

## CONNECTING THE CHAIN

### **More funding, better planning and co-ordination**

Developers of drugs for poverty-related diseases discuss how to make sure new products will reach patients in Africa.

In recent years, private charities like the Bill & Melinda Gates Foundation have helped launch public-private partnerships dedicated to deliver affordable vaccines and drugs against HIV/AIDS, malaria, tuberculosis and other poverty-related diseases in developing countries in Africa and elsewhere.

Now, participants at an Open Stakeholder Forum in Brussels agreed, **there is an urgent need for European governments and the European Commission to get more involved** in this endeavour.

Also, there is a need for **better planning and co-ordination** between the many stakeholders in the chain, to prevent valuable investments and efforts from being wasted on products or product candidates that will ultimately not reach the patients who need them.

### **Much has changed for the better**

For many years, the development pipeline for affordable medicinal products against poverty-related diseases such as HIV/AIDS, malaria, tuberculosis, and many other infectious diseases that mainly affect and kill people in very poor countries, remained nearly empty. Because neither patients nor their governments could afford the products, pharmaceutical industries had no incentive to set up early-stage research or clinical trials, let alone to invest in manufacturing and distribution capacity.

Since 2000, however, many things have changed for the better. Private charities, most notably the Bill & Melinda Gates Foundation, have helped launch public-private product development partnerships (PDPs) focussed solely on coming up with affordable vaccines and drugs. Research funding organisations have funnelled money into early-stage research by academic researchers and not-for-profit research institutes. A number of pharmaceutical companies, either on their own or as part of public-private partnerships, have entered the arena as well. And multinational organisations have pledged to help fill large funds that can be used to procure medicines by the time they become available.

It is far from certain, however, that all of these efforts will fit together like the perfectly shaped pieces of a jig-saw puzzle. Some recent examples suggest that many of the new candidate products could face serious difficulties downstream, from problems with setting up clinical trials and bureaucracy to regulatory hurdles and problems in manufacturing the drugs and getting them into the hands of patients who need them.

To use another metaphor: not all the links of the development chain are properly connected. Some links are even completely missing.

At the Open Stakeholder Forum in Brussels, about one hundred participants from Europe, Africa, North-America and Australia discussed possible bumps in the road and ways to overcome them. Among the participants were representatives of the World Health Organisation, the Bill & Melinda Gates Foundation, the World Bank, the European Commission, the European Parliament, national governments, the Wellcome Trust, UNAIDS, Médecins Sans Frontières, and many PDPs and pharmaceutical companies. The Forum was set up by the Dutch Ministry of Foreign Affairs, the European & Developing Countries Clinical Trials Partnership (EDCTP, The Hague) and the Netherlands Research Organisation (NWO, The Hague).

## **Paul Bekkers: world community has pledged support**

The meeting started on a hopeful note, with **Paul Bekkers**, AIDS Ambassador at the Dutch Ministry of Foreign Affairs, quoting recent pledges by world leaders at a high-level meeting on HIV/AIDS in New York. Their promise: to make anti-retrovirals available to all who need them by 2010. They also committed themselves to intensifying investment in, and efforts toward, research and development of new, safe and affordable HIV/AIDS-related medicines, products and technologies, and agreed to encourage pharmaceutical companies, donors, multilateral organisations and other partners to develop public-private partnerships in support of research and development.

## **Adrian Hill: huge gap in translational research**

But many problems remain. **Adrian Hill**, director of The Jenner Institute at the University of Oxford, identified huge gaps in translational vaccine science, that is, the research between basic biology and animal studies on the one hand, and Phase II or Phase III clinical trials on the other. With strong research institutes and leading pharmaceutical companies, Europe has considerable strengths in vaccinology, Hill said, but much of that capacity is not used because European governments neglect the funding of translational research as the “boring part” of innovative development.

Public sector investment is urgently needed, Hill said, but European governments and the European Commission are failing, especially when compared to the US and private foundations. “The challenge is scientific,” Hill said. “We do not know how to make a highly effective HIV/AIDS, malaria or TB vaccine. The problem will have to be solved by properly funded translational scientists.”

## **Chris Hentschel: urgent need for clinical trial capacity**

**Chris Hentschel**, president and chief executive officer of the Geneva-based Medicines for Malaria Venture (MMV), spoke more generally about the 'long and expensive road to a new medicine'. Hentschel said currently MMV has a 'development bolus' in Phases II and III, and a rapidly growing need for clinical trial capacity, exacerbated by the trend to test many different drug combinations in an attempt to ward off drug resistance, especially in tuberculosis.

Hentschel also identified other potential late-stage problems for newly developed drugs, such as illegal counterfeits on poorly regulated markets and the potential for multi-year delays even after new products have received market approval. Such delays should be shortened by drawing up global access plans, Hentschel said they should address availability, affordability, acceptability, quality, and delivery.

Hentschel showed that most of MMV's funding is provided by the Bill & Melinda Gates Foundation. Some EU member states are significant donors too, he said, but in general the EU and the European Commission have failed to seriously engage with the public-private partnership engine that is now driving innovation in the fight against poverty-related diseases, he said.

## **Simon Croft: some tropical diseases still neglected**

There are more poverty-related infectious diseases than the 'big three', **Simon Croft**, director of research and development at the Drugs for Neglected Diseases initiative (DNDi) in Geneva, next told the audience. Some of those neglected diseases actually hold big challenges, as well as opportunities, for developing and delivering affordable drugs. Developers targeting diseases such as Leishmaniasis, Trypanosomiasis, Chagas disease, Buruli ulcer, and dengue face the same problems as those focussing on HIV/AIDS, malaria and tuberculosis, Croft said, but their lack of funding is an even greater problem, which DNDi is trying to address.

## **Ian Boulton: Real challenges come after regulatory approval**

To illustrate the many challenges facing pharmaceutical companies engaging in not-for-profit product development, **Ian Boulton**, director for Commercial Strategy at the Diseases of the Developing World, Global Commercial Strategy dept. of GlaxoSmithKline at Brentford (UK), pointed at Novartis Pharma's experiences with Coartem, a so-called artemisinin combination therapy (ACT) to treat malaria. In 2001, a slide based on Novartis data showed, WHO forecast that 2 million doses of the new combination treatment would be needed in 2005. In 2004, that forecast jumped thirtyfold, to 60 million doses. Despite huge logistical difficulties, Novartis managed to have manufacturing capacity for 30 million doses online by 2005. In the end, however, only 14 million doses were procured in 2005. Who should carry the financial risk of such wildly fluctuating, non-binding forecasts, Boulton wondered? Experiences like this, he said, will make other industry partners even more cautious. There is a need, Boulton concluded, for early and reliable forecasting and supply chain management planning. Such planning should take into account, among many other things, that vaccine manufacturing has a lead time of about 6 years from the start of construction of facilities to the release of the first vaccine lot.

## **Peter Manyike: a regional public-private partnership**

A clear example of a successful regional product-development partnership was given by **Peter Manyike**, interim co-director for clinical and scientific affairs and medical and regulatory affairs manager at the South African AIDS Vaccine Initiative (SAAVI). SAAVI was established in 1999 by the South African government and Eskom, the country's main energy utility company. SAAVI's mission is to develop an affordable, effective and locally relevant preventative (and possibly therapeutic) HIV vaccine for southern Africa. The partnership is currently extending its activities into laboratory sciences, clinical trials, community involvement, social science, ethics and law. It has four products in Phase I clinical trials, and three in Phase II.

## **Mary Moran: PDPs are the most efficient drug developers**

**Mary Moran**, founder and director of the Pharmaceutical R&D Policy Project (PRPP) at The George Institute for Public Health in Sydney (Australia), set out to address the 'Donor Dilemma': with a plethora of approaches, groups and ideas going around, what's the best place to invest? Should donors fund industry? Public research? Or PDPs? There's a lot at stake, Moran said: Billions of euros may be spent wisely... or not.

For a recent study, Moran analysed 63 neglected disease drug development projects carried out between 1975 and 2004. Three quarters of them were managed by PDPs, she found, and those projects performed best from a donor and public health perspective: They had the best health outcomes in terms of suitability, affordability, efficacy and safety, and resulted in the most innovative products at the lowest cost. Drug development times were as good, if not slightly better, than the industry standard.

Not all PDPs were equally effective, however, Moran found. Apart from the lack of funds, some projects were hamstrung by a lack of commercial drug-making expertise.

Despite the pipelines newly filled by successful PDPs, there still is a huge public funding gap, Moran noted. Eighty percent of the funding for poverty-related diseases comes from philanthropic sources, and only a few governments are actively involved: the United Kingdom, the United States, Switzerland and The Netherlands. (Ireland followed suit very recently.) The European Commission, Moran said, accounted for less than one percent of the funding.

Moran's message to donors: fund PDPs, since their approach is most effective; be clever and tough; and judge projects only on their ability to get products, NOT on secondary goals you may want to achieve, such as creating European innovation networks.

To address the Donor Dilemma, Moran proposed a new Industry R&D Facilitation Fund (IRFF): a single, simple mechanism for government donors to fund industry R&D input into all PDPs for all neglected disease drug projects. The fund would target R&D gaps, automatically allocating funds to the most efficient groups or projects, mainly through existing structures.

## Floor Debate: eagerness to come together

Many participants got the chance to join in a House of Commons-style debate on six propositions, all phrased provocatively to generate a lively discussion. Generally speaking, the debate displayed a great sense of solidarity between participants, placing the common goal over potential divisions.

The first proposition gathered very little support: “To prevent market fiascos, donors should fund industry, not universities and PDPs, to do early-stage product development.” A few participants agreed industry is most experienced in delivering candidate drugs all the way to the market, however most, including some industry representatives, were not ready to hand it all over. Neither side suffered defections during the debate.

Many participants did change sides during the debate on the second proposition: “Many stakeholders base their strategies for product development more on ideology than on facts.” It was acknowledged that stakeholders sometimes have been polarised, yet a rapidly growing part of the audience seemed to agree that where possible facts should decide what approach is supported, regardless of the ideologies people may hold.

Perhaps not very surprisingly, not many participants were ready to flat-out support proposition number 3: “We need a new co-ordinating body to connect ‘push’ and ‘pull’ funding schemes.” The devil was in the word “new”; however, since in the discussion many indeed expressed the need for more co-ordination and priority-setting, yet felt that it can or should be handled by existing structures or platforms, not by new bodies.

Proposition number 4, “Building clinical trial capacity should be done by development agencies, not research funders,” gained not very strong support. That being said, many participants expressed support for the idea of development aid joining the game, if only because it controls much more money than research funders currently do.

Proposition 5, “We need only one PDP for each poverty-related disease. Where there are more, they should merge,” generate lively discourse, and there was no agreement on whether merging would enhance efficiency or rather would create monopolies and bureaucracy. However, mergers were not ruled out in case where it would make sense.

The final proposition, “Guaranteed procurement funds will probably not result in the most effective or most affordable medicines,” provoked passionate debate, exposing some doubts on whether guaranteed procurement funds as currently used could hinder price competition, for instance from generic producers in newly emerging economies.

## Koos Richelle: Funding product development is political choice

Fully acknowledging that the European Commission has not yet put funding PDPs at the top of its agenda, **Koos Richelle**, Director-General of the European Commission’s EuropeAid Co-operation Office, elaborated on the fragmentary nature of development policy within the European Union. Ninety percent of the Union’s development aid is spent by member states following their

own agendas, Richelle said. The European Commission for its part is moving away from funding projects, including medicinal product research and development, towards large-scale funding of entire country sectors. “We are convinced that we should build structures for the future and not disperse funds to small projects” such as drug development chains, he said. “They can be done by other donors. (..) That is a political choice that has been made for the Commission.” As things stand at the moment, Richelle said, the European Commission is not about to change course.

Building health care systems and capacity to perform clinical trials in poor countries could be another matter, Richelle said: long-term capacity building is high on development agendas, and judging by recent pledges from EU member states, billions of additional euros will become available over the next few years. Many donors, Richelle said, will have difficulties finding ways to spend that money wisely. Unfortunately, getting them to fund clinical trial capacity building will take separate discussions with about 30 donors, since the EU currently has no central platform where general issues such as poverty-related diseases are discussed. For the European Commission, funding clinical trial capacity building through development aid would be a completely new activity, Richelle said. “We simply have never considered doing it.”

Although he wasn't very optimistic, Richelle did not rule out a more active EU involvement in drug development, but this can only happen as a result of political action, he said. “Sometimes people will say ‘we have to act’, and suddenly everyone will come together. However, the issue you are dealing with is complex,” he cautioned. “Nothing is impossible, but under the present circumstances, it will not be easy,” he said.

## **Jacques-François Martin: Development involvement will be needed**

Using the privilege of the Chair, Jacques-François Martin brought to mind an old study concluding that investments in health care will produce strong economic growth: add one year to the average life expectancy of a country and its GDP will increase by 4 percent, according to the study. Martin also quoted figures showing the density of health workers in sub-Saharan Africa is ten times lower than in Europe and the U.S., and ageing populations in rich countries may even expand that gap. Many health workers in Africa will migrate to rich countries if they will get the chance. All of this underscores the need for development aid agencies, including those of the EU, to seriously start considering investments in health care and clinical trial infrastructure in Africa, according to Martin.

From the debate, Martin concluded there was broad consensus on the need for some sort of coordination of the activities of a rapidly growing number of PDPs as well as other players in the field, albeit not necessarily by a new body. Perhaps the World Health Organisation could revisit its mission on this particular issue, Martin suggested.