3: Challenges and solutions working with RAs in both developed and developing countries (Michael Brennan, Aeras)

Regulatory authorities in different settings have different strengths and weaknesses:

Developed countries

- Strong, high capacity
- Structured processes, timelines
- Provide advice in advance of submission

But:

- GMO hurdles in Europe
- Article 58 unproven for vaccines (only 2 drugs have gone through)
- FDA just stated that it can license vaccines for diseases not endemic to the US, but there are many questions about this mechanism, including the link (if any) to prequalification

NRAs in emerging countries (DCVRN)

- Qualified by WHO (apparently two levels of participation in network, full membership requires WHO approval)
- Experienced with clinical trial review and approval

But:

- Have mostly products already licensed elsewhere
- Don't have much in-house capacity

Other developing country NRAs

- Lack of legislation governing regulatory issues
- Dependent on universities, MoH to evaluate dossiers
- Sometimes conflicts with in-country manufacturers

WHO

- Perceived as honest broker
- Prequalification process important
- Leader in NRA capacity building, assessment

But:

- Not a regulatory agency (this seems a bit of a gray area)
- Decisions often made by ad-hoc committees instead of in-house

Regional fora like AVAREF offer the possibility of joint review

Presentation 4: Overview of EMEA article 58 (Roland Dobbelaer (with EMEA until recently))

- The Article 58 procedure is virtually identical to the "marketing authorization" procedure that is conducted for a product to be sold in the EU: same dossier; same level of assessment; same peer review process.
- Three differences:
    - For products not to be marketed in EU
    - Eligibility for mechanism must first be determined by WHO
    - Called an "opinion". This may (unfortunately and erroneously) imply a less rigorous assessment.

- Original rationale was in large part to accommodate European manufacturers who needed licensure in the country of manufacture for registration elsewhere
- When the risk-benefit ratio is different in Europe vs in developing countries, stakeholders from WHO and from low income countries could be brought into the decisionmaking.

Presentation 5: WHO prequalification (Drew Meek and Carmen Hernandez Rodriquez, WHO prequalification unit)

- The prequalification idea and process began with vaccines; a different unit is responsible for drugs and, now, diagnostics
- The process covers all vaccines, but only HIV, TB, and malaria for drugs, diagnostics
- Vaccines must first be licensed by an NRA in the country of manufacture, and this NRA must be approved by WHO (another WHO unit assesses NRAs)
- The primary purpose is to determine suitability for purchase by UNICEF and PAHO, which procure vaccines for most developing countries
- The application includes considerations of stability in more extreme environments, presentation issues specific to developing country use, as well as efficacy and safety.
- It is done in collaboration with NRAs; the WHO unit also provide some assistance to these entities.

Session Summary

Variety of regulatory pathways, options

- EMEA Article 58, the new FDA process, WHO prequalification, and regional networks of NRAs all offer new opportunities for PDPs seeking efficient but rigorous regulatory pathways for their products, but many of these mechanisms are relatively new and untested.
- Substantial confusion persists about these mechanisms, especially WHO prequalification
- There are important differences between processes for vaccines and drugs (and, of course, insecticides), and the appropriate pathway will be different for different products.
- Ensuring that review is as rigorous as developed country review (and is so viewed) is essential: the PDPs cannot afford the perception that a lower standard is being applied.

Capacity of developing country NRAs

- The capacity of NRAs, especially in endemic countries where PDPs must conduct trials and ultimately license their products, is a universal concern. Finding a way to address this is probably the highest priority to emerge from the session.
- Networks of NRA are a promising vehicle for capacity building and possible for joint review. An intermediate stage is to have a unified dossier format but retain country-by-country review to protect sovreignty. ASEAN is doing this and EMEA started like this.

- PDPs face conflicts of interest in addressing this issue alone (as they are seeking speedy approval for specific products): this is an ideal opportunity for joint action.
- WHO is already working on this and should have a leading role.

The Intergovernmental Working Group on Public Health, Innovation and Intellectual Property (IGWG)

- The final IGWG plan of action and WHA resolution highlights the importance of overcoming regulatory barriers and of building NRA capacity (as well as many of the other issues raised in the current meeting).
- This process is an important, government-led mechanism for addressing these issues.
- The PDPs should seek to harmonize their efforts in this area, where possible, with those of the group now being set up to implement the IGWG plan of action.