Really ending river blindness: Mark Sullivan and John Reeder

By Robin Davies

Two Australians successfully navigated the incredibly complex web of international drug development to better fight the scourge of river blindness.
Immediately opposite the main entrance of the World Health Organisation (WHO) headquarters in Geneva is a statue of an African boy leading his blind father with a stick. It is there to commemorate the global fight against river blindness, or onchocerciasis, a debilitating and neglected tropical disease caused by a worm and transmitted by the bite of the blackfly, which breeds in fast-flowing rivers.

River blindness is overwhelmingly a disease of sub-Saharan Africa and is endemic in 31 countries. It is estimated that approximately twenty million people are currently infected, including more than a million with vision loss. Nearly 200 million people are at risk of infection. The bite of the blackfly transmits microfilariae, or baby worms, that can grow into large adult worms that live in nodules under the skin. The female adults give birth to millions of microfilariae that migrate to the skin and eyes, and it is the body’s immune response to the natural turnover of the microfilariae that cause the symptoms of the disease. While it can lead to partial or full blindness over a long period of time, the disease also has a large impact on the way a person feels. It causes flu-like symptoms, along with skin issues such depigmentation, scarring and constant itching.

From 1974 to 2002, river blindness was the target of a high-profile, multi-agency elimination campaign – led, surprisingly, by the World Bank under Robert McNamara in the Bank’s first investment in a health program. While the disease still creates a heavy burden, enormous progress has been made through a combination of vector control measures, starting in the early years of the program, followed by the introduction of an effective oral treatment for the disease. According to WHO, approximately 150 million people are treated each year, 600,000 people have been saved from blindness and 25 million hectares of previously high-risk arable land have become available for agriculture.

This progress owes a very great deal to the discovery of what was originally a veterinary drug, ivermectin, by William C. Campbell and Satoshi Omura, who received the 2015 Nobel Prize for medicine for their work. Repurposed for the treatment of river blindness, ivermectin is administered annually (and in some cases, biannually) in community-directed mass drug administration programs, over many years. It has been shown to be very effective in the majority of cases, and well-tolerated. In many places, ivermectin has led to the complete elimination of river blindness. The pharmaceutical company Merck has donated several
billions of doses to affected communities in Africa in line with a commitment they gave in 1988 to provide ivermectin free of cost for as long as needed, in whatever quantities needed and wherever needed.

While ivermectin is frequently described as a rare example of a true “wonder drug”, it is not a perfect treatment for river blindness. Ivermectin does not work well in everyone, with around one third of people not clearing the worms from their skin. Most people will have worms back in their skin again within one to three months of treatment. Increasing the dosing frequency to biannual increases costs and is very difficult to achieve, particularly in less accessible regions. Even if they have access to an annual dose, the majority of people will have many months of symptoms and pose a transmission risk during that time, making elimination slower and far more difficult to achieve. John Reeder, profiled below, comments:

As we’re getting towards elimination, having to go out every single year to give ivermectin is going to be a logistical problem, and as countries see less and less of the disease, they’re less and less likely to do it.

For this reason, around twenty years ago, an alternative oral medicine began to be assessed for its efficacy against river blindness. This was moxidectin, a drug from the same family as ivermectin that had also been developed as a veterinary medicine by a subsidiary of the pharmaceutical company Wyeth. WHO’s Special Programme for Research and Training in Tropical diseases, known as TDR, suggested developing moxidectin for use against river blindness to Wyeth and then entered into a partnership with them to make it happen.

Moxidectin was shown to be more efficacious than ivermectin in clinical trials: it cleared the microfilariae from the skin in more people, to a greater extent and for longer than ivermectin and, because it persists in the skin for much longer, annual treatment is at least as effective as biannual ivermectin. But then, as is the way in the pharmaceutical industry, Wyeth was swallowed in 2011 by a larger company, Pfizer. Pfizer decided not to continue their involvement in the program, but was willing to pass ownership of it to TDR and provided some funding to help complete the Phase III clinical trial.

Overall, TDR (or rather its donors, including Australia for a time) supported the pivotal phase III clinical trial over a number of years, drawing on its 40-year
history of partnership with low and middle income country scientists, putting together complex trials in remote and difficult circumstances. The results of the Phase III trial undertaken in Liberia, Ghana and DRC between 2009 and 2012 were eventually published in The Lancet in early 2018. The trial clearly demonstrated the superiority of moxidectin over ivermectin in reducing parasite burden in the skin and therefore accelerating progress towards elimination.

This is where we meet John Reeder. John is a naturalised Australian medical researcher, of Mancunian extraction, who has headed TDR since early 2012. An infectious diseases specialist with a particular interest in malaria, he was formerly at the Burnet Institute in Melbourne. Before that, he headed the Papua New Guinea Institute of Medical Research in Goroka for six years.

John was excited about the potential of moxidectin, not only as a treatment for river blindness but potentially also for other neglected tropical diseases such as scabies. However, WHO is not well-equipped to lead the development of a drug right through the process of obtaining market authorisation from one or more so-called “stringent regulatory authorities” – that is, advanced regulatory bodies like the US Food and Drug Administration (FDA).
For that, TDR needed an industry partner. John’s scientific review committee was very insistent that he should actively seek the outside expertise needed to take the drug through to registration. At the same time, TDR could not license the drug to a profit-seeking entity. TDR was effectively taking the role that is played for other medical products by various global Product Development Partnerships. These organisations are publicly subsidised non-profits that capitalise on the drug development and manufacturing expertise of the pharmaceutical industry sector to build the pipeline of new drugs for neglected diseases. John says:

This wasn’t an easy thing to take on. It wasn’t an easy sell. It was a drug with no market, no real chance of profit, and in fact, a potential cost of somewhere in the region of US$20 million to take through to the next stage of FDA approval.

At a very opportune moment, and in quite a roundabout way, John found himself in discussions with Mark Sullivan, an Australian drug development expert with a strong pharmaceutical industry pedigree and a non-profit perspective. Mark had
been recommended and referred to John by several mutual acquaintances in the Australian medical research community, most notably Gus Nossal, with whom John had worked when Nossal was Director at the Walter and Eliza Hall Institute. At the time Nossal also sat on TDR’s board.

In 2005, after working in London and California for some fifteen years in the pharmaceutical industry, mainly on mid and late-stage clinical trials of drugs for HIV and hepatitis B, Mark had decided it was time to return to Australia. At the invitation of Professor David Cooper, he became Chief Operating Officer of the HIV Vaccine Program at what is now the Kirby Institute:

> That, for me, was the eye-opener that my industry background could be applied to help bring the necessary standards, quality, and organisation to an academic program, and I thought that there really must be a number of different drugs, vaccines, opportunities that were sitting in academia with no real mechanism to take them further into the development pathway without someone with an industry background.

He subsequently founded a unique organisation, Medicines Development for Global Health, with the objective of undertaking the end-to-end development of drugs for neglected diseases.

John’s business model was markedly different from that of the Product Development Partnerships and indeed globally unique. He operated without upfront public subsidies and intended to take products all the way through to registration without a pharmaceutical industry partner. These products could cover the costs of their own development, and at least some of the costs of production and distribution, through differential pricing in developed and developing country markets. More obscurely, they could qualify for “priority review vouchers” from the US FDA. These vouchers entitle their bearers to expedited assessment of a subsequent product and, being transferable, may also be sold for very significant sums of money in the tens to hundreds of millions.

After lengthy discussions between John and Mark, and a six-month due diligence process, WHO signed over to Mark all rights to moxidectin in 2014 on the expectation that any profits generated would be reinvested into making the drug as affordable as possible to end-users. Achieving the registration of moxidectin would be an expensive process, and in the case of river blindness there was
unlikely to be any significant dual market opportunity. However, there was a venture capital opportunity.

The Global Health Investment Fund (GHIF) had been established in 2016 by a group of public and private investors, with underwriting by the Gates Foundation. GHIF is a closed-end social impact venture capital fund intended to demonstrate that financial returns can be generated by investments in global health products. Based on the positive results of the Phase II trial of moxidectin and the advanced status of the Phase III trial, Mark was able to persuade GHIF to invest US$10 million, about 10% of its total capital, in the development of moxidectin against the expectation that a priority review voucher would be awarded upon market authorisation of the drug by the FDA.

The drug registration process is phenomenally arduous, involving mind-boggling amounts of technical documentation and endless to-ing and fro-ing in response to questions from the assessors. It is nothing if not a gigantic coordination exercise involving a vast assemblage of experts. As Mark says:

> It’s one of the largest logistical efforts that exists. And it’s not an overstatement to say that there are literally thousands of scientists who are involved in the production of any new drug application. So, in our particular submission, there were nearly 500 separate documents that went in, and each of those could be as short as probably 15-20 pages. On average, they’re around 1,000 pages. The biggest one was about 60,000 pages. And underlying that is around four million pages of data.

Unlike pure medical research, drug development is not something that one can train for in an academic setting. Mark started out with an undergraduate degree in biochemistry and microbiology from Deakin University in Geelong, where he grew up. That got him a job as a clinical trial monitor – a person who undertakes site visits, confirms data and ensures a study is running in the way that it should be. From there he built his understanding of the drug development and global market authorisation process piece by piece over many years.

Expertise of this kind is very rare in Australia, no matter how much world-class medical research expertise we might have. Mark says:

> The training is largely on the job: handholding, watching, observing your senior
colleagues, being checked, reviewed, and so on. It’s not a career that you ever see in anybody’s list. It doesn’t come up in potential career options, and yet it’s a fantastic and varied career that you only find out about, like for me, by accident.

When, in June 2018, moxidectin was finally approved for the treatment of river blindness (in people 12 years and older) by the FDA, this was unprecedented. It was not only the first new drug against river blindness in 30 years, it was the first time an Australian sponsor had ever achieved the registration of any novel drug by the FDA. And it was the first time that any not-for-profit organisation had done so without a pharmaceutical industry partner. Moreover, in John’s view it was the first time the priority review voucher system had been used genuinely for the purpose for which it was designed.

The FDA approval duly delivered Mark a priority review voucher which, as planned, he offered for sale. Price expectations had moderated somewhat since he first secured financing from GHIF; the number of vouchers awarded had grown and the very high prices commanded by the early vouchers could no longer be expected. Nevertheless, after a period of time Mark’s voucher sold for a significant though undisclosed sum and he was able to use the proceeds to repay his investors, with funding left over for investment in the manufacturing and distribution of moxidectin and further trials of the drug for paediatric use and other indications.

How did Mark feel when he got news of the FDA decision?

I had just come back from India. In fact, I was transiting up to Sydney through Melbourne Airport, and it was almost like a sense of relief. We knew the drug
was absolutely good enough, but you just never know until that letter comes in, you really don’t. So, it was a lovely moment. It took quite a long time for it to genuinely sink in. And I think that the celebrations still are yet to come, to be frank with you. You really do feel that you want to move on and just get to the next thing once it’s done. So, it’s a funny feeling. It’s very strange, very hard to describe.

Mark’s interests do not end with the registration of moxidectin; nor indeed do John’s. Mark is now working with WHO to deliver the data that they need to help make a recommendation for the use of moxidectin in river blindness elimination programs. Further field work is needed in order to determine a paediatric dose of moxidectin for children aged 4-11 years. A study is being undertaken to look at both annual and biannual administration of both moxidectin and ivermectin to see which would lead to faster elimination. And another study is being undertaken to generate product safety data across a larger population. Mark is also exploring ways of generating additional funding to support the manufacturing and distribution of the drug, whether from philanthropic sources or possibly through differential pricing.

TDR continues to work closely with Mark in a technical capacity as he undertakes this additional work. John and Mark’s original conversation had been about new treatments for scabies. Mark is now turning his attention to the use of moxidectin as a single-dose oral treatment for scabies, which is endemic in northern Australia and a major health problem in remote indigenous communities—both in its own right and because it can lead to rheumatic heart disease. At present, the treatment of scabies involves applying permethrin cream from head to foot, leaving it on overnight, treating all contacts as well and in each case repeating the treatment one week later — a fairly unrealistic treatment regimen. Ivermectin could be used to treat scabies but two treatments would still be required, and it is currently approved for this indication in Australia only as a last resort.

Developing moxidectin for the treatment of scabies will be a hard road. For one thing, there will be no priority review voucher opportunity in this case: the FDA issues only one voucher per molecule, regardless of the indication. Therefore the costs associated with the development of moxidectin as a treatment for scabies, if not met by public subsidies, can only be recouped through differential pricing. Mark believes this is a feasible strategy. He is now in full development mode for
scabies treatment across multiple trial sites. In addition, he is exploring the use of the drug for several other worm-caused diseases – namely lymphatic filariasis, stronglyoidiasis and soil-transmitted helminthiasis. Mark says:

So, we have a large amount of work that we’re doing. That’s funded through our priority review voucher, and we still haven’t had a handout from anyone, and we’ve been very proud to be quite independent and self-funded. And we are absolutely determined to carry this drug into the field – not personally, but certainly through appropriate NGOs – but to make it available to really disrupt this field the best and the most positive way we possibly can, by being very open with data-sharing, working with the communities, generating the data that, to be frank, many other organisations just wouldn’t bother with.

The path that John and Mark agreed upon in 2014 looks very high-risk even in retrospect. Their prospects of success must have seemed extremely uncertain to them at the outset. However, they and their social impact investors gambled and won. This was perhaps a special case in that the drug was well and truly tested and awaited only somebody with the right expertise and sufficient financing to take it through to registration. Mark and his company appeared on the scene at just the right point in time, as did GHIF, and both were able to take advantage of a particularly innovative piece of public policy machinery in the United States — mainly the priority review voucher program. But, special case or not, this was a long shot that hit the centre of its target.

Mark was named 2019 Victorian Australian of the Year for his achievement in developing moxidectin for the treatment of river blindness. An exhibition at the National Museum of Australia showcased personal items selected by each of the state and territory recipients of the same award. Mark bent the rules and chose a small version of the statue of the boy leading his blind father with a stick, loaned to him by one of the early pioneers of ivermectin treatment, the great Australian ophthalmologist Professor Hugh Taylor.
John, as an international civil servant, could not really have expected the same recognition. He has, however, received internal WHO recognition of sorts through his acquisition of a second hat in June 2019: he is now also Director of WHO’s Research for Health Department within the organisation’s new Science Division. He is simply happy that moxidectin is no longer in his “parking lot”:

“This is, I think, one of the positive aspects of organisations like TDR. I guess we were one of the first product development partnerships in some ways, because moxidectin was developed with public money from donors, Australia included, which means we are not trying to gain a profit back, and we try and be open with all access to data. So, we’re just very happy if other people can pick this up and use it even further.”

It’s thanks to the judgement and courage of both of these Australians that a superior new treatment for river blindness now exists, and that elimination of the disease is now a brighter prospect. But it is also thanks to the foresight of those who devised the US priority review voucher program and those who put together GHIF. Like drug development itself, this process was a complicated and precise dance involving many actors.

Robin Davies is an Associate of the Development Policy Centre, and an Honorary Professor at ANU. Listen to Mark and John discuss their work on the Indo-Pacific
Centre for Health Security’s podcast ‘Contain This’.

If you’d like to learn more about John and Mark’s use of the priority review voucher, read this article.