Clinical research organizations (CROs) can play an important role in helping pharmaceutical companies, not-for-profit organizations and governments to develop new therapies for neglected diseases in developing countries.

Faiz Kermani

Not everyone in the world has enjoyed the benefits of the medical advances now available as there exists a tremendous gap between those in industrialized countries and those in less developed regions.¹ The difference in the impact of diseases between these two regions of the world can be considerable (Figure 1). Developing countries often lack the healthcare infrastructure and strategy to combat infectious diseases in the way that industrialized countries do (Figure 2).

This unfortunate situation has attracted much negative media coverage and the pharmaceutical industry has frequently found itself criticized for not doing more to ensure access to its medicines in developing world regions. Although the populations of developing countries are often large, their purchasing power is low and so there is little commercial incentive to invest in these regions.¹

The international medical agency Médecins Sans Frontières (MSF) has been critical of the pharmaceutical industry, stating that one-third of the world’s population lack access to essential medicines and that prices are too expensive for such products if they are available in developing countries.² An additional problem is that the current R&D focus of the pharmaceutical industry is not aligned with the areas of unmet medical need in developing countries (Figures 3 and 4). Agencies such
as MSF have called upon the pharmaceutical industry to pay more attention to these so-called 'neglected diseases'.

In their defence, pharmaceutical companies say that the healthcare situation in developing countries is complex and cannot be addressed by the simple provision of cheap treatments. Although they admit that a system for affordable drugs must be devised, they believe that other issues must be tackled such as the general healthcare infrastructure, establishment of efficient drug distribution systems and training for healthcare personnel. To do this effectively they argue that better cooperation with governments and international agencies is needed. Companies believe that anything other than a collaborative approach will end in failure and will not result in a long-term approach to dealing with these countries’ problems.

Of Patents and Politics
The pharmaceutical industry invests heavily in R&D and thus wishes to see a return on its investment. It is, therefore, in favour of a system for effective intellectual property (IP) protection, which ensures that others cannot illegally copy its discoveries.

On a global basis, the laws relating to pharmaceutical patents are in principle regulated by the World Trade Organization’s (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). The philosophy behind the TRIPS agreement is to ensure that the manner in which IP is protected also serves social goals, but the agreement has been put to the test by the ongoing global HIV crisis.

Within the TRIPS agreement there exists the concept of ‘compulsory licensing of patents on essential medical technologies,’ where a government allows someone else to produce a patented product; that is, a company other than the pharmaceutical company that produced the original brand name drug. Under TRIPS Article 31, countries may use compulsory licensing for domestic pharmaceutical supplies during health emergencies. Unfortunately, there has been considerable debate over what constitutes a ‘medical emergency’. This has led to controversial legal battles between the pharmaceutical industry and both the South African and Brazilian governments. These countries have argued that the AIDS crisis represents such an emergency situation and allows them to take appropriate measures to ensure that their citizens can gain access to affordable treatments. The opposition of the pharmaceutical industry to these measures has attracted considerable public criticism.

To prevent future incidents, the WTO has attempted to build flexibilities in its guidelines so that the AIDS pandemic and other urgent healthcare situations can be addressed. In October 2001, a deal was struck at the WTO ministerial meeting in Qatar allowing countries facing a medical emergency to set aside the usually rigid WTO rules concerning patents. At this meeting it was actually stated, for the first time, that AIDS could be considered a medical emergency for the purposes of TRIPS. There have been further WTO discussions to develop flexibilities in the guidelines, but a solution that will be acceptable to all parties has proved elusive.
The arguments over drug pricing and legal clauses for IP rights have been a diversion from what is really necessary to tackle disease in developing regions.

**Figure 3 Leading causes of death in children in developing countries in 2002.**

<table>
<thead>
<tr>
<th>Cause</th>
<th>Total deaths (thousand)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perinatal conditions</td>
<td>2000</td>
</tr>
<tr>
<td>Diarrheal diseases</td>
<td>1500</td>
</tr>
<tr>
<td>Lower respiratory tract infections</td>
<td>1200</td>
</tr>
<tr>
<td>Malaria</td>
<td>1000</td>
</tr>
<tr>
<td>Measles</td>
<td>500</td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>250</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>200</td>
</tr>
<tr>
<td>Whooping cough</td>
<td>100</td>
</tr>
<tr>
<td>Tetanus</td>
<td>50</td>
</tr>
<tr>
<td>Other causes</td>
<td>150</td>
</tr>
</tbody>
</table>

Sources: The World Health Organization; Centers for Disease Control and Prevention

**Collaboration**

It is unrealistic to expect a quick solution to these difficulties, but this does not mean that progress cannot be made in the area of neglected diseases.

In some respects, the arguments over drug pricing and legal clauses for IP rights have been a diversion from what is really necessary to tackle disease in developing regions — an effective global strategy, featuring cooperation between governments, pharmaceutical companies and nongovernmental organizations. Whilst the arguments rage between the pharmaceutical industry and its critics, there are collaborative projects that are ongoing and should be further encouraged.1

The Special Programme for Research and Training in Tropical Diseases (TDR) represents the most successful, high profile international effort to tackle neglected diseases (Table 1). It was established in 1975 and is cosponsored by the United Nations Children’s Fund (UNICEF), the United Nations Development Programme (UNDP), the World Bank and the World Health Organization (WHO). TDR aims to improve overall global cooperation to develop medicines for neglected diseases and ensure that effective disease control measures are developed and implemented.

TDR has drawn up a list of 10 neglected diseases where it intends to concentrate its efforts.1 Rather than running research facilities itself, TDR encourages and funds the research efforts conducted by others in this important field.1 Out of the 1450 new chemical entities introduced to the global market between 1972 and 1997, only 13 were targeted at neglected infectious diseases — in collaboration with the pharmaceutical industry, TDR has been responsible for half of these.6

One area that offers hope at an international level is the setting up of Public–Private Partnerships (PPP) that have a not-for-profit focus in tackling neglected diseases (Figure 5). One recent study found that out of 79 identifiable PPP initiatives, 34 were based in North America, 40 in Europe, 4 in Asia and 3 in Africa.7 Although the partners involved are highly motivated, if PPPs are to have any real chance of success they must make effective use of their limited resources and have long-term funding.
Many CROs have gained considerable experience in working in developing regions of the world and apart from their clinical input they can also assist PPPs with regulatory strategy for these areas.

The public partners must also harness the strengths of the private sector as these organizations have the experience of transforming initial investments into real products and have specialized systems in place to measure the productivity of the R&D process.

A Role for CROs?
Clinical trials form a major part of drug development and a number of pharmaceutical and biotech companies are now outsourcing projects in this area to clinical research organizations (CROs).

There are a number of reasons for why companies would outsource a clinical project, but CROs can offer advantages in terms of cost effectiveness, time lines, access to relevant technical expertise and appropriate geographical coverage. As PPPs depend on gaining access to external technologies and expertise to survive, CROs can provide a valuable service when it comes to planning clinical trials for compounds exhibiting promise in treating neglected diseases.

A number of CROs are already working with not-for profit organizations in this challenging field and the arrangement is likely to be mutually beneficial. As well as the commercial arrangement serving a social goal, the CRO can benefit through extending its therapeutic and geographical experience. Similarly, the PPP will benefit from a partner that can help reduce risk on the project and can provide insight from its experience on other clinical projects.

Many CROs have gained considerable experience in working in developing regions of the world and apart from their clinical input they can also assist PPPs with regulatory strategy for these areas.

CROs can also expect to become involved in neglected disease projects being run by pharmaceutical companies themselves. Although general media coverage has been low, a noticeable change is apparent in how companies are approaching neglected disease therapeutic areas — this is partly because of those within such organizations who do wish to see the industry play a more proactive and benevolent role. For example, AstraZeneca has recently opened a dedicated research facility in Bangalore (India) focussing on tuberculosis and Novartis has opened an Institute For Tropical Diseases in Singapore.8,9 GlaxoSmithKline’s drug discovery unit in Tres Cantos (Spain) is running projects in the field of malaria and tuberculosis and its facility in Rixensart (Belgium) is focussed on developing vaccines for a
number of under-served medical areas. Other companies are likely to pay close attention to these initiatives as they decide how they wish to be actively involved in developing drugs for neglected diseases.

### Retaining the Right Focus

Although there have been calls by pressure groups for governments and the industry to pay greater attention to diseases in the developing world, certain observers believe that the current focus is skewed and may result in a number of regional diseases becoming even more neglected.

In a high profile editorial in *The Lancet* in July 2004, David Molyneux of the Liverpool School of Tropical Medicine in the UK outlined how the concentrated approach to certain, specific diseases in developing countries was obstructing improvements for a variety of tropical viral, bacterial and parasitic infections, acute respiratory infections and diarrhoeal diseases of children. It was argued that this was a lamentable situation as the cost to treat these other tropical diseases was low and the approaches needed were known and could be easily implemented. Furthermore, by effectively ignoring these diseases, the author expressed his concern that policy makers would inadvertently disrupt the efforts being made to tackle them and thus leave people in developing countries at further risk. As an example, Molyneux referred to river blindness (onchocerciasis), which he stated could be treated for a cost as low as 10 cents.

### Outlook

Although there are concerns over the current approaches to diseases of the developing world, research is being done in this field and there is an ever-growing number of collaborations between interested parties in the field of healthcare. More attention will need to be given to the results so that they facilitate further work on the entire class of diseases that are considered ‘neglected’ and encourage greater cooperation and better resource allocation on such projects. Through their specialist knowledge, particularly in clinical development, CROs have an important role to play in making these initiatives a success.

### References

2. www.accessmed-msf.org/campaign/faq.shtm
3. www.wto.org/english/tratop_e/trips_e/trips_e.htm
5. www.wto.org/english/tratop_e/dda_e/dda_e.htm
13. www.liv.ac.uk/lstm/about/newsDiseasesNeglected.htm

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**Table 1 Current TDR disease portfolio and research strategy.**

<table>
<thead>
<tr>
<th>TDR disease category</th>
<th>Description</th>
<th>Research focus</th>
<th>Classification of priority diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDR Category I Diseases</td>
<td>Emerging or uncontrolled diseases</td>
<td>Acquisition of new knowledge, and the design of new disease control tools and systems</td>
<td>African trypanosomiasis, dengue and dengue haemorrhagic fever, leishmaniasis</td>
</tr>
<tr>
<td>TDR Category II Diseases</td>
<td>Control strategy available, but disease burden persists</td>
<td>A wide-ranging focus, but concentrating on the development and testing of new disease control tools and strategies</td>
<td>Malaria, schistosomiasis, tuberculosis</td>
</tr>
<tr>
<td>TDR Category III Diseases</td>
<td>Control strategy proven effective Disease burden falling Elimination planned</td>
<td>Improvement and wider dissemination of existing tools and strategies, and risk avoidance</td>
<td>Chagas disease, leprosy, lymphatic filariasis and onchocerciasis</td>
</tr>
</tbody>
</table>