BIG PHARMA'S – COST-CUTTING CHALLENGER –

A non-profit organization is proving that drug development doesn't have to cost a billion dollars. Can its model work more broadly?

BY AMY MAXMEN

First, there was the pitching and rolling in an old Jeep for eight hours. Next came the river crossing in a slender canoe. When Nathalie Strub Wourgaft finally reached her destination, a clinic in the heart of the Democratic Republic of the Congo, she was exhausted. But the real work, she discovered, had just begun.

It was July 2010 and the clinic was soon to launch trials of a treatment for sleeping sickness, a deadly tropical disease. Yet it was woefully unprepared. Refrigerators, computers, generators and fuel would all have to be shipped in. Local health workers would have to be trained to collect data using unfamiliar instruments. And contingency plans would be needed in case armed conflict scattered study participants — a very real possibility in this war-weary region.

This was a far cry from Wourgaft's former life as a top executive in the pharmaceutical industry, where the hospitals that she commissioned for trials were pristine, well-resourced and easy to reach. But Wourgaft, now medical director for the innovative Drugs for Neglected Diseases initiative (DNDi), was confident that the clinic could handle the work. She was right. With data from this site and others, the DNDi will next year seek approval for a sleeping-sickness tablet, fexinidazole. It would be a massive improvement on existing treatment options: an arduous regimen of intravenous injections, or a 65-year-old arsenic-based drug that can be deadly.

The DNDi is an unlikely success story in the expensive, challenging field of drug development. In just over a decade, the group has earned approval for six treatments, tackling sleeping sickness, malaria, Chagas' disease and a form of leishmaniasis called kala-azar. And it has put another 26 drugs into development. It has done this with US$290 million — about one-quarter of what a typical pharmaceutical company would spend to develop just one drug. The model for its success is the product development partnership (PDP), a style of non-profit organization that became popular in the early 2000s. PDPs keep costs down through collaboration — with universities, governments and the pharmaceutical industry. And because the diseases they target typically affect the world's poorest people, and so are neglected by for-profit companies, the DNDi and groups like it face little competitive pressure. They also have lower hurdles to prove that their drugs vastly improve lives.

Now, policymakers are beginning to wonder whether their methods might work more broadly. "For a long time, people thought about R&D as so complicated that it could only be done by the biggest for-profit firms in the world," says Suerie Moon, a global-health researcher at the Harvard T.H. Chan School of Public Health in Cambridge, Massachusetts, who studied PDPs and joined the DNDi's board of directors in 2011. "I think we are at a point today where we can begin to take lessons from their experience and begin to apply to them non-neglected disease," she says.

In that vein, the DNDi has started research on alternatives to pricey drugs for hepatitis C, and is spearheading an effort to create antibiotics for drug-resistant infections, a problem that pharmaceutical companies have been slow to contend with. If successful, the work could challenge standard assumptions about drug development, and potentially rein in the runaway price of medications. "We can't match our financial figures one to one," says executive director Bernard Pécoul. "But we believe that DNDi can demonstrate that a different model is possible for R&D."

THE PIPELINE

When medical charity Médecins Sans Frontières (MSF; also known as Doctors without Borders) won the Nobel Peace Prize in 1999, its members decried the lack of lifesaving drugs for diseases of the poor, and used the Nobel prize money to kick-start the DNDi. Pécoul, a soft-spoken Frenchman who had been with MSF for 20 years, took the helm when the initiative launched in Geneva, Switzerland, in 2003. Pharmaceutical executives were sceptical. Drug development is an expensive, complex, decade-long endeavour. "In the early days, we saw DNDi as a bit amateurish," recalls François Bompart, a medical director at the Paris-based drug company Sanofi. "We thought, they cannot be serious."

Pécoul and his team started with a safe project. In 2001, the World Health Organization had called for malaria drugs that combined ingredients to slow the spread of resistance to the single best available agent, artemisinin. But the poverty of most people who need malaria drugs meant that the private sector had little incentive to create and test such combination therapies. Pécoul contacted Sanofi, which owned two malaria treatments: one based on artemisinin, and the other on the

DNDi medical director Nathalie Strub Wourgaft examines a child in Sudan.

NEIL BRANDVOLD/DNDI

slower-acting amodiaquine. He proposed a deal in which the DNDi would pay for and run clinical trials on a pill that combined the two drugs. In return, Sanofi would not patent the pill and would sell an adult course of treatment for no more than $1, half that for children. "To me it sounded very aggressive and not reasonable, since the two drugs separately were two to three times that," says Bompart.

But Pécoul convinced Sanofi that the move would be good for the company's public image. He also compromised, allowing Sanofi to stipulate that it could reach the low price gradually. As it turned out, by the time the pills were approved in 2007, manufacturing costs had come down far enough for the company to meet the target price right out of the gate. Hundreds of millions of pills have since been distributed in Africa. All told, the project cost the DNDi about $14 million, a tiny sum in the world of drug development. It has since replicated the process to develop other combination therapies (see 'Discount drugs').

Although they improve on existing therapies, some of these combinations remain inadequate. The DNDi's sleeping-sickness therapy NECT, for example, reduces a standard treatment from 56 intravenous infusions to 14. That is still problematic in affected countries: clean needles can be hard to come by, and long hospital stays are often impossible. People need a pill.

Drug development from scratch is arduous and expensive. It begins with experiments on hundreds of thousands of chemicals in the lab, looking for one that kills a pathogen without harming the host. The DNDi does not have a laboratory, so it does this through collaborations. It searches for promising leads in compound libraries generated by biotechnology and pharmaceutical companies. Many firms are willing to share access to these precious libraries because the diseases that the DNDi targets will not result in blockbuster drugs, so it is not infringing on their turf. The DNDi then contracts high-throughput screening centres, such as those at the Institut Pasteur Korea in Seongnam and the University of Dundee, UK, to test them out. "We use the same technique that pharma does," says Rob Don, director of discovery and preclinical research at the DNDi, "but we do it for less."

In 2007, such efforts identified fexinidazole, a compound that had shown promise against single-celled parasites but was pulled from development before reaching clinical trials. The DNDi turned it into a tablet, and passed it to its clinical-development team two years later.

The DNDi approached Sanofi again and promised to take care of trials if the company could file for regulatory approval. Sanofi warned that human trials would not be easy, because sleeping sickness is not common and people who get it tend to live in remote, unstable regions. But with the existing therapies being so dreadful, Wourgaft argued that any improvements from fexinidazole would be clear. "The delta between what we bring and what exists is huge. You don't need a magnifying glass on thousands of patients to see it." She set up multiple small trial sites in the Democratic Republic of the Congo and the Central African Republic and pooled their data.

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CLINICAL CHALLENGE

Wourgaft says that the studies were the hardest she has ever run. In addition to logistical challenges, civil war erupted in the Central African Republic shortly after the study launched, and rebel groups repeatedly robbed a clinic there and threatened the Congolese surgeon leading the trial. "I squeeze all my energy into each project," Wourgaft says. "It's as if I'm using forceps to deliver a baby — and the baby is an elephant."

The final trials on fexinidazole conclude this year, and Wourgaft is hopeful that the data will earn regulators' stamp of approval. The project has so far cost the DNDi about $45 million — and it stands to help 21 million people at risk of the disease in Africa. In a few months, Wourgaft will launch another trial, on a completely new oral

DISCOUNT DRUGS

The Drugs for Neglected Diseases initiative (DNDi) has produced several drugs in the past decade for a fraction of what pharmaceutical companies are said to spend. Factoring in the cost of failed candidates (not included below), the DNDi estimates that it can develop combination therapies for between US$10 million and $45 million, and make a completely new drug from scratch for $110 million to $170 million.

Drug | Disease	Research	Early safety and proof-of-concept trials	Late safety and efficacy trials	Access and additional studies	Total cost
COMBINATION THERAPIES					
SSG&PM | Kala-azar (visceral leishmaniasis)	Not needed for combinations of approved compounds		$10.5m	$2.5m	**$13m**
NECT | Sleeping sickness			$4m	$3.6m	**$7.6m**
NOVEL DRUGS					
Fexinidazole | Sleeping sickness	$8.1m	$5m	$32m	$17m*	**$62m**
SCYX-7158 | Sleeping sickness	$25m	$4.1m	$20.8m	$17m*	**$67m**

*Projected estimates until 2020

SOURCE: DNDI

drug — SCYX-7158 — that may cure people with sleeping sickness in a few days. The DNDi estimates that its development up to approval will cost around $50 million.

BREAKING BILLIONS

For more than three decades, economists at the Tufts Center for the Study of Drug Development in Boston, Massachusetts, have collected proprietary data from pharmaceutical companies, and used it to calculate the average cost of developing a new drug. The most recent estimate is $1.4 billion. This is used to justify exorbitant drug prices — companies must recoup their investments. But many don't think it has to cost that much. Even the chief executive of London-based pharmaceutical giant GlaxoSmithKline, Andrew Witty, has called billion-dollar estimates "one of the great myths of the industry". He attributed the huge sums to spending too much time on failures. Drug candidates can be killed as a result of safety concerns, poor efficacy or profitability worries, and he argued that companies could save money by dropping bad leads sooner. Others say that the figure is inflated by large and excessive trials done to prove that a new drug works just slightly better than an existing one.

By averaging the cost of projects in its portfolio, the DNDi says that it can develop a new drug for between $110 million and $170 million. Like the Tufts estimate, these prices include a theoretical cost of failed projects.

The DNDi admits to enjoying perks that pharma does not have. It keeps overhead costs low because its organization is virtual. The research organizations that it contracts probably charge the group less than they would a for-profit company. The DNDi also relies on scientific consultants who work for low pay because they relish the chance to make lifesaving drugs without considering competitors, investors and marketing. "DNDi gets a lot for free," says Richard Bergström, director-general of the European Federation of Pharmaceutical Industries and Associations in Brussels. "My companies do a lot of pro bono work, and so do universities."

Still, the organization reckons that such in-kind contributions account for just 10–20% of its expenditure. It saves much more through efficient collaboration (avoiding duplicated effort by screening pooled libraries, for example) and a focus on desperately needed drugs. Clinical trials can be smaller, faster and cheaper when the people who run them don't have to struggle to show barely perceptible improvements. And the DNDi kills candidate compounds only if they fail on safety or efficacy — it doesn't have to worry about marketability. By contrast, a few for-profit companies froze candidate drugs for hepatitis C after Gilead Sciences of Foster City, California, brought powerful drugs to the market. "A lot of R&D failures in pharma are commercial rather than scientific," says Don. "We keep going until it gets to market or scientifically fails."

The DNDi has earned respect from the industry, even though its founding organization has been antagonistic to big pharma. "Although DNDi came out of MSF, they don't let ideological viewpoints get in the way of making progress," says Jon Pender, vice-president of government affairs at GlaxoSmithKline. He and others praise Pécoul's skills at negotiation, and the DNDi's pragmatic approach to development challenges.

Policymakers have taken notice, too. Last year, the World Health Organization asked the DNDi to consider antibiotics for drug-resistant infections in the developing world; in May, the initiative announced that it would start the GARD (Global Antibiotic Research and Development) partnership with $2.2 million in seed funding. GARD will start by repurposing and combining existing antibiotics to treat a few diseases, including gonorrhoea and infections in newborn babies. Marja Esveld, a research adviser at the Netherlands ministry of health, is watching it closely. "We are worried about the rising costs of pharmaceuticals," she says, "and so for us, GARD is also a kind of experiment to see if the DNDi model can work for the development of drugs in the Western world."

Not everyone is convinced. Economist Ramanan Laxminarayan, director of the Center for Disease Dynamics, Economics and Policy in Washington DC, says that pharmaceutical companies have an incentive to make antibiotics for multidrug-resistant infections because patients in the United States and Europe will pay to get them — and non-profit organizations cannot hope to compete. Once the drugs exist, he says, subsidies could ensure that they are affordable.

Pécoul disagrees: he doesn't think that subsidies, donations or tiered pricing can ensure accessibility. "We need appropriate products and a sustainable market for those products," he says. That environment has not materialized for other conditions: Gilead's hepatitis C drugs, for example, are listed at more than $74,000 for a course. And their potency against some strains of the virus is questionable, says Pécoul. When he and his team learned about other hepatitis drug candidates being frozen, he launched a project to turn them into treatments that more people could use and afford. They're also attempting to combine existing drugs.

If the group succeeds with this and with antibiotics, it will have shown that its model can be applied to diseases that affect developed countries. "I hope we provide lessons that can be used by others," says Pécoul. But companies won't simply adopt the DNDi's methods, because they do not generate profit. The investors who keep firms alive are concerned with the bottom line. Pécoul says that a transformation would require government involvement and a reorganization of the development process. It would need a system to prioritize what treatments are needed and which companies and organizations could collaborate; and it would require forethought about how the final products would reach those in need. It means shifting away from profit-based incentives to things such as prizes and government funding. Today's profit-driven approach is not only expensive, Pécoul says, it fails huge swathes of the population.

When Wourgaft reflects on the differences between her career in pharma and her work at the DNDi, she thinks not about the cost of research and development, but about the value of a human life. She recalls one trip to a Congolese sleeping-sickness trial site. She sat on a cot beside a woman in the middle of a psychotic episode, and spoke to her desperate husband. Later, she learned that the woman survived because of the DNDi's treatment. "When you see that, you know the value of what you're doing," she tells me. "We are trying to fix diseases that are lethal — this is really serious medicine." ■

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