



LIVES ON THE EDGE:

**TIME TO ALIGN MEDICAL RESEARCH AND
DEVELOPMENT WITH PEOPLE'S HEALTH NEEDS**

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ABOUT MÉDECINS SANS FRONTIÈRES (MSF)

Médecins Sans Frontières (MSF) is an independent international medical humanitarian organisation that delivers medical care to people affected by armed conflicts, epidemics, natural disasters and exclusion from healthcare. Founded in 1971, MSF has operations in over 60 countries today.

ABOUT THE MSF ACCESS CAMPAIGN

In 1999, on the heels of MSF being awarded the Nobel Peace Prize – and largely in response to the inequalities surrounding access to HIV/AIDS treatment between rich and poor countries – MSF launched the Access Campaign. Its sole purpose has been to push for access to, and the development of, life-saving and life-prolonging medicines, diagnostics and vaccines for people in MSF programmes and beyond.



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EXECUTIVE SUMMARY

Every day, Médecins Sans Frontières staff confront significant gaps in the availability of medical tools to address the health needs of the people we aim to care for, in crisis-affected communities in more than 60 countries. These gaps – which have persisted for as long as MSF has been in operation – contribute to preventable deaths and exacerbate ongoing humanitarian and medical crises.

Filling these gaps with effective, affordable vaccines, diagnostics and treatments that can be used in a range of contexts, including under-resourced and unstable places, could save innumerable lives.

In this report, MSF illustrates how our staff and patients around the world are impacted by the way biomedical research and development is predominantly conducted today.

The report also looks at a broad range of policies aimed at changing this dynamic by incentivising the development of medical tools that truly respond to patient and public health needs, and ensuring they are made broadly accessible.

There are at least four harmful consequences of the way medical research and development is conducted today:

❖ **Failing to deliver for diseases that aren't sufficiently lucrative.** The current biomedical innovation system is overwhelmingly driven by financial interests;¹ pharmaceutical companies develop drugs based on the likely return that a product will offer through sales. The result is a lack of investment in drugs, diagnostics and vaccines to meet the needs of people who can't afford to pay high prices, or who don't constitute a sizeable or lucrative market. MSF experiences the consequences of this acutely: for example, with the lack of treatments or vaccines for Ebola virus during the 2014 pandemic; the inadequate or non-existent treatments for neglected diseases such as Chagas disease and visceral leishmaniasis; and the long, toxic and insufficiently effective treatments routinely used to treat drug-resistant tuberculosis.

❖ **Failing to prioritise according to public health needs.** With current incentive mechanisms, the biomedical innovation system concentrates investment on products that will sell well, and not necessarily on existing public health priorities. For example, the urgent need for new antibiotics has been widely documented, but governments have been slow to put in place the right incentive mechanisms to encourage development of new antibiotics, and this medical priority remains unanswered by pharmaceutical companies.² MSF is witnessing first-hand the emergence of antibiotic resistance in our projects, including in child nutritional centres in Niger and in adult trauma patients in Syria and Jordan. Industry is abandoning work in other areas critical to public health, including anti-infectives such as tuberculosis medicines.^{3,4,5} Governments have

failed to implement the necessary incentive mechanisms to ensure that therapeutic importance – and not solely financial reward – influences product development prioritisation.⁶

❖ **Failing to deliver affordable products.** High prices are inherently linked to a reliance on patent monopolies as the way to finance biomedical R&D. Patents and other forms of intellectual property rights give companies exclusive rights to make and sell a product with no fear of competition, leaving producers largely free to charge what they please.

Many people, medical providers and governments face unsustainably high prices for medicines, such as for the hepatitis C drug sofosbuvir that costs up to US\$1,000 per pill. MSF is working to scale up immunisation against pneumonia, the leading cause of death for young children



A nurse verifies blood-type compatibility before administering a blood transfusion to eight-year-old Adut Chuor Kujal, who is receiving treatment for cerebral malaria at an MSF hospital in Aweil city, South Sudan.

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worldwide, but the high price of the vaccine has been a barrier. As a treatment provider supporting more than 230,000 people on lifelong antiretroviral (ARV) treatment, MSF needs access to salvage regimens that contain newer HIV medicines such as raltegravir and etravirine, but they are priced at least 18 times higher than first-line treatment.⁷

Patent monopolies and high prices are often justified as the only way to sustain new investments in R&D.⁸ Yet increased patenting has not resulted in increased innovation for medical products.⁹ Only one out of the world's ten largest drug companies reports spending more on research than it does on marketing.⁶ The evidence shows that drug prices are not reflective of R&D costs, but are instead largely determined by what the market can bear.

❖ **Failing to use scientific and financial resources efficiently and effectively.**

Existing incentive mechanisms hamper collaboration among researchers. Exclusive intellectual property rights encourage scientists to work in isolation from, and in competition with, one another. Follow-on innovation is also restricted; for example, creating a multidrug regimen or a combination pill can't easily happen if the relevant patents are owned by competing companies.¹⁰ This siloed approach has blocked the development of new therapies against tuberculosis that MSF has long called for. Secrecy around clinical trials and safety data can also lead to adverse patient outcomes with tremendous financial, social and health consequences.¹¹

Economists point to the excessive 'financialisation' of the industry - a broad trend afflicting medical research and development today, whereby maximising shareholder value becomes the primary objective of pharmaceutical companies, rather than delivering innovation that answers to a public health need. The substantial financial rewards earned by industry, rather than being ploughed back into innovation, are used to boost shareholder and executive rewards.

Though they are largely known to policy makers, the failings of biomedical R&D have yet to be properly addressed, despite MSF and other actors calling for change for more than a decade. It is possible to steer, finance and coordinate biomedical innovation differently; this would require political leadership to cease delegating to market forces the overwhelming responsibility for developing new tools to answer global public health needs. Part of the resistance to reform stems from a resigned acceptance of the shortcomings of biomedical innovation. Many important policy discussions today mistakenly take as a given that patent monopolies are the only solution to incentivise and finance pharmaceutical R&D. But these failures are not inevitable. MSF argues that four main strategies should be employed to start addressing the shortcomings of biomedical innovation.

❖ **Governments should demand transparency.**

Undoubtedly, R&D needs to be paid for. But how much does it cost to develop a drug? The raw data is rarely available, as company investments are not disclosed and real R&D costs are not disaggregated. Existing academic studies give widely varying figures. The most widely-cited figures of \$802 million (2003)¹² and \$2.6 billion (2016)¹³ are based on industry-funded

studies whose methodology has been widely challenged by observers, and even by Big Pharma leaders, for including sizeable, arbitrarily inflated 'time costs' and costs of failure.¹⁴

The Drugs for Neglected Diseases *initiative* (DNDi) is a collaborative, non-profit drug R&D organisation co-founded by MSF that pursues a patients' needs-driven approach to developing new treatments for neglected diseases. Having developed six new therapies over the past decade, DNDi¹⁵ has estimated the cost to develop a new chemical entity in the field of neglected diseases at between €100-150 million (\$113-169 million*), including accounting for 'failures'¹⁵ - essentially the money spent on other drug candidates that aren't ultimately approved for market. Although this does not represent an immediately comparable figure to industry, it does indicate that innovative R&D approaches can potentially be more efficient than traditional pharmaceutical business models, and provides an order of magnitude of what is possible using an alternative not-for-profit model.

Lifting the veil on real R&D costs would have significant repercussions for the debate around the fairness of drug pricing and the appropriate levels of reward for drug development. Efforts to ascertain real costs could be voluntary, through transparency initiatives driven by the pharmaceutical sector. Or mandatory measures could be required by governments. For example, for medicines whose early-stage development was led by the public sector, transparency on the costs of later-stage development could be included in any intellectual property licensing agreement.

* Note: all currency conversions done using xe.com on 15 April 2016, except where otherwise noted.

❖ **Governments should change the incentive mechanisms that steer and finance biomedical innovation.**

Governments support medical innovation through multiple avenues: through monopoly-protected high prices, as global spending on medicines now reaches \$1 trillion each year; through publicly-funded research, which accounts for 30 percent of the estimated \$240 billion yearly total global investment across all health R&D¹⁶; and through additional incentives and policy measures that are designed to encourage innovation.

It is critical that governments seek to leverage these extensive contributions to safeguard and promote access to medicines, so that public health needs are met. Promising, yet poorly-designed publicly-funded incentive mechanisms should be reformed, so that they are able to contribute to a better, fairer, more effective and more efficient biomedical innovation system. For example, MSF has repeatedly called for the reform of the US Priority Review Voucher programme for neglected diseases, which in its current form can be exploited by companies who don't actually meet the objective of furthering neglected disease research. Conversely, potentially effective policies that could allow governments to leverage their investments have been largely left unused, such as legislation which authorises governments to licence patents held by drug companies on inventions developed thanks to publicly-funded research.

But tweaking existing incentive mechanisms is not enough. To overcome the systemic shortcomings in pharmaceutical R&D, it is necessary to break the link that today binds biomedical innovation to drug sales and exclusivity rights. A number of initiatives that embrace this principle of 'de-linkage' exist already and deserve policymakers' attention, as they have yielded clear results. In co-founding DNDi, MSF worked to enshrine 'de-linkage' principles in the

development of affordable treatments for neglected and tropical diseases, including a patent-free antimalarial treatment. Another example is the Meningitis Vaccine Project, which ensured that medical requirements for sub-Saharan Africa and affordability concerns were prioritised early in the product development process. The result was an affordable vaccine against Meningitis A that was rolled out with great results by MSF and others across the Meningitis Belt. These examples, where there is no link between the financing of the R&D and product revenue through sales, are proof of concept for 'de-linking' or separating the cost of R&D from the price of the resulting product.

Policymakers can now build on these examples to put in place incentive mechanisms to encourage medical innovation that answers priority public health needs and delivers affordable products. Prize funds are one idea worth exploring. With a history that predates the patent system,^{17,18} prizes would allow governments to steer R&D efforts towards priority needs. Unlike patents, which are awarded regardless of the social value of the end product, prizes are awarded only after pre-determined milestones are met. Publicly-funded prize money could be paid out in exchange for the innovator surrendering exclusivity rights, enabling an affordable price that is a lot closer to the cost of production. The viability of prize funds as a mechanism for stimulating biomedical innovation has been proven on numerous occasions, including for rapid point-of-care diagnostic tests to identify highly-resistant bacterial infections; for diagnostic tests for upper respiratory tract infections; and for stabilising technology to protect vaccines against elevated temperatures or accidental freezing.

❖ **Governments should set priorities, coordinate efforts and ensure sustainable financing.** MSF, together with other civil society organisations and some governments, has

actively participated in a ten-year process hosted by World Health Organization (WHO) which has recently proposed two things: a WHO Observatory,¹⁹ mandated with mapping ongoing research and development, the financing of such R&D and the various gaps and needs; and a proposal for a Research and Development Fund which could potentially start to finance R&D in ways that promote access, transparency and essential health needs. While significant, these outcomes are just a first step towards systematic reform.

❖ **Governments should act to meet the needs of patients in MSF programmes and beyond.**

Accepting the shortcomings of today's medical innovation system is a political choice, and the failure to address the fundamental reasons behind the lack of drugs to treat diseases faced by people in MSF programmes and the unsustainably high prices of drugs is thus an ongoing political failure. Ever since MSF called for an R&D treaty in 2001, we have witnessed slow but important progress to seek reform that delivers better health outcomes for people around the world. A landmark WHO report published in 2012 called for a 'binding global instrument for R&D and innovation for health'.

Today, with access and innovation challenges multiplying in both rich and poor countries, there are increased signs of governments seeking to do more, including at the United Nations and through dialogues at the G7 and G20. For MSF, our measure of success ultimately depends upon the ability of all people, in MSF programmes and beyond, to have access to the medicines they need, regardless of what disease they may face, or what they can pay or where they live. Until we reach that goal, we will continue to bear witness to the failings of our current system of medical research and development, and to demand justice and change.

DIAGNOSIS: HOW AND WHY MEDICAL R&D IS FAILING US

As a humanitarian organisation that delivers medical care to crisis-affected populations, Médecins Sans Frontières (MSF) witnesses first-hand how biomedical innovation is failing to meet the needs of the people we care for. It is precisely these failures that prompted MSF to create the Access Campaign in 1999, a dedicated unit within the medical humanitarian organisation that seeks to increase access to better drugs, diagnostics and vaccines for patients in MSF field programmes and beyond.

In 2003, together with several governmental research institutions, MSF co-founded the Drugs for Neglected Diseases *initiative* (DNDi), a collaborative, non-profit drug research and development (R&D) organisation with a patients' needs-driven approach to developing new treatments for neglected diseases. MSF continues to be one of DNDi's core funders and operational partners.

The financing and prioritisation of drug development today overwhelmingly relies on pharmaceutical companies

recouping their R&D investments through charging high prices, and protecting those prices through patents and monopolies. While it has long been acknowledged that this system has huge detrimental consequences for people in low- and middle-income countries, the failures of biomedical innovation are resonating like never before for people and policymakers in high-income countries. Far from being a problem that only affects neglected populations in poorer developing countries, there

is now growing recognition that people in wealthier countries are also hit by the shortcomings of the system that drives and finances biomedical innovation today.

These failings are systemic: it is precisely because of the way biomedical R&D is conducted that it is failing to meet the health needs of the people it purports to serve. This chapter will examine four ways in which today's predominant model for drug development is failing for people in low- and middle-income countries.

1. FAILING TO DELIVER FOR DISEASES THAT AREN'T SUFFICIENTLY LUCRATIVE

The current biomedical innovation system is overwhelmingly driven by financial interests: pharmaceutical companies choose to develop drugs based on the likely profit that a product will offer, through sales.

This simple reality means that the medical needs of people who can pay high prices trump the needs of the poor, as the potential return on investment through sales revenue determines research and development priorities. The result is a severe lack of investment in medical tools – drugs, diagnostics and vaccines – to meet the needs of people who can't afford

to pay high prices, or who don't constitute a sizeable or lucrative market under the current system.

A 2002 analysis of new chemical entities developed between 1975 and 1999 found that only 1.1% were treatments for tuberculosis (TB) and tropical diseases, despite them causing 11.4% of the global disease burden.²⁰ The following decade saw some important progress in R&D for global health: between 2000 and 2011, of the 850 new therapeutic products registered, 4.4% were for neglected diseases.²¹ However, according to the same study, only 4 of

the 336 new chemical entities brought to the market during the same period were for neglected diseases (including malaria) - just 1.2% of the total (see Figure 1). In 1990, the '10/90 gap' phrase was first used to describe the fact that less than 10% of global resources devoted to health research were put towards health needs in developing countries, where over 90% of all preventable deaths occurred.²² A quarter of a century later, this fatal imbalance between global disease burden and drug development priorities remains a significant barrier to meeting people's medical and health needs.

* The two studies quoted did not use the same list of neglected diseases, as classifications had changed. The 2002 study looked at tropical diseases (defined as parasitic diseases [malaria, African trypanosomiasis, Chagas disease, schistosomiasis, leishmaniasis, lymphatic filariasis, onchocerciasis, intestinal nematode infections], leprosy, dengue, Japanese encephalitis, trachoma, and infectious diarrhoeal diseases) and tuberculosis. The later study identified 49 neglected diseases, separating them into five categories: malaria, tuberculosis, diarrhoeal diseases, NTDs (the WHO list of 17 NTDs), or other neglected diseases (list of 19 diseases not fitting into other categories).

❖ 1. Failing to deliver for diseases that aren't sufficiently lucrative continued

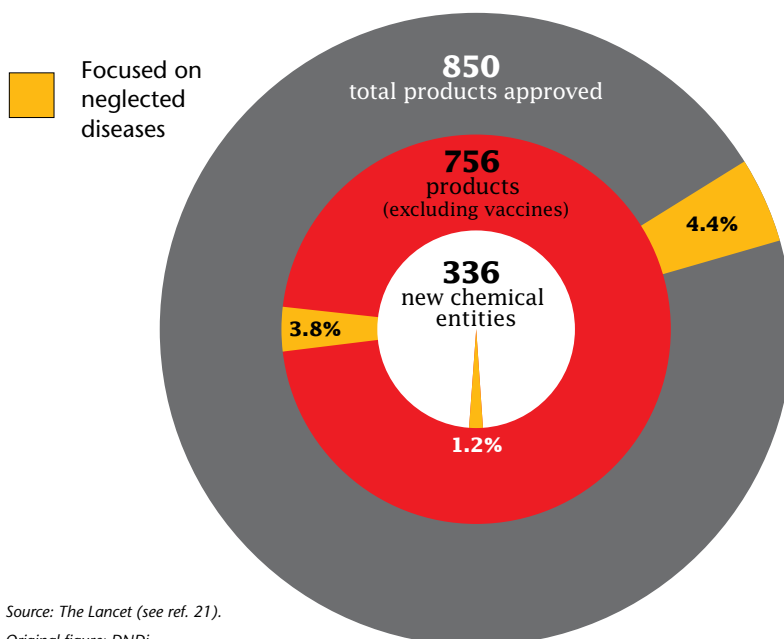
The fact that MSF frontline health workers lacked a treatment or a vaccine for Ebola virus as the outbreak engulfed Guinea, Sierra Leone and Liberia in 2014 is a poignant illustration of this problem. But the problem of inadequate or non-existent treatments and vaccines was a challenge for MSF long before 2014. Since 1999, MSF has treated people with Chagas disease, a

parasitic disease endemic to South and Central America that causes damage to the heart and central nervous system. Chagas disease is the leading cause of infectious heart disease (cardiomyopathy) in Latin America, but the existing treatment was developed over 40 years ago, carries significant side effects, and has limited efficacy. In 2014 MSF treated almost 10,000

people a year for visceral leishmaniasis (also known as kala azar), a parasitic disease prevalent in South Asia and East Africa that attacks the immune system and is almost always fatal without treatment. Many widely used treatment options are highly toxic, burdensome for healthcare systems to administer, or extremely difficult for people to adhere to.

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FIGURE 1: FATAL IMBALANCE IN HEALTH R&D (2000 TO 2011)



“**Ebola emerged nearly 40 years ago. Why are clinicians still empty-handed, with no vaccines and no cure? Answer: because Ebola has been, historically, geographically confined to poor African nations. The R&D incentive is virtually non-existent. A profit-driven industry does not invest in products for markets that cannot pay.**”

Dr Margaret Chan,
WHO Director-General (2014)



WHY SHOULD MEDICAL RESEARCH & DEVELOPMENT MATTER TO A HUMANITARIAN ORGANISATION?



Dr Manica Balasegaram

“For me, the answer is simple. It’s been, unfortunately, tied into my MSF field experience from day one, as it is undoubtedly tied to the experience of many other MSF staff working in the resource-limited and unstable contexts where MSF lives and breathes.

In 2001, MSF sent me, an emergency physician, to work in rural Uganda near the Sudan and Congo borders. What I saw there, and in subsequent missions that followed, stood in stark contrast to my previous life working in the well-resourced settings of the West. I found myself using archaic drugs that were toxic or increasingly ineffective to treat extremely sick people, including people dying from opportunistic infections of HIV and young children repeatedly infected with drug-resistant malaria. We lacked the necessary tools to tackle outbreaks of exotic parasitic diseases, like visceral leishmaniasis and human African trypanosomiasis (aka sleeping sickness).

It was tragic to see 15 years ago. What’s worse is that this tragedy is still unfolding today. In recent years, MSF has seen increasing numbers of people infected with drug-resistant tuberculosis, which

is exceedingly difficult to treat – and to endure treatment for. In an attempt to provide better options for our patients, MSF has taken the step of launching two clinical trials in search of more effective TB treatments. In the Ebola outbreak, where MSF played such a prominent role, we also engaged in trials and studies to evaluate treatments, vaccines and diagnostics. MSF also works to gain access to new drugs, diagnostics and vaccines at affordable prices, in an effort to properly care for people seeking medical assistance in our clinics across the world. As medics, trying to provide assistance to populations living in difficult circumstances, what could be less unexpected?

The sad reality is that MSF has seen these problems persist over decades, leaving us continually frustrated at not being able to provide a level of care that is often taken for granted in high-resource settings. The tools we need are often unaffordable or unusable in resource-poor contexts, or simply don’t exist. MSF intervenes in this medical research ecosystem in multiple ways, including by advocating for others to engage in R&D to address specific medical needs, by conducting studies and funding R&D initiatives, and even by sponsoring clinical trials.

More than two decades ago, we launched a clinical trial to improve the treatment for meningitis. In our Nobel Prize acceptance speech in 1999, we called for “change, not charity” and subsequently set up the MSF

Access Campaign, dedicated towards fighting for better tools for our patients. A few years later, MSF and a group of partners set up and co-founded the Drugs for Neglected Diseases *initiative*, which has gone on to deliver six new treatments for neglected diseases that are affordable and suitable for use in developing countries, and continues to break new ground in collaborative R&D. And somewhere, in rural Uganda, an emergency physician working in a sleeping sickness programme was unwittingly transformed into a clinical researcher. I helped MSF launch one of the first clinical trials for a new drug combination to treat sleeping sickness, in an attempt to replace the failing and toxic treatment we had hitherto been using to treat the disease.

Over the last decade, the market failure has persisted. While global health actors have emerged to address gaps in innovation and access, especially for HIV, TB and malaria, much still needs to be done to meet the public health needs of today. News headlines constantly remind us of the high prices of drugs and vaccines; we’ve seen first-hand the world’s lack of preparedness to deal with new and emerging infectious diseases, and the global threat of anti-microbial resistance hangs over our collective heads. Can you imagine an era when we can’t even treat common infections? Sadly, in MSF, many of us have been there, done that. ”

**DR MANICA BALASEGARAM,
EXECUTIVE DIRECTOR OF MSF’S
ACCESS CAMPAIGN (2016).**

R&D IN FOCUS: EBOLA

PROMISING INNOVATION SIDELINED, LEAVING MEDICS WITH NO TOOLS WHEN THE OUTBREAK HITS

“ We’re all sorry. We’re sorry that we don’t have a medicine proven safe and effective to kill the Ebola virus. We’re sorry that we don’t have a vaccine. We’re sorry that we’ve failed to stop the epidemic... We’re fighting a forest fire with spray bottles. ”

**ELLA WATSON-STRYKER,
MSF HEALTH WORKER,
SIERRA LEONE (2014).**



Jaraitu, an Ebola survivor and professional caregiver to children separated from their parents during treatment, holds a young child with Ebola at MSF's Ebola management centre in Freetown, Sierra Leone.

If contracted, Ebola is one of the world's most deadly diseases. It is a highly infectious viral haemorrhagic fever that can kill up to 90% of the people who catch it, causing terror among infected communities. The outbreak declared in West Africa in 2014 was the largest ever, claiming more than 11,300 lives in the six affected countries (Guinea, Liberia, Mali, Nigeria, Senegal and Sierra Leone).

From the very beginning of the 2014 epidemic in West Africa, MSF responded in the worst-affected countries, Guinea, Liberia and Sierra Leone, by setting up Ebola treatment centres and providing psychological support, health promotion activities, surveillance and contact tracing, as well as engaging the international community to respond. At its peak, MSF employed over 4,300 staff to combat the epidemic across Guinea, Liberia and Sierra Leone. MSF now continues to provide healthcare to Ebola survivors and to local populations in countries whose already weak health systems were damaged by the outbreak, through the development of new medical projects including paediatrics and maternal and child health.

During the outbreak, the ability of front-line doctors to respond was severely hampered by the lack of effective diagnostics, treatments and

vaccines. With Ebola perceived as a disease causing small-scale outbreaks in poor rural communities in Central Africa, discovery and research and development efforts had been extremely limited. In the mid-2000s, concerns around bioterrorism had motivated some security-focused investments into tools to combat haemorrhagic fevers. The VSV-EBOV vaccine candidate was one of the most promising projects to emerge, but the story of its development illustrates how little public health need is able to steer medical innovation.

Initial studies at a Canadian government laboratory confirmed its potential effectiveness as a vaccine to prevent contracting Ebola. In 2010, the Public Health Agency of Canada sought an industrial partner to pursue the development of the vaccine. The government decided to license out the vaccine to NewLink Genetics, a small US company, for approximately \$205,000. The project then stalled. The Canadian government retained rights over the vaccine candidate but chose not to exercise its right to license the development to another company when NewLink failed to complete even basic safety trials in humans.

When the West African Ebola outbreak hit in 2014, the safety profile of the

vaccine was therefore still unknown, and only a very limited supply had been manufactured. At last, the vaccine candidate was sub-licensed from NewLink to Merck and was finally made available in clinical trials to people at risk in Guinea in March 2015. Had NewLink (or others) conducted basic Phase I trials earlier, the vaccine could have been deployed in West Africa during the outbreak and saved lives. This wasted opportunity nevertheless netted NewLink a substantial profit, despite it not having advanced the development of the vaccine, when it sold the rights to Merck for \$50 million.

During the outbreak, MSF supported and launched clinical trials to test the efficacy of experimental drugs and vaccines, while also contributing to collaborative efforts to develop effective diagnostics. In the aftermath, MSF has established an Ebola Initiative that is advocating for improving processes and policies related to the sharing of scientific data generated in outbreaks, and improving the oversight, ownership and stewardship of biological samples from survivors. MSF is also considering working with others to establish incentives to develop a multiplex diagnostic platform to improve the differential diagnosis of fever in field settings.

❖ 1. Failing to deliver for diseases that aren't sufficiently lucrative continued

TB is the now the biggest infectious disease killer in the world, taking 1.5 million lives in 2014 alone.²³ Yet until the end of 2012, no new drug had come to market for tuberculosis for nearly 50 years.²⁴ Treatments routinely used for drug-resistant tuberculosis (DR-TB), which infects almost 500,000 people each year, are long, toxic and limited in effectiveness, curing only half the people who start treatment.²³ Yet there is little financial incentive to develop and test new treatment regimens, which must contain multiple drugs to be effective.

One of the challenges for diseases like Chagas disease, visceral leishmaniasis and drug-resistant tuberculosis is that the number of people affected is often relatively small. But many diseases that affect far more people also lack appropriate medical tools, particularly when they disproportionately affect developing countries or vulnerable groups of people.

This cold logic also applies to the medical needs of children living with HIV and TB. Paediatric HIV and TB infections have become rare in wealthy countries, and so, in the absence of a viable commercial market, the needs of the 2.6 million children living with HIV²⁵

and the one million children estimated to become ill with TB each year²³ have been consistently overlooked. The development of appropriate doses or formulations suitable for children of many existing antiretrovirals (ARVs) or anti-tuberculosis drugs has lagged far behind adult treatments.²⁶

With the biomedical innovation business model built around maximising product revenues, products are developed with wealthy markets in mind; if new drugs, diagnostics and vaccines can also address medical needs in developing countries, it is often only in a second stage that they are rolled out in these countries. This means there can be a lag of several years before people in a resource-limited country can use the product. All too often, companies do not even make the effort to register new, effective medical tools for use in low- and middle-income countries, even though registration is a critical step that enables routine use of new tools. As of April 2016, Japanese pharmaceutical company Otsuka, for example, had only obtained registration for its new tuberculosis drug delamanid in Europe, Japan and South Korea, but not in any of the 27 countries with the largest burdens of drug-resistant TB.²⁷

“**[My colleague] arrived just in time to find Maya standing under a beam with a chair placed under it. Cycloserine is a filthy, filthy drug with the potential for apocalyptic neurological and psychiatric toxicity. We have no choice at present but to prescribe regimens containing cycloserine, because we currently have no better drugs available. It is so distressing.**”

Dr. Emily Wise, MSF TB doctor in Uzbekistan, recalling a patient nearly driven to suicide by the side effects of her treatment for drug-resistant TB (2013).



Dr. Arusyak Melikyan (right) is an MSF consultant working in Vanadzor, Armenia. Together with Dr. Narine Kherimyan (left), a doctor from the Ministry of Health, she follows patients with drug-resistant tuberculosis.

Continued overleaf ❖

❖ 1. Failing to deliver for diseases that aren't sufficiently lucrative continued

“No one likes the treatment – painful intra-muscular injections into the buttocks. Not just once, but for 17 painful days. All day you can hear the children crying from the pain of the injection.”

Casey O'Connor, MSF visceral leishmaniasis project coordinator, Lakien, South Sudan (2015).

Many tools fail to take into account the resource conditions in developing countries, such as the availability of qualified health staff, the capacity of health systems, and the available laboratory infrastructure. Vaccines, for example, typically need to be maintained at between 2-8 degrees Celsius from the time they leave a factory to when they are administered to a child. Maintaining this cold chain is both a logistical and financial challenge for MSF, and most developing country governments do not have the means at their disposal to effectively implement a cold chain.²⁸ Less toxic treatments for visceral leishmaniasis are available in some countries, but they too rely on having a reliable cold chain in place.

Gaps in diagnostic technologies provide a similar illustration of the limitations of relying on post-market adaptation of existing products to meet developing country needs. Access to the gold standard for monitoring HIV treatment, viral load testing, is still limited today, partly as a result of the current tests' complexities, with most manufacturers offering only very large systems designed for central and reference laboratories. While this complexity isn't a challenge in wealthy countries, people living with HIV in remote settings do not have reliable access to a power supply or highly trained staff needed for laboratory set-up.²⁹

2. FAILING TO PRIORITISE HEALTH NEEDS

A second side effect of the system driving biomedical innovation today is that research efforts and resources are driven to areas of profitability, irrespective of therapeutic need. With current incentive mechanisms, the system concentrates energy and investment on products that will sell well, but may not be the top priorities for investment from a public health perspective, or indeed may not even provide any benefit over existing treatments.

MSF programmes have documented the urgent need for new antibiotics; for example, to counter resistant infections in its surgery programme

“With the rising level of antibiotic resistance, we are almost now running out of options in some of the places we are working.”

Dr Rasheed Fakhri, MSF orthopaedic surgeon, Jordan (2013).

in Jordan. Antibiotic resistance, responsible for an estimated 700,000 deaths globally every year,³⁰ threatens the phenomenal gains made in the 20th century in treating life-threatening bacterial infections, such as sepsis, pneumonia, dysentery and hospital-acquired infections. The Chairman of the UK Review on Antimicrobial Resistance warns that, if left unaddressed, drug-resistant infections could be responsible for the deaths of some ten million people a year by 2050, and \$100 trillion in economic damage.³¹ In the US alone, antimicrobial resistance (AMR) is estimated to cost the healthcare system an annual \$20-35 billion, with additional costs to society for lost productivity as high as \$35 billion per year.² Yet in spite of the urgent need for new antibiotics, fewer than five of the 50 largest pharmaceutical companies have active antibiotic development programmes² and the antibiotics pipeline is 'almost dry'.³²

However critically needed these drugs may be, pharmaceutical companies deem investment in antibiotics to be financially unattractive. To prevent

“The market for a new antibiotic is very small, the rewards are not there and so the capital is not flowing. In cancer, people pay \$30,000, \$50,000 or \$80,000 for a drug, but for an antibiotic it is likely to be only a few hundred dollars.”

Dr Paul Stoffels, Chief Scientific Officer, Johnson & Johnson (2013).³³

resistance from developing, strict conservation policies would need to be in place to reserve and restrict the use of a newly developed product, which would therefore keep sales low. Chronic diseases that require lengthy treatments over several years provide greater prospective rewards, and thus attract more investment than short treatment courses like antibiotics.

In the absence of appropriate incentive mechanisms that need to be put in place by governments, the

medical priority remains unanswered. Conversely, the failure of governments to put in place the necessary regulations and incentive mechanisms to ensure therapeutic importance (and not solely financial reward) is the main driver of innovation, has led to a multiplicity of products being developed for which clear markets and potential profit exist, but for which medical need is perhaps secondary.

A number of recent studies focusing on drug approvals in the US and Europe have shown the extent to which industry focuses on developing so-called 'me-too' drugs - medicines which have only small clinical advantages over existing drugs, but which can be patented and bring substantial profits. One analysis found of the 1,015 new drugs and indications approved in France between 2004 and 2013, only 6.3% offered a clear therapeutic advantage, almost none were considered breakthroughs, and the majority (69.3%) offered no clear therapeutic benefit or were prematurely approved even though their clinical evaluation showed them to be more harmful than beneficial.³⁵ A second analysis surveys numerous assessments, finding that 85 to 90% of new products approved over the last four decades have provided only limited benefits.³⁶ A third study that looked not just at registered products, but specifically at new chemical entities and new biologics, found that the majority of those launched in the UK between 2001 and 2012 were only "slightly innovative" and only a quarter (26%) were "highly innovative".³⁷

Critically, the fact that a 'new' drug has limited therapeutic benefits does not mean it will be a commercial failure. Its registration allows companies to claim some small advantage, and thus a price differential, over competitors. A market saturated with rival drugs treating the same condition does, however, mean colossal investments into sales and marketing, as companies seek an edge over their rivals.

“

The priorities for innovation are tilted by the market place imperatives. So for example, a malaria vaccine that you'd probably rank in humanistic terms as one of the great innovations that you'd like to see, literally was receiving almost no funding... Whereas working on male baldness or some other things that you would not think of as necessarily important, because of the voice in the marketplace, the people that have those interests, that was getting an order of magnitude more research than something like malaria.”

Bill Gates (2013).³⁴

In contrast, promising candidates which may bring considerable therapeutic advantages for patients in MSF field programmes and beyond, but which hold little financial interest under the current system, often languish in the development stages. Pfizer showed little interest in advancing at least one antibiotic, sutezolid, which was showing promise for TB, for over a decade, yet simultaneously proved unwilling to make the compound available to other clinical research consortia to advance its development and test its potential with other existing or experimental drugs.³⁸ The roll-out of clinical trials of VSV-EBOV, the vaccine shown to be potentially highly effective against Ebola, so soon after the start of the 2014 pandemic was described by WHO as “record-breaking work that marks a turning point in the history of health R&D”.³⁹ Yet in reality, the vaccine's development languished, and only moved forward once the outbreak represented a concrete threat to Western countries (see page 8, 'R&D in focus: Ebola').⁴⁰

As well as failing to engage with critical needs like antibiotic resistance, the largest pharmaceutical companies are also dropping out of entire key public health areas, leaving unaddressed critical areas of need for patients in MSF programmes. In 2012, Pfizer announced that it would completely close down its anti-infective R&D programme.³ In 2014, AstraZeneca closed its facility in Bangalore, ending all early-stage R&D for tuberculosis, malaria and neglected tropical diseases,⁴ before announcing a

further withdrawal from all early-stage R&D across the field of anti-infectives in 2015.⁵ Novartis also withdrew from TB R&D as part of a corporate restructuring in 2014, and in 2015, Bristol-Myers Squibb announced it would close its anti-viral discovery operations.⁴¹

In making these decisions, drug companies are responding to financial incentives enabled by the current innovation model, a system that is proving extremely beneficial to the pharmaceutical industry, which has the healthiest profit margin of any corporate sector, beating out even banks and oil companies.¹⁷⁴ Companies can divest from areas of critical social need simply to boost the share price and executive compensation, regardless of the public health consequences.

These different aspects are all testament to how the public sector's failure to take responsibility for priority setting leads to the system's failure to prioritise according to medical need.

“

With commercial drug development, it's a case of the intellectual property tail wagging the therapeutic dog.”

Dr Jack Scannell, Associate, InnoGen Institute (2015).¹⁷³

3. FAILING TO DELIVER AFFORDABLE DIAGNOSTICS, MEDICINES AND VACCINES

When medicines, diagnostics and vaccines remain prohibitively expensive, it leads to rationing of medical care, whereby only those who can afford to pay, are adequately insured, or are covered by comprehensive public health provision, can benefit. The problem is felt most acutely in developing countries, where people usually pay for medical care out-of-pocket and very seldom have health insurance, and where affordable pricing is thus vital to enabling access.

In such circumstances, the high price of medical tools can quickly become a question of life and death. In 1998, when the South African Pharmaceutical Manufacturers' Association and 39 pharmaceutical companies mounted a legal challenge to prevent Nelson

Mandela's South African government from importing more affordable versions of HIV medicines,⁴² the threat posed by the price of antiretroviral medicines (ARVs) to the very survival of people living with HIV became immediately apparent.

The price of ARVs declined by 99% in the years that followed, thanks to competition from multiple generic manufacturers in India – an illustration of how unhindered competition between multiple producers is the most sustainable way of achieving affordable medicines. India now produces 80 to 90% of the ARVs used in developing countries by treatment providers – for MSF, it's 97%. But close to 20 years later, affordability remains a problem for access to medicines in developing countries, particularly

now that India must grant patent protection for newer medicines.⁵³

Some newer HIV medicines used for salvage regimens, which are needed for people who have exhausted other treatment options, are patented in India, and remain unaffordable. A salvage regimen of raltegravir, etravirine, darunavir and ritonavir costs around \$1,800 at the lowest global price available – 18 times more expensive than first-line treatments.⁷ Developing countries and treatment providers like MSF are facing, in the words of a UK Parliamentary Committee, a "treatment time bomb"; as more patients develop resistance to first-line treatments, they will need to be switched to newer, more expensive regimens.⁵⁴

THE RATIONALE FOR HIGH MEDICINE PRICES: DEBUNKING THE MYTHS

How and why are medicines priced so high as to be out of reach of the people who need them?

High prices, whether in developed or developing countries, are inherently linked to the systemic reliance on patent monopolies as the way to finance biomedical R&D. Patents on medicines give patent-holders, usually pharmaceutical companies, exclusive rights to make and sell their product with no fear of competition until all patents that obstruct competition expire. Other forms of intellectual property rights also prevent competitors. In the absence of competition, producers are largely free to charge what they please.

The high-price, monopoly-based system is entrenched globally through international trade rules. The 1994 Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement sets minimum common standards of patent protection with which all World

Trade Organization members must comply.* Over the last two decades, this has led countries to introduce or substantially increase patent protection, a uniform trend in direct contrast to the diverse approaches taken before TRIPS was implemented, when countries could determine patent rules according to their social and economic needs and constraints. Further exclusivity rights such as data exclusivity or patent term extensions are conferred to companies through additional obligations (known as 'TRIPS-plus' rules), be they implemented unilaterally as domestic legislation by individual countries, or through multilateral or bilateral trade deals, such as the recently signed Trans-Pacific Partnership (TPP)⁹ agreement.

MSF has long sought to increase people's ability to access life-saving medicines, starting in 1999 with its decision to disregard patent barriers and introduce generic treatment

for HIV in South Africa. But the pharmaceutical industry claims that patent monopolies and high prices are necessary to recoup the investments that are made in R&D, and to finance future innovation. The patent system aims to ensure that an inventor can reap sufficient rewards in exchange for publicly disclosing their invention so that society can benefit from the information and follow-on innovation can take place. Pharmaceutical companies contend that with more patent protection comes more innovation,⁸ but this argumentation is flawed, for at least four reasons:

First, because the increase in patenting around the world has not been met with increased innovation for medical products, contrary to the promise of the TRIPS Agreement. Historically, evidence suggests that patents were not a necessary condition for innovation, that the large majority of innovations occurred outside of the patent system, and

* With the exception of least-developed countries, which have a 'waiver' to not grant patents on pharmaceuticals until 'at least 2033'.

policies that limit the scope of patents act to encourage innovation (see page 18, 'Does biomedical innovation occur due to the patent system, or in spite of it?').⁴³

Second, because it simply isn't true that the proceeds from sales are being ploughed back into R&D. Evidence suggests that in practice, drug prices are not reflective of R&D costs - whether claimed or estimated.⁴⁴ Reported figures consistently indicate that people pay for much more than just what is needed to recoup R&D costs. In 2010, the last year for which the industry lobby group Pharmaceutical Research Manufacturers of America (PhRMA) published figures on *global* estimated R&D (in addition to estimated R&D by PhRMA members), the total that pharmaceutical companies reported as spending on R&D came to less than 8% of the total of global sales reported by IMS Health⁴⁵ (see Figure 2). Using a different methodology, self-reported estimates by PhRMA members puts their total R&D spend as a percentage of sales at 17.9% for 2014.⁴⁶ The five largest pharmaceutical companies spend \$60 billion annually in marketing. Only one out of the world's ten largest drug companies spends more on research than on marketing (see Figure 3).⁶ Between 2005 and 2014, 19 of the largest pharmaceutical companies collectively spent \$226

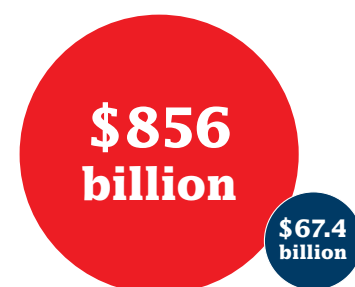
billion repurchasing their own shares, equivalent to 51% of their combined R&D expenditures over this period.⁴⁷

Third, because it ignores the simple fact that innovation without access is innovation that is useless to society. Affordability problems created by the reliance on patenting and market exclusivity are a hindrance to true innovation, which can only concretely address the problems that it seeks to address by being made widely accessible.

And fourth, the notion that price-setting for specific products bears any relation to actual R&D costs is not grounded in reality. There have been a series of dramatic price hikes in the US of off-patent drugs, as companies have exploited their monopolistic position as the sole US FDA-approved supplier of certain medicines. Martin Shkreli's overnight 5,500% price-hike for a 50-year old drug needed for HIV-related infections is one example that attracted global outrage.

The pharmaceutical industry has cast this practice as fringe behaviour, claiming that investors and venture capitalists were 'masquerading as pharmaceutical companies' but did not represent drug company practices.⁴⁸ Yet 'traditional' pharmaceutical players routinely follow the same strategies. The price of Novartis's Gleevec (imatinib) for leukaemia has risen three-fold in

**FIGURE 2:
GLOBAL SALES
VS. GLOBAL R&D
EXPENDITURES (2010)**



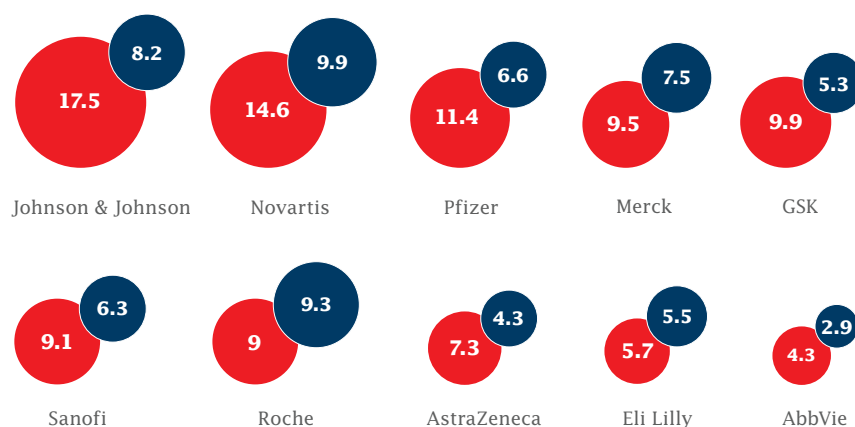
Global R&D spending (\$67.4 billion) by private pharmaceutical companies amounts to just 8% of global pharmaceutical sales (\$856 billion).

Source: KEI (see ref. 45).

the past decade;⁴⁹ Biogen raised the price of a treatment for multiple sclerosis an average of 16% a year in the ten years since 2005, with 21 separate price hikes.⁵⁰ On 1 January 2016, Pfizer arbitrarily raised the price on over 100 drugs in the US.⁵¹ Price hikes are a strategy that allows companies to maintain revenues even in the absence of successful innovative products.⁵²

Repeated high price scandals have exposed with great clarity how little pricing has to do with R&D costs, and is in fact primarily determined by what the market can bear.

**FIGURE 3:
PHARMACEUTICAL SPENDING ON SALES & MARKETING VS. R&D (2013)**



Source: GlobalData via Dadavix (see ref. 6).

● Sales & Marketing (US\$bn) ● R&D (US\$bn)



In July 2014, MSF held the first of three rounds of a mass vaccination campaign with the pneumococcal vaccine (PCV) in the Adjumani district of northern Uganda. The campaign was aimed at protecting refugee children from South Sudan from deadly respiratory infections, including pneumonia.

© Emily Gerardo

Vaccines offer a further illustration of the problem of affordability. In 2001, the world's poorest countries paid \$0.67 to buy the full WHO-recommended package of vaccines to protect a child's life. But today, with just three new vaccines added to the package – against rotavirus, pneumococcal disease and human papillomavirus – the price has risen 68-fold, to more than \$45 per child (see Figure 4). Together, these three new vaccines make up approximately 86% of the total price of vaccinating a child in the poorest countries.²⁸

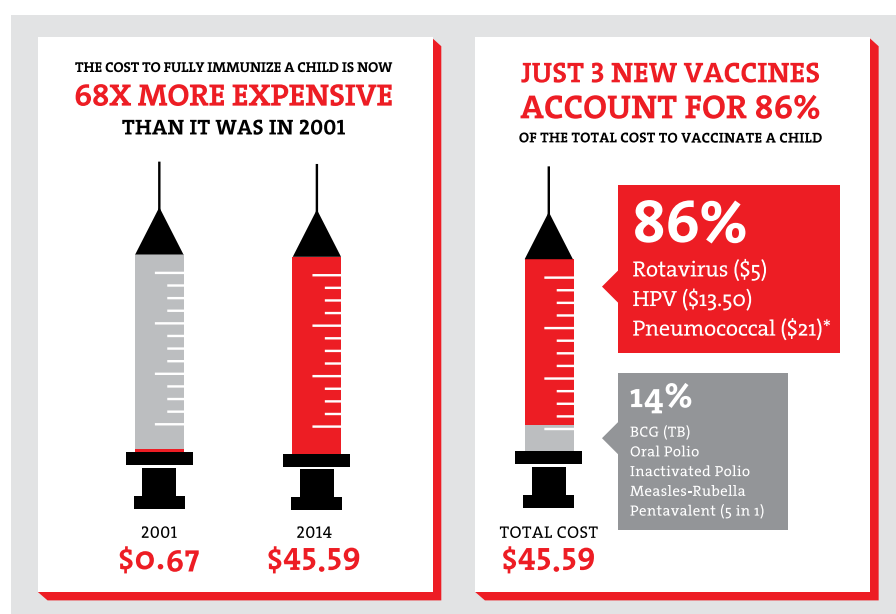
Each year, MSF vaccinates millions of people, for both outbreak response and routine immunisation activities; in 2014 alone, MSF delivered more than 3.9 million doses of vaccines and immunological products. But MSF has struggled to introduce new vaccines in part due to their high prices. MSF is working to scale up immunisation of children against pneumonia, the leading cause of death for children under five years of age worldwide, but has struggled to obtain long-term affordable access to the pneumonia vaccine.

“We celebrate whenever one of our patients is cured of drug-resistant TB thanks to treatment that includes linezolid. Unfortunately, across South Africa, many clinicians have been unable to give linezolid to everyone who needs it, because it's so expensive. Prices have recently started to drop slightly, but there's a long way to go before the drug is truly affordable. We want to offer this drug to all patients with multidrug-resistant and extensively drug-resistant TB so that they have a chance to be cured, a chance for life.”

Dr Jenny Hughes, TB doctor, MSF South Africa (2016).

Pharmaceutical companies employ various strategies to segment their markets and, or so they claim, to address the issue of affordability. One example is 'tiered pricing', the practice of charging lower prices for poorer countries. But tiered pricing doesn't necessarily result in affordable access. Although Gilead offers its new hepatitis C drug sofosbuvir (marketed as Sovaldi) to developing countries at a price that is lower than the US price of \$84,000 per treatment course, Brazil pays around \$7,500 per treatment course⁵⁵ – a price that is nonetheless unaffordable for Brazil. Companies can also license their intellectual property to generic manufacturers to allow for competition, using agreements known as voluntary licences (VLs), but these are often limited to a subset of countries. Even though licensing agreements negotiated by the Medicines Patent Pool, a UN-backed licensing facility, have improved the terms and conditions of such voluntary licences over time, many countries are still excluded from

FIGURE 4: HIGH VACCINE PRICES



© Melanie Doherty design. Source: MSF's *The Right Shot Report*, 2nd Edition (see ref. 28).

* Some pneumococcal (PCV) doses procured under the first contracts for the Gavi Advance Market Commitment are no longer receiving the AMC subsidy and are bought at \$3.30-\$3.50/dose. Based on awards made up through September 2015, 75% [1,095 million] of the AMC donor funds have been committed to GSK and Pfizer.

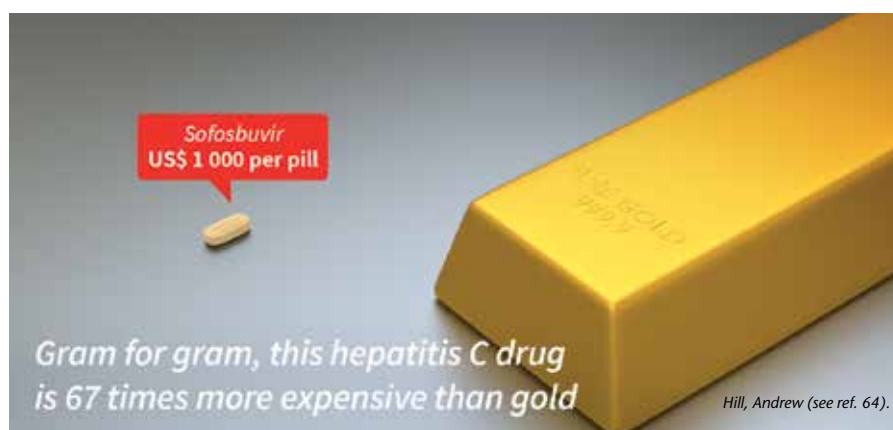
agreements due to the commercial priorities of drug companies.

Affordability is not just a concern for the poorest countries. Countries classified as middle-income countries (MICs) are caught in a particularly challenging situation regarding the affordability of health tools. Despite being home to 73% of the world's poor,⁵⁶ and expecting to account for 70% of people living with HIV and with hepatitis C by 2020,⁵⁷ for example, middle-income countries are all-too-often ineligible for price-reducing measures like pharmaceutical company discounts and generic medicines produced by way of a voluntary licence. They are thus left paying much higher prices than their capacity to pay and health needs would warrant.

For example, MICs often pay substantially more for HIV salvage regimens than the lowest global price available, which is \$1,800 per person per year (ppy): Myanmar pays \$2,929 ppy and Ukraine \$16,409 ppy.⁵⁸ The term 'middle-income' is in fact an artificial classification totally divorced from public health realities – more than half of the countries where MSF runs medical programmes are classified as MICs,⁵⁹ including India, Kenya, Lesotho, Myanmar and Swaziland.

As for vaccines, the countries that don't benefit from internationally-negotiated deals face significantly higher prices. The pneumococcal conjugate vaccine, for example, is priced between \$3.05 and \$3.50 per

**FIGURE 5:
DRUGS WORTH MORE THAN THEIR WEIGHT IN GOLD**



dose (approximately \$10 per child) for the poorest countries, but the Philippines pays around \$14 per dose (\$42 per child), and South Africa pays more than \$16 per dose (more than \$48 per child).²⁸

In addition, many MICs now face a double burden of non-communicable diseases such as diabetes, cardiovascular disease, and cancers, on top of infectious diseases, further challenging their ability to afford essential life-saving interventions.⁶⁰ Other countries where MSF works that are ranked as MICs face a total collapse of their public health system, like Syria, or severe refugee crises like in Jordan and Lebanon.

A more recent phenomenon is the fact that high drug prices are hitting the headlines in higher-income countries, as people balk at the exorbitant prices charged for treatments. In the US, prices

for branded prescription drugs doubled in five years, from 2011 to 2016.⁶¹

In 2012, a group of doctors from the Memorial Sloan-Kettering Cancer Center wrote in the *New York Times* of their decision not to give patients a “phenomenally expensive” new cancer drug produced by Sanofi; given its \$11,063 average monthly price, “ignoring the cost of care is no longer tenable”, they argued.⁶² In 2015, Bristol-Myers Squibb announced a new treatment for melanoma costing \$250,000 for the first year of treatment.⁶³ Gilead's \$84,000 price-tag for Sovaldi – or \$1,000 for every single pill – makes the drug almost 67 times more expensive than gold, gram for gram (see Figure 5).⁶⁴

“When drugs are developed with taxpayer funds, the government can and should act to bring relief from out-of-control drug pricing... There is a difference between earning a profit and profiteering. The Administration should use every tool it has to rein in the practice of pricing a drug at whatever the sick, suffering, or dying will pay.”

US Congressman Lloyd Doggett (2016).⁶⁵



MSF is one of the biggest providers of HIV care in Myanmar. Free distribution of antiretroviral therapy (ART) was started in 2003.

R&D IN FOCUS: HEPATITIS C WHEN PUBLIC HEALTH POTENTIAL LOSES OUT TO PROFITEERING

“ The price of this hepatitis C treatment is already forcing medical practitioners in France to choose between patients, as to who will get to receive it. This is rationing, and it recalls the rationing in the 1990s for HIV/AIDS. The situation is all the more unacceptable given that it is artificially created, as the price can’t be justified either by the cost of production, or by investment into research and development. ”

Dr. Mego Terzian, Médecins Sans Frontières France, President (2014).

MSF is currently rolling out screening, diagnosis and treatment programmes for hepatitis C in Cambodia, India, Kenya, Mozambique, Myanmar, Pakistan, Uganda and Uzbekistan, while speaking out for affordable prices for patients in MSF programmes and beyond. One of the objectives is to catalyse demand for newly-available direct-acting antiviral (DAA) medicines, which hold the promise of transforming hepatitis C treatment by shortening its length, eliminating heavy side effects and radically improving cure rates. But the story of the development and roll-out of sofosbuvir, one such DAA medicine, illustrates how the tremendous public health potential of this tool risks being lost.

Sofosbuvir was developed by a small biotech company, Pharmasset, with some support from the US government. As it advanced through the development pipeline, the drug emerged as a front-runner in a new class of treatments for hepatitis C, likely to reach the market first among competitor drug candidates. At this point, Gilead acquired the drug by buying the company for \$11.2 billion. With market projections for the new class of hepatitis C drugs hitting

\$20 billion a year by 2020, Gilead was willing to pay a hefty price in anticipation of capturing the lion’s share of the early sales, before other drugs entered the market.⁶⁶

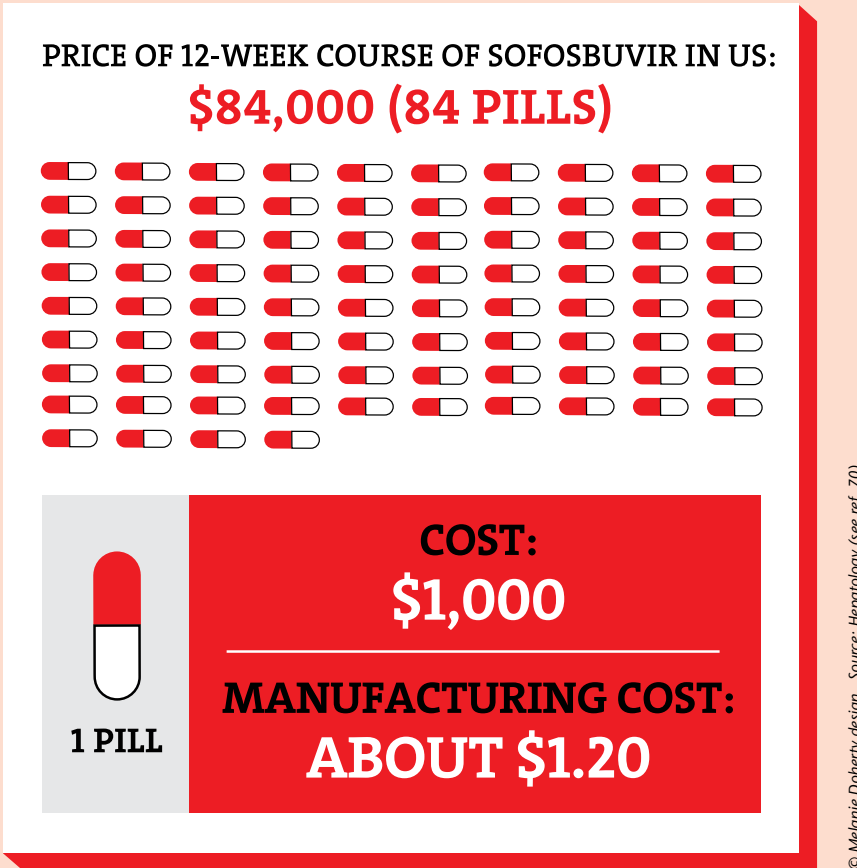
Pharmasset had planned to sell the drug ‘profitably’ for \$36,000 per treatment.⁶⁷ Although Gilead played little role in the drug’s development, the company decided to double the price that Pharmasset had planned to sell the drug for, prompting healthcare spending projections to skyrocket. Economist Jeffrey Sachs has described the acquisition as “the deal that is bankrupting America”.⁶⁸

The US Senate Committee on Finance recently published an investigational report on the price of this drug and its impact on the US health system; in the report, they note that despite repeated requests, Gilead has failed to provide them with costs solely attributable to the drug’s development.⁶⁹

More fundamentally, the story of sofosbuvir illustrates how relying on patent monopolies and market exclusivity also means accepting that the benefits of medical research may not be made broadly accessible. A drug like sofosbuvir, for example, has the potential to revolutionise hepatitis C treatment because of its ease-of-use and high cure rates; if it were made affordable and available to everyone who needs it, hepatitis C could potentially cease to be a public health problem.

Researchers have documented that the cost of producing sofosbuvir is estimated to be \$101 per treatment course,⁷⁰ a fraction of the \$84,000 price being charged by Gilead (see Figure 6) and the cost of production is expected to fall further.⁷¹ A high-volume, low-price strategy would ensure widest possible access and saving millions of lives worldwide, while also curbing the virus’s spread.

**FIGURE 6:
HOW MUCH DOES IT COST TO PRODUCE SOFOSBUVIR?**



© Melanie Doherty design. Source: Hepatology (see ref. 70)

INDUSTRY'S NEW NARRATIVE: VALUE-BASED PRICING

As the argument that high prices are needed to justify R&D gradually becomes more untenable, the industry is switching to a different and highly contestable narrative: instead of being needed to recoup the cost of research and development, industry now justifies high prices based on the purported value of the innovation for the patient and health system writ-large.

In the face of outrage over the excessive prices of its new hepatitis C medicines, Gilead has justified its pricing on the basis of downstream savings to the health system, arguing it should be rewarded for costs averted because patients would otherwise require costly liver transplants.⁷⁷ "Following that logic," critics point

out, "all antibiotics have been vastly under-priced since the introduction of penicillin some 60 years ago".⁷⁸ Pierre Chirac, president of French medical journal *Prescrire*, asks why the cynicism of this pricing strategy shouldn't be replicated across the healthcare system to other products and services – in complex deliveries, shouldn't midwives demand remuneration on a par with the monetised value of the additional years the newborn can expect to live, thanks to their intervention?⁷⁹

This is the wrong model for drug companies or governments to employ to determine pricing policies. Should the pricing of life-saving medicines follow the same rationale as consumer goods like airline tickets or luxury goods that are priced according to

their perceived value, rather than costs of production, plus a reasonable profit? In the situation where a patient's health or even life depends on accessing a certain medicine, their willingness to pay for the medical product is largely independent of the medicine price. This means pharmaceutical companies, backed by unchecked monopoly power, can raise prices far beyond the cost of production, and the demand will remain high, regardless of the price charged. In today's scenario, the price charged for a medicine is fully divorced from any relation to production costs or the cost of R&D – and when generic competition is not able to correct for the possibility of monopoly abuse, its upward trajectory may know no limit.

The issue has become equally contentious in countries which, unlike the US, actively regulate the amount spent on patent-protected pharmaceuticals. In England, the soaring price of new cancer drugs has meant that the National Institute for Health and Care Excellence (NICE), which acts as a gatekeeper for the budget of the National Health Service, has not been able to approve many new therapies for routine use. In 2010, in response to growing public disquiet at what was perceived as a form of rationing, the government set up the Cancer Drugs Fund (CDF).⁷² This has not solved the problem, which resurfaces on a regular basis: within four years, the Fund was severely overspent; since 2014 its budget has been increased twice.⁷³

By 2016, the fund will have spent more than £1 billion (\$1.4 billion),⁷⁴ and has been forced to review and cut the least cost-effective drugs from its list, ceasing to offer patients a dozen drugs treating breast cancer, multiple myeloma, bowel cancer, pancreatic cancer, cervical cancer and leukaemia.⁷² With price tags in the region of £90,000 (\$129,500) ppy for Roche's Kadcyla (trastuzumab emtansine),⁷⁵ for example, even the CDF's more generous allowances stop short of being enough to ensure the medicines are affordable – so much so that the immediate future of the CDF is uncertain.⁷⁶

In France, in December 2015, the Ligue contre le cancer – which spends around €38 million (\$43 million) a year on cancer research, making it the largest French non-governmental funder of cancer R&D – condemned cancer drug prices as 'exorbitant, unfair and unbearable' and warned that if unabated, price inflation for new drugs posed a direct threat to the French medical system.⁸⁰ Studies have also shown how in the elaboration of the 2013 treatment guidelines for HIV in France, "economic considerations significantly influence and, in some instances, take precedence over the scientific evidence".⁸¹ Concerns around affordability, in other words, are competing with evidence-based medicine to determine how Western countries make therapeutic choices for their people.

Some examples that have captured the media's and policymakers' attention recently have concerned price hikes for older medicines. Even when research costs have long been recouped, and medicines are no longer protected by patents, some countries can still face a monopoly situation that perpetuates high prices.

In the latest iteration of a revenue-maximising strategy that the company has become infamous for, Valeant Pharmaceuticals bought the rights to two heart disease medicines in February 2015, and as the sole supplier, promptly hiked the price up by 525% and 212%.⁸³ In September 2015, Rodelis Therapeutic

bumped up the price of cycloserine, a drug developed in the 1950s used to treat multidrug-resistant tuberculosis, from \$15 per pill to \$360 – a 2,000% increase. The same month, Martin Shkreli's Turing Pharmaceuticals acquired the rights to Daraprim (pyrimethamine), a life-saving treatment also developed in the 1950s and used to treat various parasitic infections, including for people living with HIV, and then raised its price from \$13.50 per pill to \$750 – a 5,500% increase.⁸⁴

These examples illustrate the problems that are associated with allowing monopolies on health care products, and the failure of governments to protect people from profiteers and price-gouging.

“

I probably would have raised the price higher... Health care prices are inelastic and I could have made more profits for my shareholders, which is my primary duty. My investors expect me to maximise profits, not to minimise them, or go half or go 70%, but to go 100% of the profit curve.”

Martin Shkreli, then-CEO of Turing Pharmaceuticals (2015).⁸²

4. FAILING TO USE SCIENTIFIC AND FINANCIAL RESOURCES EFFICIENTLY AND EFFECTIVELY

The predominant system for incentivising drug development today – the granting by governments of exclusivity and monopoly rights to industry – is thus a system which neglects diseases of the poor, diverts investment away from priority medical need towards financial gain, and entrenches high prices. The system is also inefficient, for two reasons.

Firstly, because existing incentive mechanisms actually hamper the ability of researchers to deliver. While it is hailed as a driver of innovation, intellectual property actually acts as a hindrance.

During the research and development stages, reliance on market exclusivity pushes scientists and companies to work in isolation from, and in competition with, one another. Secrecy and lack of transparency is encouraged in order to gain first-

to-market advantage. Information around R&D costs and methods are kept hidden, discouraging follow-on innovation that can drive prices down or improve health outcomes; instead of learning from others' mistakes, poor investment decisions are made simultaneously by multiple companies.

Researchers speak of the 'multi-billion dollar mistake' being repeated again and again by separate research teams working in isolation, and unable to gain from each other's learning. This also has an impact on the speed at which breakthroughs are made.⁸⁵ For example, in TB, where a combination of novel drugs will be needed to deliver a game-changing treatment regimen, many organisations working in the area of regimen development have encountered obstacles in accessing new drug compounds for testing as part of improved treatment regimens.

These include TB Alliance, the UK's Medical Research Council (MRC), the Open Source Drug Discovery project (OSDD) and RESIST TB. The delays slow scientific progress, which means patients have to wait longer for new treatments to become available.

Aggressive patenting strategies can also block follow-on innovation, by actively preventing competitors from pursuing promising avenues. An analysis by the Massachusetts Institute of Technology and the National Bureau of Economic Research found that gene-level intellectual property barriers, to take one example, had "persistent negative effects on subsequent innovation", and that one company's intellectual property policies were found to have "led to reductions in scientific research and product development on the order of 20 to 30 percent."¹⁴²

DOES BIOMEDICAL R&D OCCUR DUE TO THE PATENT SYSTEM, OR IN SPITE OF IT?

There is mixed evidence on whether or not medical innovation is delivering more or fewer approved drugs over time. A systematic review that evaluated 21 articles assessing innovation rates found 9 studies that reported positive results and 11 negative results, with 1 study not reaching a result.⁸⁶ In terms of improved therapeutic value, though, the picture is clearer. Of 42 studies assessing innovation in drug development, "assessments using therapeutic value generally agree that transformative pharmaceutical innovation is rare across the multiple settings studied".⁸⁶

The overall poor performance of the pharmaceutical industry over the last two decades to deliver improved therapeutic options for society has coincided with a historically unprecedented and dramatic expansion of intellectual property protections – starting with the establishment of the World Trade

Organization and continuing with ever-increasing levels of protection in rich and poor countries. Historical evidence from the US National Bureau of Economic Research "suggests that patents were not a necessary condition for innovation, and the large majority of innovations occurred outside of the patent system". The research goes further to note that in fact policies which limit the scope of patents, such as compulsory licensing, have encouraged innovation, while policies that strengthen monopoly power have unambiguously discouraged innovation.⁴³

Other recent economic research goes even further – noting that while the patent system may improve incentives to invent and to obtain patents (which is not a measure of R&D productivity), the overall effect on innovation is negative. More broadly, the research notes that "while weak patent systems may mildly increase innovation with mild

side effects, strong patent systems retard innovation with many negative side effects".⁸⁷

Finally, the researchers note that "the political demand for stronger patent protection comes from old and stagnant industries and firms, not from new and innovative ones". The Economist, in a widely cited article from 2015, noted that the patent system, in lieu of spreading knowledge has instead "created a parasitic ecology of trolls and defensive patent-holders, who aim to block innovation, or at least stand in its way unless they can grab a share of the spoils".⁸⁸

While the pharmaceutical industry continues to argue that patents are the critical ingredient to encourage medical innovation, the use and abuse of the patent system also points to a widespread practice of filing trivial patents to extend the exclusivity periods under which companies can seek monopoly rents.

Conversely, some essential public health tools were able to be developed precisely because companies were free to undertake follow-on innovation, without being constrained by patent barriers. The development of fixed-dose combinations (FDCs - where different drugs are put into a single pill) of antiretrovirals for HIV, for example, was only possible because Indian generic manufacturers were not hampered by exclusivity rights. MSF and other treatment providers bear witness to how FDCs have proved decisive in massively simplifying HIV and malaria treatment in developing countries.

Exclusivity rights prevent this kind of innovation by blocking out or slowing down research and development on combinations of multiple compounds, when the patents on the different medicines are owned by competing pharmaceutical companies.

MSF has long advocated for a new, shorter, better combination regimen for the treatment of drug-resistant

TB. The first new TB drugs to emerge after nearly 50 years urgently need to be tested in combination to see if this can radically shorten and improve the current regimen, as hoped. To date, no studies looking at combining the two new drugs – Johnson & Johnson's bedaquiline and Otsuka's delamanid – have started. To help fill this gap, MSF will soon initiate two clinical trials, in partnership with leading medical organisations, to test new and shorter TB regimens using the new TB drugs and other promising compounds.

For hepatitis C, exclusivity rights have prevented the development of some promising new drug combinations. Despite initial outstanding results and high efficacy across all genotypes of hepatitis C, exclusivity rights put an end to Bristol-Myers Squibb's collaboration on a combined hepatitis C therapy associating its own compounds with those held by competitors, after these had been bought up by Gilead.⁸⁹

Because secrecy extends to clinical trials and safety data, this system also leads to adverse patient outcomes with tremendous financial, social and health consequences.¹¹ The World Medical Association lays down the ethical principles for medical research involving human subjects in the Helsinki Declaration, which states that all clinical trials should be registered and all results - whether positive or negative - should be fully reported.⁹⁰

Yet it is estimated that around half of all the clinical trials that have ever been carried out have never reported results.⁹¹ Doctors rely on making informed choices about the safety and efficacy of drugs in order to choose the most beneficial treatment for the people they treat. When clinical trial data are kept secret and the reporting of results are biased, informed decisions about providing the best possible treatment are impossible to make.

The ethical imperative for making data from clinical trials available is strong.



A patient from Abidabad in Pakistan during his first week of hepatitis C treatment with MSF, using the new direct-acting antiviral medicines.

Continued overleaf ❖

❖ 4. *Failing to use scientific and financial resources efficiently and effectively continued*

Patients enrol in clinical trials, and subject themselves and their health to the risk of serious adverse effects of new medicines, because they wish to advance scientific knowledge in a certain medical field for a greater common good. The data that is created through clinical trials belong to the patients that volunteer and it should subsequently be possible for them to see how such data are being used. Full disclosure is particularly important.

One particular recent example concerns a study looking at a novel treatment for Ebola, brincidofovir, which was unexpectedly stopped early.⁹² The abbreviated study results for this trial were published, but the reasons why the trial was stopped, after the enrolment of only four patients, are still unknown. The drug's developer, Chimerix, claimed that the incidence in Monrovia had declined so sharply that it would preclude any statistically significant results. However, many Ebola scientists considered this claim as an excuse, since the company did not seek to continue the trial in any of the many other sites which were still experiencing high numbers of cases.^{93,94}

In April 2015, WHO re-affirmed the ethical imperative of clinical trial results reporting, defining reporting

timeframes and also calling for older but still unpublished trials to be reported.⁹⁵ In its statement, WHO asserted that the common practice of non-disclosure negatively affects understanding of the scientific state-of-the-art; leads to inefficiencies in resource allocation for both R&D and financing of health interventions; creates indirect costs for public and private entities, including patients themselves, who pay for suboptimal or harmful treatments; and potentially distorts regulatory and public health decision making.¹¹

Secondly, the system for incentivising drug development is inefficient because governments are failing to insist on a fair return in exchange for the exclusivity and monopoly rights granted to industry. Left unchecked, the pharmaceutical industry that people rely on to make medicines are spending their money for purposes other than researching and developing new treatments. Economists describe this as the excessive 'financialisation' of the industry—a broad trend afflicting medical research and development today—whereby maximising shareholder value becomes the primary objective of pharmaceutical companies, rather than delivering innovation that answers to a public health need.

One illustration of this phenomenon is the trend for major pharmaceutical companies – rather than take risks themselves – to buy up smaller, more productive companies⁹⁶ once the riskier preclinical and early clinical research has proven successful,⁹⁷ and thereafter selling new medicines at excessively high prices to recuperate acquisition costs and earn substantial profit margins.

Gilead's approach to sofosbuvir is perhaps the clearest example. The promise of potential new hepatitis C treatments also spurred Merck to acquire Idenix pharmaceuticals for \$3.8 billion in 2014, more than three times the company's value, despite it having no products on the market and posting less than \$1 million in revenue for the previous year.⁹⁸

Similarly, Pfizer's business model is based on acquiring proven blockbusters such as Lipitor (anti-cholesterol), Prevnar (pneumococcal vaccine) and Botox (known most widely for its cosmetic anti-wrinkle applications) by merging with smaller competitors, and is relatively unsuccessful in generating revenue from drugs it develops itself.⁴⁷ One consulting firm study found that drug companies that consistently

“

Up until the 80s and early 90s, the whole approach in pharmaceutical companies was ‘we need to be doing good research, we need good products, good people, and good projects and that takes time’. But then companies started saying ‘we’re not getting enough return on investment here’; people at the top were keen on making money, and the science and the patients somehow got lost.

The mass merger and acquisition phase began, when companies felt that it was easier to swallow up another company that had products rather than trying to change the way they did things themselves. A huge amount of expertise and promising projects were simply ditched because they didn’t fit in with this ‘let’s make money quick’ approach. For me, the biggest swear word in my vocabulary is ‘shareholder value’.”

Prof. Michael J. Parnham, Fraunhofer Institute for Molecular Biology and Applied Ecology IME (September 2015).

did well in certain therapeutic areas were earning more than 70% of their sales from products developed by other companies.⁹⁹

Another notable trend is the decision by industry to allocate surplus funds for schemes that inflate share prices, instead of spending on biomedical R&D.⁹⁶ Share buybacks, for example, are when a company buys back its own shares from the marketplace, which reduces the number of outstanding shares and simultaneously boosts their market value.

In December 2014, Merck spent \$8.4 billion to acquire Cubist Pharmaceuticals, a drug developer that specialises in combating hospital 'superbug' methicillin-resistant staphylococcus aureus (MRSA). Less than three months later, Merck announced the closure of Cubist's early-stage research unit, laying off 120 staff. Three weeks later, Merck announced that it would spend an additional \$10 billion buying back some of its own shares.¹⁰⁰

In the first three quarters of 2015, Pfizer, which previously shuttered its anti-infective research unit in 2013, paid out \$11.4 billion in share buybacks and dividends, more money than it earned in profits in the same period. The company spent \$139 billion on buybacks and dividends in the past decade, compared to \$82 billion on R&D¹⁰¹ (see Figure 7).

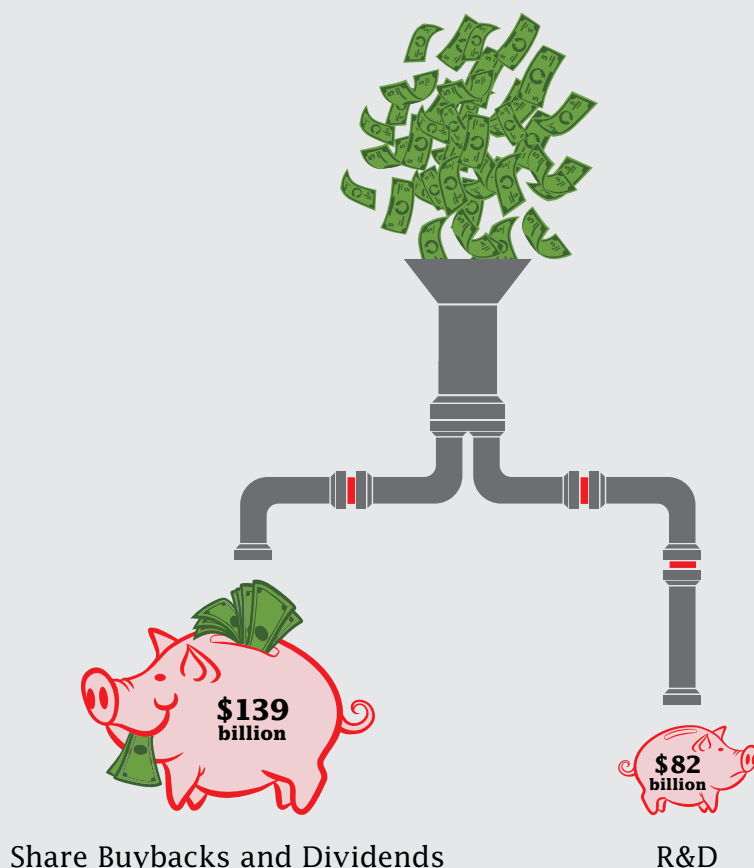
Such activities 'cannibalise' innovation.¹⁰¹ A company's earnings are the financial foundation for innovation; yet instead of investing in innovation, industry has favoured a strategy of investing to keep share prices high.⁴⁷

A recent UK report on antibiotic resistance explained that the lagging innovation in antibiotic development could be countered if the world's two largest pharmaceutical companies invested the same amount in antibiotic R&D as they plan to spend on share buybacks.¹⁰⁰ Some economists attribute this to insider corporate interests, given how executive pay is closely linked with share price.¹⁰²

But these practices come at the expense of public health and people's needs.

Overall, the picture is thus one of a confiscation of innovation. The public sector makes substantial contributions to research and development upfront, through grants, subsidies and tax credits. At the same time, governments grant exclusivity rights to industry, which skews the R&D away from areas of need, entrenches high prices and leaves the public paying twice for the results of innovation. The substantial rewards earned by industry, rather than being ploughed back into research and innovation, are used first and foremost to boost shareholder and executive rewards. Part 2 will detail what policy makers should do in order to put an end to this abdication of public responsibility and address this combined market and policy failure.

FIGURE 7: PFIZER'S INVESTMENTS IN SHARE BUYBACKS AND DIVIDENDS, COMPARED TO R&D (2004-2014)



From 2004-2014, Pfizer reported spending \$139 billion on buybacks and dividends, compared to \$82 billion on R&D.

Source: Reuters (see ref. 101).

TREATMENT: **POLICY OPTIONS TO ALIGN MEDICAL R&D WITH PEOPLE'S HEALTH NEEDS**

The failings of biomedical R&D outlined earlier are largely known to policy makers. Yet to date, despite MSF and other actors calling for change for more than a decade, insufficient political attention or focus has been paid to reforming the system. It is possible to steer, finance and coordinate biomedical innovation differently – but this would require the political will and leadership to challenge the status quo and cease delegating to market forces the overwhelming responsibility for developing new tools to answer global public health needs.

Part of the resistance to reform stems from a resigned acceptance of the shortcomings of biomedical innovation, as if these failures, however regrettable, are inevitable. Many important policy discussions today, for example, take as a given the idea that patents and other

forms of exclusivity rights are the solution to incentivise and finance pharmaceutical R&D, regardless of the growing evidence of the problems brought about by a biomedical innovation system financed through high medicine prices and unconditional public funding.

But these failures are not inevitable. This report argues that four main strategies should be employed to begin addressing the shortcomings of biomedical innovation so that it can better deliver affordable products that answer to the priority health needs seen in MSF treatment programmes and beyond.

1. DEMAND TRANSPARENCY ON R&D COSTS

As a medical humanitarian organisation, MSF needs and welcomes innovation that equips us with more and better medical tools to improve treatment options and outcomes for the people with whom we work. Undoubtedly, R&D has a cost, and someone does need to pay, and appropriate incentives and mechanisms need to be in place to support these efforts.

But how much does it actually cost to develop a medical product? And how much could it cost, were it to be financed and incentivised differently?

Answering these questions is difficult. Fundamentally, the raw data is rarely available as companies aren't transparent with their R&D costs. We are thus forced to rely on estimates based on confidential data. A 2011 systematic review of studies of the average or median cost of drug development found, for example, that out of 13 identified studies, 10

lacked transparent data. The review concluded that "no published estimate of the cost of developing a drug can be considered a gold standard".¹⁰³

Annex 1 compiles all identified cost estimates or reported figures for drug development. They range widely with regard to methods and data, making direct comparisons difficult. The studies' estimates of costs range from \$30.3 million to \$2.6 billion, in 2013 dollars.

Despite this opacity and the considerable variety in estimates, industry, media and policymakers often state as fact that it costs \$1 billion or, more recently, \$2.6 billion to develop a drug. The \$1 billion figure stems from a 2003 industry-supported study using confidential data that reported a cost estimate of \$802 million (in the years that followed, this was adjusted for inflation up to \$1 billion+).¹² The methods and results of this single source have been widely challenged, including by industry itself.

“
[The \$1 billion figure is] one of the great myths of the industry... It's entirely achievable that we can improve the efficiency of the industry and pass that forward in terms of reduced prices... It's not unrealistic to expect that new innovations ought to be priced at or below, in some cases, the prices that have pre-existed them... We haven't seen that in recent eras of the [pharmaceutical] industry but it is completely normal in other industries.”

Andrew Witty, CEO of GlaxoSmithKline (2013).¹⁰⁴

In 2014, the estimate was updated to a dramatically higher new price of \$2.558 billion.¹⁰⁵ This new number was unveiled at a press conference, with scant details of the analysis. Sixteen months and many media headlines later, the study was finally published in full in March 2016.¹³ Yet, controversy around the figure continues. Describing it as “questionable”, *The Economist* commented that it “says more about the failures and inefficiencies of the drug giants’ in-house laboratories [between 1995 and 2007] than it does about how much it should cost to bring a new treatment to market now”.¹⁴

One major point of contention is around the costs that can be included in an estimate of R&D costs. The \$2.6 billion, like the \$1 billion estimate before it, is not a reflection of only the costs related to the development of a given drug; it includes other elements, over and above these costs.

First, it includes the cost of failures: essentially the money a company spent on other drug candidates that they cannot recoup through sales, as no product will be brought to market. Determining with exactitude how to quantify failure is challenging: how much failure should we reasonably expect? How much failure should we reasonably reward? Existing estimates on the overall likelihood of success range from 7% to 70%, from various sources and samples.

Second, and even more controversial, it includes the cost of lost investment opportunities: the money a company could have made if it had, instead of spending on R&D, invested it elsewhere. The \$2.6 billion figure awards companies a generous return of more than 10% on such investments. This money that theoretically could have been earned if the pharmaceutical company had decided to do something other than pharmaceutical research and development is then added on to the headline estimate of how much it costs to develop a drug.

All told, the \$2.6 billion estimate effectively takes every \$1 invested in clinical trials costs and inflates that dollar to more than \$9 through various ‘adjustments’ of this sort.¹⁰⁶ Annex 1 describes in more detail other questions that make it difficult to point to any one reliable ‘average cost’ of R&D estimate.

It’s not always clear what is going in to these figures, but it is clear what is not. Public funding for R&D is significant, even more so for riskier early research. At later stages of the innovation cycle, public funding continues to play a role, for example, through R&D tax breaks and other incentives. Yet an accounting of this public sector share of the risk-taking and the burden of expenses is absent from the \$2.6 billion, obscuring the fact that whatever the true costs of developing a new drug, the public contributes significantly to the process and pays in full again to access the resulting products.

It’s also clear that a better way is possible. In 2014, DNDi published a study outlining the key lessons they have learnt in their ten years of operation. The study included a breakdown of their spending on product development, showing that within ten years and with a budget of approximately €182.5 million (\$205 million), they have been able to deliver six new treatments for neglected diseases, as well as establishing a strong drug development pipeline with 12 new chemical entities (NCEs) in pre-clinical and clinical development.¹⁵ The study goes on to estimate, based on this experience that it will cost between €100-150 million (\$113-169 million) to develop an NCE in the field of neglected diseases, including accounting for ‘failures’ – essentially the money spent on other drug candidates that aren’t ultimately approved for market.¹⁵ The figure does not include in-kind contributions of molecules, expertise, and other non-monetary contributions from partners,

which DNDi suggests average 20% of their total budget per year. As such, this does not represent an immediately comparable figure to industry estimates given the entirely different methodologies used.

Nevertheless, it does indicate that innovative R&D approaches can potentially be more efficient than traditional pharmaceutical business models. It also illustrates an order of magnitude of what is possible using an alternative not-for-profit model that promotes open collaboration, leverages expertise from a wide range of partners in a non-competitive way, and focuses on affordability and access from the outset.

Other non-profit drug development partnerships have also estimated costs or are realising success at a fraction of the purported costs of industry. In 2001, the TB Alliance estimated that to discover and develop a novel tuberculosis treatment costs between \$115 and \$240 million, including adjustments for failures and capital. The MenAfriVac project – detailed on page 28 – showed us that an adapted vaccine could be developed for just \$50 million, without adding in additional costs for failures or capital.

It is imperative that governments, universities, civil society and other actors push for transparency on costs of R&D. Without being able to adequately assess R&D costs it is all the more difficult to improve upon them, or to devise the most effective incentive mechanisms that can estimate financial needs for innovations of public health importance. Lifting the veil on real R&D costs would also significantly improve the debate around medical product pricing strategies, as the lack of transparency around costs hinders our ability to engage in informed debate on the relationship between the two, and to hold the pharmaceutical industry to account.

Continued overleaf ❖

ALSO NEEDED: TRANSPARENCY ON CLINICAL TRIALS

While this report focuses on R&D costs, transparency is also needed for clinical trial data. In recent years, some progress has been made. New laws have been adopted in the EU requiring public disclosure of clinical study reports for all new (but crucially not old) clinical trials, for example. Medical journals have proposed conditions for publication of articles that aim to further incentivise clinical trial data reporting and disclosure. And a collaboration between the Wellcome Trust and some pharmaceutical companies has led to the creation of a voluntary database, to which access is given only upon review of a duly motivated request.¹⁰⁷

Yet transparency on clinical trials is still patchy and incomplete. Considerable resistance from industry continues to hamper its realisation. The pharmaceutical industry recently sought to have clinical trial data included in the definition of trade secrets in new EU legislation, for example.¹⁰⁸ The company at the heart of the January 2016 clinical trial scandal in France, which left one person dead and five people hospitalised, also refused to release crucial documents about the trial, claiming that the commercial confidentiality of the trade secrets they contained overrode the public interest in knowing the content of the documents.¹⁰⁹

There is an urgent need to provide public access to registers of clinical trials and introduce global retroactive requirements to disclose clinical trial data and results. Such data would contain both positive and negative data sets and should be specified down to independent (anonymised) patient level for all clinical trials (failed trials, withdrawn trials, successful trials and trial data for medicines already on the market).

Such a measure would fully respect the rights of the patients involved and meet the requirements of the Helsinki Declaration. It would prevent the widespread practice of selective reporting of results. Data sharing in the scientific community of both positive and negative data sets would avoid wasteful duplication of trials and be a boost to pharmaceutical innovation.

These efforts should be applied system-wide. Such efforts could be voluntary: organisations, governments and companies could form a pharmaceutical industry transparency initiative to encourage voluntary sharing of data from the pharmaceutical sector, including costs of research and development and manufacturing, clinical trial data, and patent, registration and price information. The United Nations, and UN-backed organisations including the Medicines Patent Pool and the Global Fund to Fight AIDS, TB and Malaria, already collect some information, though it is far from being systematic and sufficient.

“

If a prescription drug demands an outrageous price tag, the public, insurers and federal, state and local governments should have access to the information that supposedly justifies its cost. ”

Preamble to New York State Senate Bill S5338 (2015).¹¹⁰

Or governments could implement mandatory measures. Certainly governments already have significant leverage to make such demands. They could, for example, require transparency in exchange for the grant funding they provide to develop specific compounds. In the case of a compound whose early development was led by the public sector, transparency on the costs of its further development could form the part of any licensing agreement with industry. Or transparency could form a condition for pharmaceutical companies to receive rewards, be they priority regulatory review vouchers, tax credits or prizes.

In the last 18 months, more than a dozen US stakeholder groups have introduced pharmaceutical cost transparency proposals that would require pharmaceutical companies to disclose R&D costs among other data to justify US drug prices. Legislation has been introduced in various US states to mandate transparency of R&D costs, and at the federal level, President Obama's Fiscal Year 2017

Budget request, in response to the Administration's "deep concerns" about "rapidly growing prescription drug prices," proposes to provide the US Department of Health and Human Services with the "authority to require drug manufacturers to publicly disclose certain information, including research and development costs".¹¹¹

Although none of these initiatives have yet been enacted into law, they provide evidence of the growing appetite to lift the cover on the black box of R&D costs. Precedents exist; in the United States and elsewhere, industry has already been forced to disclose various practices, including reporting payments, meals and entertainment provided to doctors for research, consulting and speeches.¹¹² Clinical trial transparency, though incomplete, has been expanded.¹¹ In order to design more effective innovation policies and suitable incentive mechanisms to develop the products that treatment providers like MSF need, the cost of R&D and pricing of medicines should become the next focus of policy makers' attention.

2. CHANGE THE INCENTIVES

Changing the incentive mechanisms that drive and finance R&D, whoever is paying, will be critical to improving the outcomes of biomedical innovation and addressing the failures of the system. Policy makers should consider three overarching approaches:

i) STOP PURSUING DAMAGING POLICIES

The introduction of the TRIPS Agreement over two decades ago was the single largest expansion of intellectual property rules worldwide. Since then, the US, the European Union (EU), and other leading developed countries, pushed by the pharmaceutical industry, have tirelessly pursued stricter 'TRIPS-plus' rules that seek to lengthen, deepen and expand intellectual property protection for medicines far beyond the already extensive protections included in the TRIPS Agreement. Some of the

main mechanisms that have been employed to expand intellectual property protections include bilateral and regional free trade agreements, including the Trans-Pacific Partnership (TPP) Agreement.

The pharmaceutical industry expends enormous effort advocating for these new 'TRIPS-plus' rules. It also discourages governments, even those facing enormous health and humanitarian challenges, from using the legal tools at their disposal – known as 'TRIPS flexibilities' – that could encourage follow-on innovation to existing medical tools, or could overcome affordability barriers by allowing more affordable generics to reach the market faster.

In 2014, for example, the pharmaceutical industry was exposed for having paid for a secretive campaign to derail efforts by South Africa - which has some of the highest

rates of HIV/AIDS and drug-resistant TB in the world - to introduce common-sense, pro-public health reforms to the country's intellectual property laws and policies, and basic safeguards to ensure affordable medicine prices.¹¹³

Governments should resist demands for additional exclusivity rights, which only deepen the extent to which the current system is broken by entrenching unaffordability and rationing while failing to stimulate innovation that answers to priority health needs.

ii) DEMAND MORE IN EXCHANGE FOR PUBLIC SECTOR INVESTMENT

Governments prop up the pharmaceutical industry through multiple avenues: through the high prices induced by the patent system, and through considerable direct public funding of R&D.

PAYING TWICE FOR INNOVATION

“The price at which imatinib has been offered for sale by Novartis around the world has caused me considerable discomfort... This goes against the spirit of the patent system and is not justified given the vital investments made by the public sector over decades that make the discovery of these medicines possible.”

DR. BRIAN DRUKER, ONE OF THE SCIENTISTS BEHIND THE DEVELOPMENT OF CANCER DRUG IMATINIB (2007).¹¹⁴

The levels of governmental support for biomedical innovation are far from negligible. The public sector makes substantial contributions to research and development upfront, through grants, subsidies and tax credits. In fact, 30% of the estimated \$240 billion yearly total global investment across all health R&D comes from the public sector (see Figure 8).¹⁶

The US National Institutes of Health (NIH), for example, provides over \$30 billion annually in government funding for medicine research.¹¹⁵ Public contributions are even greater for riskier basic, early-stage research, which carries a lower likelihood of success: by some accounts more than four-fifths of all funds for basic research to discover new drugs and vaccines come from public sources.¹¹⁶

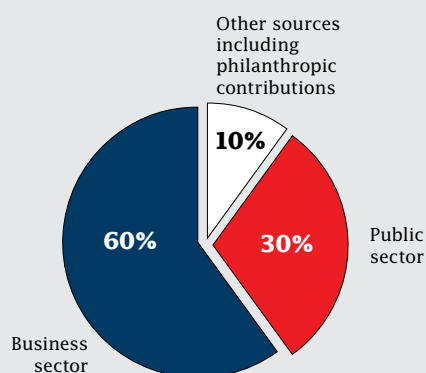
Public sector funding also contributes a disproportionately high share of R&D funding for most important drugs. The NIH funded 75% of the new molecular entities granted priority review by the US Food and Drug Administration (FDA) between 1993 and 2004¹¹⁷ - drugs that represent “significant improvements in the safety or effectiveness of treatment, diagnosis, or prevention of serious conditions when compared to standard applications”.

One example is the new TB drug bedaquiline: public sector investment in the clinical trials for the drug's development even outweighs the investment by Johnson & Johnson, the patent holder. Adjusted for risk, the NIH, TB Alliance and partners spent \$42.7 million; adjusted for risk

and the tax credit it received, Johnson & Johnson spent \$23.4 million.¹¹⁸

At the same time, more than \$1 trillion is spent every year on purchasing medicines, a figure projected to reach \$1.4 trillion by 2020.¹¹⁹ The tax-paying public are thus paying twice for medicines: once through taxes, which are then redistributed as support to R&D through government-backed incentives and direct payments, and a second time through high prices.

FIGURE 8: PUBLIC-SECTOR FUNDING OF R&D



Source: The Lancet (see ref. 16).

Continued overleaf



MSF has worked with the local health authorities in Oaxaca State, Mexico, to initiate Chagas diagnosis and treatment in Santa María Tonameca Municipality. The inhabitants in San Pedro Pochutla and Mazunte towns now have access to medical care for Chagas in primary healthcare facilities.

© Consuelo Pagaza/MSF

Governments also implement or finance a number of additional mechanisms to encourage R&D. Considering the failings of biomedical innovation, these additional incentive mechanisms should be conditioned to ensure that they contribute to a fairer, more effective and more efficient biomedical innovation system better able to answer to public health needs. But however laudable their intentions, many publicly-funded incentive mechanisms do not achieve this goal, and may thus need revising to ensure they can best contribute to promoting valuable biomedical innovation.

MSF has repeatedly called for the reform of the US Priority Review Voucher programme, for example, which was laudably intended to stimulate research into neglected diseases, yet in its current form has become a poorly designed give-away that companies can exploit without actually furthering neglected disease research (see page 27, 'Existing incentive mechanisms in need of improvement').

Conversely, potentially effective policies that do allow governments to leverage their investments and demand something in return, are left unused. The US Government has, for example, so-called 'march-in' rights, which allows it to license relevant

intellectual property to third parties, if the patent was obtained thanks to publicly-funded research. Yet the rule has never been used for public health purposes, in spite of at least five requests,¹²⁰ most recently in January 2016 when 51 members of Congress asked the US NIH to intervene in order to put an end to price-gouging by pharmaceutical companies.⁶⁵

At least 17 countries provide for publicly-funded researchers to retain intellectual property rights of publicly-funded inventions, yet few of these retain government rights to address abuses.¹⁷ Considerable efforts are also underway to introduce similar mechanisms in other countries, where the public sector and universities generate considerable scientific research that could be transformed into effective medical tools.

In general, governments must start to recognise that their investments and subsidies in research and development merit something more in return than just the product itself. Governments should actively redress a situation where public funding of R&D, patent-based monopolies and subsidies or mechanisms that boost rewards or lower the risk of R&D are granted without any public benefit being demanded in return.

Incentives should thus be designed by policy makers with a view to ensuring access and affordability, including any licensing of intellectual property, of any final product that is developed thanks to substantial public support. This can be achieved by setting terms and conditions when a company is licensed a publicly-funded invention, for example by limiting intellectual property rights, by setting a price ceiling, or by granting public entities the power to enforce affordable prices or generic competition to bring down prices. Savings on medicine prices could free up resources that could be devoted to significantly expanding government investment in medical research, in a way that is steered towards areas of critical need.

Governments must continue their vital role in investing in basic and translational medical research that is steered towards critical health needs. With suitably tailored incentive mechanisms, governments could do much to address the failures of biomedical innovation, and encourage companies to do more to deliver appropriate and affordable technologies to patients, instead of accepting high prices as inevitable and allowing R&D investments to be skewed predominantly towards the financial priorities induced by the patent system.

EXISTING INCENTIVE MECHANISMS IN NEED OF IMPROVEMENT

Recent years have seen a flurry of public attempts to address the shortcomings of the biomedical innovation system and boost R&D that is neglected by financial imperatives. This includes push funding to pay for clinical trials; tax incentives to eventually defray and reduce R&D costs to companies, increasing the public share of those costs; and even prizes that provide companies with regulatory rewards valued at several hundred million dollars. These vary considerably in their approach – some are pull incentives, others are push incentives. Many initiatives, however, need reforming, either to prevent their abuse, or to ensure that they actually meet their stated intentions. Examples include:

❖ **The US FDA's Priority Review Voucher (PRV)** programme, launched in 2007, aims to stimulate research into neglected diseases by rewarding a company that successfully registers a product for eligible neglected diseases with a voucher, which essentially fast-tracks the review process for a subsequent drug candidate seeking FDA approval. The programme was extended to rare paediatric diseases in 2012, and a total of nine PRVs have been issued.¹²¹ Vouchers can be used or sold by the company they are awarded to, with the most recent of four known sale prices reaching as high as \$350 million in 2015,¹²² demonstrating the significant financial value of a PRV. In its current form, however, the PRV programme for neglected diseases is poorly designed. Vouchers have been awarded to products that have

not been made sufficiently accessible: Knight Therapeutics, for example, was awarded a PRV for registering the leishmaniasis drug miltefosine, but its supply has been erratic, as the company requires that its customers – including MSF – order the product in quantities larger than what is actually needed in field programmes.¹²³ Vouchers have also been awarded for treatments that have long been in use in other countries, thus rewarding companies for existing products rather than encouraging new research to benefit people affected by neglected diseases. In addition to miltefosine, which MSF had been using for eight years before a PRV was awarded, Novartis received a PRV for a pre-existing anti-malarial drug.¹²⁴ MSF has repeatedly called for the reform of the PRV so that it can better meet its stated objectives.

❖ **The US Orphan Drug Designation** programme awards a tax credit of 50% on qualifying clinical R&D expenditure on drugs for diseases that the US FDA qualifies as 'orphan'. The objective is to boost research for diseases which hold little financial interest for pharmaceutical companies. But companies receiving the tax subsidy have no obligation to ensure that the product is accessible or affordable; the average cost per patient per year for an orphan drug is now estimated at \$137,000.¹²⁵ The Orphan Drug Act (which established the Orphan Drug Designation programme) also provides companies with a seven year

period of market exclusivity upon the market approval (by the US FDA) of the relevant product.¹²⁶ Companies can also obtain orphan drug status for multiple uses of the same drug, by slicing up the overall market of a drug into smaller components, each targeting a particular subset of patients for what overall is a relatively common disease. The legislation, which generated tax credits of over \$2.3 billion between 2006 and 2010,¹⁷ is thus used to finance drugs which end up being extremely expensive.¹²⁷ More than 30 countries offered tax breaks for R&D in 2014¹²⁸ that reimburse companies for up to half of their out-of-pocket research costs. The US Orphan Drug Tax Credit illustrates the need to design incentives in a way that ensures they actually contribute to a fairer, more efficient innovation system.

❖ **The European and Developing Country Clinical Trials Partnership (EDCTP)**¹²⁹ is a €2 billion (\$2.18 billion) public research programme that funds all stages of clinical trials, with a disease-specific scope covering HIV/AIDS, malaria and tuberculosis, but also emerging epidemics of particular relevance to Africa, such as Ebola, as well as some neglected infectious and parasitic diseases. Yet the EDCTP retains no ownership or say over the intellectual property generated in its programmes, and does not do enough to ensure that end products that have benefitted from this public funding during crucial stages of the development process are either accessible or affordable.

iii) EMBRACE NEW APPROACHES

But policymakers should go further than ensuring that existing incentive mechanisms meet their stated objectives, and in exercising valuable but underused rights to improve access in return for their investments. In order to overcome the systemic shortcomings in pharmaceutical R&D described in this report, policymakers should actively seek to break the link that today binds biomedical innovation to drug sales and high prices backed by exclusivity rights. Public policies that drive industry to embrace new approaches to R&D, and that do not rely on exclusivity as the method to incentivise innovation, are urgently needed.

A number of initiatives have clearly shown the value and potential of innovation that 'de-links', or separates, the cost of R&D from the price of the resulting product.

The Meningitis Vaccine Project (MVP), a partnership between PATH, the Serum Institute of India and WHO which

resulted in the development of a vaccine against Meningitis A, is one example of what can be achieved when de-linkage is used to ensure that medical needs and affordability concerns are built into the product development process from the outset. The product was designed to meet the specific needs of the Meningitis Belt in sub-Saharan Africa, and included a technology transfer agreement with the Serum Institute that committed the company to a minimum supply and an affordable price. The new MenAfriVac vaccine was WHO-prequalified in June 2010 and rolled out, including by MSF, in countries across the Meningitis Belt, and at an affordable price of \$0.40 to \$0.50 per dose. As such, it was a low-cost effort to adapt an urgently-needed vaccine designed for use in countries with low capacity to pay. With this vaccine, MSF and others have achieved dramatic results in reducing mortality and morbidity from meningitis A in the region.¹³⁰ Subsequently, MenAfriVac was also the first vaccine to be licensed for use outside of the cold chain, illustrating

the success of the project in developing a product particularly tailored to real-life conditions in low-resource contexts.¹³¹

MSF itself has taken an active role in pursuing de-linkage principles. In 2003, MSF co-founded the Drugs for Neglected Diseases *initiative*, together with five public health research institutes (including four from endemic countries) and the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. The not-for-profit initiative was established to develop treatments for neglected populations, and its innovative business model is successfully carrying out R&D using a de-linked approach. Public and private contributions pay for the cost of R&D upfront, rather than through sales of the resulting products. This allows DNDi to identify priorities based on public health needs; to promote the broadest possible sharing of research knowledge and data; and to offer products at sustainably low prices.

Continued page 31 ❖

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The Meningitis A conjugate vaccine has led to a revolution in the way medical providers manage outbreaks of meningitis in the so-called Meningitis belt. Through the extended protection offered by this vaccine, thousands of lives have been saved since MSF first participated in its rollout in 2010, along with national health authorities in the region.

Key to its success in our view has been the way the vaccine was designed and developed. From the outset the product was designed specifically for use in the Meningitis belt. This meant much more than simply targeting the most prevalent strain of the disease; affordability and access through adequate supply was built in to the product profile from the outset.

Every single step of the development process ensured that these criteria were being met. Opportunities for technology transfer were identified from the start and a commercial partner brought in who was able to commit to the access and affordability conditions. Early on too, countries where the vaccine was to be rolled out were consulted in order to ensure buy-in to the project.

It's been an astonishing success. The take away message from this project is that innovation is a whole process and you can't just look at one part of the process if you want a project to succeed. It also shows what can be achieved if medical need is the top priority and affordability is thought about from the very start. ”

Dr. Myriam Henkens, MSF International Medical Coordinator (2016).

R&D IN FOCUS: SLEEPING SICKNESS DELIVERING FOR PATIENTS

“ I was a lab researcher studying the parasites that cause sleeping sickness when I read about MSF bemoaning the desperate need for a new treatment for the disease in its projects. It was clear that there was no good system in place to bring together existing research knowledge in order to develop it into better treatments for patients. This was the key observation that led to the creation of DNDi as a way of bridging this gap and the journey to develop a new treatment for sleeping sickness provides a good illustration of how DNDi works.

The DNDi team developed the ideal product profile for the new treatment after discussions with clinicians working in the places where people are affected by sleeping sickness. Our priorities were therefore to develop a safe and effective treatment that was oral – in place of the existing old, toxic and injectable drugs – easy to use, thermostable, cheap to produce and affordable as an end product.

Armed with this profile, the team identified a family of existing compounds that were active against the parasite and with further mining of compound libraries, narrowed the search down to one particular compound, fexinidazole, that had a promising profile.

Where we departed from industry practices at this point is that the drug candidate we uncovered was not patentable. It had been partially developed by a company but was then shelved and the patent had expired. Most market-driven companies would have backed off at this point, given the lack of commercial incentive to make money on the drug, but this was not



Blood is collected from a newborn baby for a sleeping sickness test in Yambio Hospital, South Sudan.

a barrier for DNDi. We don't need to make money back out of the drugs we produce, and this gives us many more possibilities when scoping for new compounds.

Based on promising but incomplete pre-clinical data the company shared with us, we embarked on a full preclinical development in line with current scientific and technical standards, and subsequent clinical testing. It's really a vast project management endeavour and we needed to collaborate with many different partners who could bring the different skills and experience required. Against all expectations, given what people say about the chances of failure in drug development, fexinidazole passed successfully through phase one and two trials and DNDi are currently expecting the result of phase three trials later in 2016.

What is absolutely key both to the development of fexinidazole and our other projects is that we are able to build upon ALL the existing knowledge and compounds; we are not restricted by whether the drug is patented or not. A pharmaceutical company driven

by commercial imperatives would never have advanced a new compound not protected by patents. But since DNDi is not dependent on sales to invest in research, it is able to pursue the best science.

DNDi estimates that it will cost around €25 million* (\$28.2 million) to develop fexinidazole from the pre-clinical stage right up to access of the treatment to the patient. This shows that it is possible to develop drugs on a much leaner budget than is often assumed.

Our approach has worked very well thus far in getting drugs developed for diseases as complicated as sleeping sickness that would otherwise be neglected by the market. But there's no reason why it couldn't be applied to the development of other more 'mainstream' pharmaceutical products such as cancer drugs or medicines for hepatitis C. Watch this space! ”

-- DR. ELS TORREELE, FOUNDING MEMBER OF DNDi AND R&D PROJECT MANAGER, CURRENT DNDi BOARD MEMBER AND DIRECTOR OF ACCESS TO MEDICINES & INNOVATION AT THE OPEN SOCIETY FOUNDATIONS (2016).

* This cost includes 'in kind' contributions but not capital costs, nor opportunity costs or attrition rates.

R&D IN FOCUS: ANTIBIOTIC RESISTANCE A TEST CASE FOR DE-LINKAGE PRINCIPLES?

Through our recent humanitarian work in Jordan, Iraq, Syria, Afghanistan, Pakistan and Palestine with war-wounded people and refugees, MSF has documented high levels of multidrug-resistant pathogens. In our surgical programmes in Jordan, for example, over half of orthopaedic and maxillofacial surgery patients admitted arrive with a multidrug-resistant infection. These antibiotic-resistant infections threaten people's lives and greatly increase costs of care.

Unlike many other public health priorities, antimicrobial resistance is attracting political attention at the highest level. Conservation and rational use of antibiotics, along with stimulating research and development of new treatments to address antimicrobial resistance (AMR), are now recognised as critical imperatives.

Research and development (including both for new drugs and new diagnostics to guide their appropriate use) forms an essential part of the WHO's Global Plan of Action on AMR.¹³² The 2015 G7 Leaders' Declaration¹³³ acknowledged the need for the development of new antibiotics, therapies, vaccines and diagnostics, with a subsequent Health Ministers' Declaration¹³⁴ both calling for a UN High Level Meeting in 2016 on AMR that may include R&D, and making note of specific R&D incentives to develop new antibiotics, including a WHO-supported R&D facility that has since been established.¹³⁵ It is expected that the 2016 G7 will continue to look in greater depth at incentive models for the development of new drugs and diagnostics.

Yet the current biomedical innovation system is ill-equipped to address the challenge of R&D for antimicrobial resistance. While it is largely uncontroversial to say that the current patent-based model of



A patient at MSF's reconstructive surgery project in Amman, Jordan, awaits his second surgery on his jaw.

medical innovation is at odds with the need for strict conservation of new antibiotics,¹³⁶ progress to develop new incentive models has so far been slow. European efforts to explore and test new, commercially-viable R&D models through the Innovative Medicines Initiative* have so far shown little progress, and US initiatives such as the funding of research projects through BARDA** or the GAIN Act,^{***} for example, have either focused on providing R&D subsidies to industry or further extending product monopolies, without consideration of how this will be at odds with the necessary subsequent stewardship, access and conservation strategies.

At the World Economic Forum in 2016, a 'Declaration by the Pharmaceutical, Biotechnology and Diagnostic Industries on Combating Antimicrobial Resistance' recognised that antibiotics need to be developed using new incentive mechanisms, but did not fully commit to a 'de-linked' model of R&D, and instead focused upon other funding measures and market incentives that could also feature some elements of a de-linked R&D model.

The Drugs for Neglected Diseases *initiative*, with the support of WHO, is establishing a global antibiotic research and development facility, (GARD)¹³⁷ which will focus on global health needs and ensure that any new products are also suitable for resource-limited settings. This facility will be based on the principles of de-linkage, in that the costs of R&D will be financed through other means than high prices and sales volumes. Such a model looks particularly promising in addressing the incentive challenge of 'creation-conservation' that antibiotic R&D entails, and addresses the access and suitability challenges for developing countries.

Despite such promising measures, governments still need to work together to establish a systematic approach to incentivise the development of appropriate drugs and diagnostics to address antibiotic resistance. Collective action, whether via WHO, the UN or even the G20, is urgently needed to ensure appropriate incentives are able to respond to this medical need.

* The public private partnership between the European Commission and EFPIA, 'The Innovative Medicines Initiative', launched the AMR programme 'New drugs for bad bugs' (ND4BB) which issued its first call for proposals in this area in May 2012. Drive AB is a €10 million (\$11.4 million) project under ND4BB which focuses on developing a new economic model for development of new antibiotics. Read more here: <http://drive-ab.eu>

** In 2010, the Biomedical Advanced Research and Development Authority (BARDA) established a programme to focus on developing novel antibiotics to address biological threats and antibiotic resistance through establishing public-private partnerships with industry. Participating companies receive reimbursement for drug development activities in real time.

*** The Generating Antibiotic Incentives Now (GAIN) Act, part of the FDA Safety and Innovation Act (FDASIA), was signed into law in 2012 and provides five years of extra exclusivity, Priority Review and fast-track designation for companies that develop certain antibacterial and antifungal drug products intended to treat serious or life-threatening infections.

❖ 2. *Change the incentives* continued

To date, DNDi has delivered six new treatments that are all affordable, adapted, and non-patented. The anti-malarial artesunate-amodiaquine (ASAQ), for example, was developed in partnership with Sanofi and others in 2007, and is available for less than \$1 per treatment course for adults, and less than \$0.50 for children. ASAQ was prequalified by WHO in 2008, and is registered in close to 40 countries. To date, 400 million treatments have been distributed. In addition, DNDi has created the most robust pipeline ever for some of the world's most neglected diseases: there are currently 30 R&D projects covering six disease areas, including 15 potential NCEs.

DNDi's experience shows the value of open models of innovation and open access initiatives in speeding up scientific research and reducing overall R&D costs, as well as the value of collaboration. While DNDi is relatively small-scale, it demonstrates the potential of using other approaches to the patent system to foster medical innovation that answers priority public health needs and delivers affordable products to neglected patients.

These lessons now need to be applied beyond the relatively narrow domain of neglected tropical diseases and malaria, or beyond the mere

adaptation of existing products. Policymakers can now build on them in a bid to move toward a more systemic approach that does not need to rely on ad hoc philanthropic funding. This will require a more ambitious approach, and the introduction of incentive mechanisms that must be scalable, replicable, and broadly applicable.

Prize funds are one incentive mechanism worth exploring. With a history that predates the patent system, prizes involve giving out payments on the achievement of pre-determined results, either at regular milestones or at the end of a project. Architectural design prizes were used in the 15th century,¹⁷ and prizes are what spurred the development of a simple method for the precise determination of a ship's longitude at sea in the 18th century, Lindbergh's transatlantic flight in 1927, and advances in spaceflight, for example.¹⁸ Unlike grant funding, which is only able to target one potential research group at a time, prizes allow several promising research proposals to be taken forward; multiple different approaches can thus be tried out simultaneously.

Prizes are particularly interesting as they offer an incentive that could progressively replace the granting of exclusive monopoly rights. If

medical need is pre-determined and well-framed, it could steer R&D towards need, unlike patents awarded regardless of the social value of the product. They can include contractual conditions which guarantee affordability of end products: as a condition for receiving publicly-funded prize money, the innovator surrenders exclusivity rights, so prices can be a lot closer to the cost of production.

Prizes have in recent years gained attention again,¹⁷ and a few recent examples demonstrate their viability as a mechanism for stimulating biomedical innovation. The US Department of Health and Human Services launched a diagnostic prize of \$20 million for the development of rapid point-of-care diagnostic test to identify highly-resistant bacterial infections. The European Commission (EC) awarded a €1 million (\$1.13 million) prize to a German company for developing a point-of-care rapid test that can identify patients with upper respiratory tract infections that can be managed safely without antibiotics. The EC also awarded a €2 million (\$2.26 million) prize to a German company in 2014 for stabilising technology to protect vaccines against elevated temperatures or accidental freezing. A further £10 million (\$14.4 million) prize, the Longitude Prize, concerns the development of an affordable, accurate, rapid and easy-to-use point-of-care test kit for bacterial infections.

These examples demonstrate the potential broad scope and replicability of incentive mechanisms that follow de-linkage norms. Initiatives of this type should be coordinated with similar incentives from other governments and philanthropic funders of biomedical innovation, in order to coordinate and align priorities, and ensure the development of new tools to meet essential health needs.



A nurse organizes samples at the Tengani health centre in the Nsanje district of Southern Malawi. The samples will be delivered over a hundred kilometres away in Thyolo, where they will be tested in a viral load laboratory.

WHAT ROLE FOR PRODUCT DEVELOPMENT PARTNERSHIPS?

Over the past decade, the emergence of non-profit product development partnerships (PDPs) has been a significant development in neglected disease R&D.

PDPs have been defined as organisations that raise funds from a wide range of public and philanthropic sources, select the projects that offer the probable highest health return for investment, and closely monitor and manage the progress of the portfolio they have invested in, on a not-for-profit basis.¹³⁸ They now manage a large proportion of products in the pipeline for global health, and with a total of \$3.4 billion invested in 2014,¹³⁹ accounting for 38% of R&D funding (outside of NIH funding) in 35 neglected diseases.¹³⁹

This represents significant progress from the state of affairs in 2001, when government and not-for-profit or philanthropic funding for neglected disease R&D totalled only about \$100 million per year for

TB, malaria, sleeping sickness, and leishmaniasis combined.¹⁴⁰ Estimates from the current pipeline show that an average of 4.7 new drugs* each year could be delivered for neglected diseases through 2018 – a significant improvement, if it is realised, compared with the 2.4 new drugs averaged each year for the period 2000-2011.²¹

But it is far from enough. The overall proportion of NCE approvals for neglected diseases is still insufficient and highlights the persistence of the 'fatal imbalance' between global disease burden and therapeutic product development for neglected diseases.¹⁴¹ These advances do not yet represent the kind of 'game-changing' scientific breakthroughs that are needed.

While they are without doubt valuable additions to the R&D ecosystem, PDPs and other ad hoc R&D initiatives cannot be considered to be the whole solution to the systemic lack of innovation or the sole way to address the needs of neglected people.

Concerns exist around the sustainability of PDPs' revenue streams.¹³⁸ Just three funders – the Gates Foundation (\$294 million, 56%), UK DFID (\$79 million, 15%) and USAID (\$57 million, 11%) – collectively provided 82% of all PDP funding in 2014,¹³⁹ raising questions as to what would happen if one of these funders were to withdraw or considerably reduce investment. There is also a need for coordination to set priorities and avoid both duplication and gaps.

And critically, PDPs have taken an inconsistent approach to ensuring access and putting de-linkage into practice. In lieu of developing and marketing global public goods, some PDPs aim, like their industry partners, to segment markets and seek higher returns in wealthy markets. Governments that fund PDPs should encourage them to set priorities effectively, coordinate with other entities, and ensure products are affordable, available and suitable for the countries where they are intended for use.

* This definition includes new chemical entities; new formulations; fixed-dose combinations; and new indications.

“The challenge for the prize system is that for it to work, you have to have really big prizes, with robust funding. This is feasible. The US spent an estimated \$413 billion for drugs last year under the monopoly system, an increase of \$85 billion in two years. If the drugs could be priced as generics, cutting out all the inflated costs of the current monopoly system, we could imagine US spending on drugs coming down to around \$50 billion or less a year. That would mean a savings of more than \$360 billion a year by getting rid of the temporary monopoly. Some of the savings could be made available for funding prizes. So it's not about getting new money, but re-allocating the money that's already being spent to generate innovation.

Once you de-link the rewards to the innovator from the price of the product, you can design much more intelligent and targeted reward systems. You can, for example, give more prize money to a product which improves outcomes over other existing drugs, and less money to a product which simply matches those outcomes. You can solve a lot of the inefficiencies in the current system which you can't really do using the existing system that is based on prices.

Drug development requires a combination of instruments. You want combinations of grants, subsidies and incentives. Grants are particularly important when you are not sure if there's a commercial application, or if you are focused on advancing the science. Grants are useful for all stages of research, including all stages of clinical trials, and they are necessary to sustain the activity of academic researchers.

But the monopoly on products has to go. It will be important to have people embrace the long-term goal of de-linkage. There is really no way to address the flaws of the R&D system, including both the poor design of the existing incentives and the massive and unfair restrictions on access, without abandoning high prices as the primary mechanism to fund R&D.

With the de-linkage principle in the driving seat, governments and other people who pay for health care can work with predictable budget constraints, and they have the practical ways to eliminate rationing of treatment based on price, and so you can vastly reduce the unfairness in the current system. I am convinced financing of drug development will see big transformative reforms, and that the delays in implementing those reforms will be extremely costly and harmful to patients, everywhere, but of course, most dramatically people living in developing countries.”

JAMES LOVE, DIRECTOR OF KNOWLEDGE ECOLOGY INTERNATIONAL (APRIL 2016).

R&D IN FOCUS: TUBERCULOSIS

THE '3P' PROJECT—DELIVERING BETTER TB TREATMENT, FASTER

In 2014, MSF treated 23,300 patients on first- or second-line TB treatment, in contexts that range from chronic conflict situations, such as Sudan, to programmes that focus on providing care to vulnerable patients in stable settings such as Uzbekistan. Multidrug-resistant TB is not impossible to treat, but the drug regimen is arduous, taking up to two years and causing many side effects. MSF field programmes bear witness to the urgent imperative to improve the treatment for MDR-TB, as well as an ultimate need to develop new treatment combinations to treat all forms of TB effectively, safely, quickly, affordably and simply.

Reaching this goal means transforming the current status quo, as just eight new chemical entities are currently in the development pipeline, and the annual funding gap for TB R&D is estimated at around \$1.3 billion.¹⁴⁴ The need for entirely new combinations of drugs multiplies the scale of the challenge. Today's biomedical innovation environment is one based on secrecy, rivalry between scientists, and exclusivity rights around developed products. However, medically-appropriate research on combinations of compounds and the development of entire drug regimens necessitates an open collaborative approach that

allows multiple drug combinations to be tested in parallel - fostering sharing between different entities of scientific data, clinical trial results, and flexible licensing of end products.

The '3P Project' proposes to use three novel mechanisms to financing and coordinating R&D in a bid to deliver affordable, effective new regimens for TB, through an open collaborative approach to conducting drug development:

- **Push funding** would finance R&D activities upfront, through grants;

- **Pull funding** would incentivise R&D activities, through the promise of financial rewards such as milestone prizes, to be delivered once certain R&D objectives are achieved; and

- **Pooling of intellectual property and data** would ensure open collaborative research and fair licensing of the final products, to enable competition and lower prices.

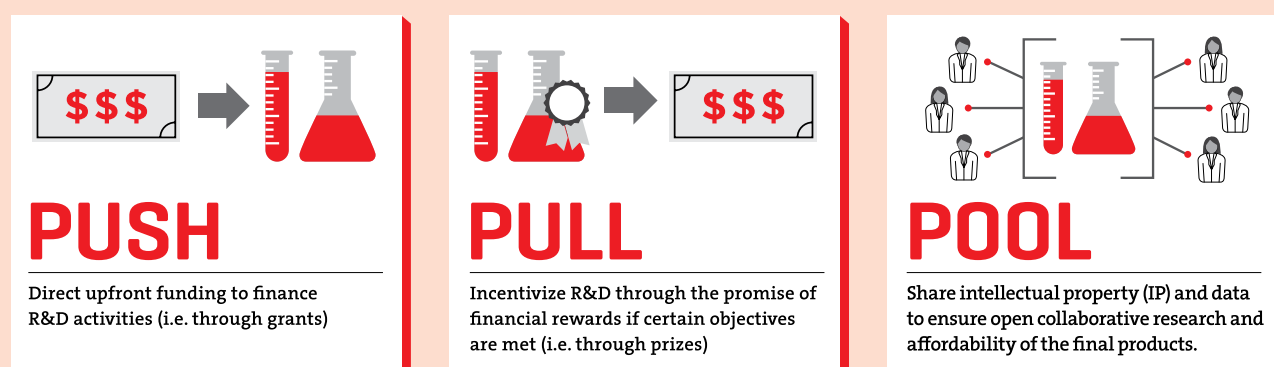
Together, these approaches would attract multiple actors to enter into the R&D process, would reduce risks, and increase the number of compounds in the clinical development pipeline. They would reduce the duplication of research

efforts, thereby saving time and money. They would facilitate progression of compounds through the pipeline, ensuring that preclinical successes are brought forward to clinical trials. By testing candidate compounds together at an early stage, and thus identifying drug-drug interaction and potential combinations earlier, they would accelerate the timeline for the development of new regimens. Overall, the increased investment and coordination of disparate sources of funding through both push and pull mechanisms would enhance the work of product development partnerships such as the TB Alliance in designing and testing regimens for all forms of TB.

Critically, the use of these mechanisms that are able to de-link the cost of R&D from the price of the resulting treatments would ensure affordability of the final medicines. Financial rewards would be linked to an obligation to share scientific and clinical data and intellectual property rights. Once a regimen receives regulatory approval, the individual drugs or fixed-dose combinations could thus be licensed to multiple manufacturers, allowing competition to lower prices to a level affordable in developing countries and ensuring sustainable sources of quality-assured drugs.

FIGURE 9:

THE 3P PROJECT: AN OPEN, COLLABORATIVE APPROACH TO TB REGIMEN DEVELOPMENT



© Melanie Doherty design

3. SET PRIORITIES, COORDINATE EFFORTS, AND ENSURE SUSTAINABLE FINANCING

Alongside the patchwork of investments by national governments, philanthropies and industry to address particular failings of the current R&D system, there are accelerating efforts at the international level to address these failures on a more systematic basis.

In 2015, in recognition of the serious market failures and unaddressed medical needs for anti-microbial resistance, emerging infectious diseases, and neglected diseases, leading experts, including MSF and DNDi, called for existing global efforts to address these challenges to be reconciled, by considering an umbrella framework for specifically financing and coordinating R&D that delivers innovation, while securing patient access. They also called for the establishment of a sizeable, sustainably-financed global R&D fund and mechanism that promotes coordination, collaboration, and the

use of new and innovative incentives to cover these medical priorities.¹⁴⁵

MSF and other organisations, including some governments, have also invested in a decade-long process, led by member states of World Health Organization (WHO), to generate global consensus around a set of principles and actions which governments can take to ensure that medical innovation works more effectively to address the medical needs of people in developing countries.

In 2006, a WHO-convened Commission on Intellectual Property, Innovation, and Public Health¹⁴⁶ called on WHO to take the lead in addressing issues where intellectual property acts as a barrier to innovation and access to medicines. This led to the establishment of an Intergovernmental Working Group on Public Health, Innovation and Intellectual Property which was charged with creating a framework to secure

sustainable R&D for the diseases that disproportionately affect developing countries.¹⁴⁷ In 2008, after two years of negotiations, countries adopted the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property.¹⁴⁸ One of its outcomes was the creation in 2010 of the Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG). The report of the CEWG, published on 5 April 2012, recommended that Member States begin a process towards establishing a legally-binding convention on R&D for the health needs of developing countries, under Article 19 of the WHO Constitution.

While this recommendation was not taken up by Member States in 2012, they decided as a first step to initiate work on joint priority setting, coordination and financing for a specific set of diseases.



During the 2014 Ebola outbreak in Sierra Leone, a clinical health officer hands over medication for a patient to a member of MSF staff inside Kailahun Ebola management centre's high-risk zone.

© Sven Torfinn

As a part of this process, in 2013, Member States decided to create the WHO Global Observatory on Health Research and Development, with the goal of collating information on health R&D, including what health R&D is being conducted, where and by whom, with a view to identifying the gaps and opportunities for additional health R&D. While the Observatory is not intended to set priorities for R&D, by identifying and categorising ongoing efforts, it can help reduce

duplication and enable funders and research entities to determine where to direct energies and resources.

WHO is also considering the establishment of a pooled R&D Fund, to be housed within WHO TDR, the Special Programme for Research and Training in Tropical Diseases, that will provide financing towards specific biomedical R&D initiatives that address key health needs. Critically, such funding is intended to finance R&D

projects that satisfy the basic principles of the CEWG, namely de-linkage of the delivery price from R&D costs, the use of open knowledge innovation and licensing for access.¹⁴⁹ While not intended to address all public health needs, the Fund thus represents an opportunity to immediately address many areas of critical need, including neglected diseases, antibiotic resistance and emerging infectious diseases.

MERS, EBOLA, ZIKA: COULD R&D FOR GLOBAL HEALTH EMERGENCIES SET A PRECEDENT FOR HOW TO CHANGE THE BIOMEDICAL INNOVATION SYSTEM?

The Ebola outbreak proved to be an exceptional event that exposed the reality of how inefficient and slow health and aid systems are to respond to emergencies. 'Business as usual' was exposed on the world stage, with the loss of thousands of lives.¹⁵⁰ Yet the outbreak has also led to unprecedented interest in addressing these critical R&D failings for highly-infectious pathogens like Ebola, MERS and, most recently, Zika, which may hold some lessons that could be replicated for other public health needs.

Among the recent initiatives to respond to these fast-emerging problems is the *WHO Global Blueprint for R&D preparedness and rapid research response during future public health emergencies due to highly infectious pathogens*¹⁵¹ which has been developed by the WHO Secretariat with R&D stakeholders, including MSF, since December 2015, and which is currently the most advanced, holistic and comprehensive proposal under discussion.

In parallel, expert working groups have been launched and concluded to provide a framework and technical input into how such initiatives could operate, though MSF continues to have some concerns with some of the proposed initiatives. The Institute of Medicines and the US National Academy of Sciences published a

'Report of the Commission on a Global Health Risk Framework for the Future' that sought to provide normative guidance to WHO and others on a framework to develop and distribute relevant health technologies to tackle infectious diseases. The UN Secretary General has additionally convened a panel on the Global Response to Health Crises that included recommendations to address key R&D gaps.

However, in spite of early global commitments to share clinical data in real-time during the Ebola outbreak in West Africa, some promising Ebola R&D projects were conducted in isolation, or even in secrecy.

One striking example is the clinical development of two Ebola vaccine candidates, for which no information on the study design or even the products being tested were shared by the study sponsors until 2016. Likewise, when the promising antiviral favipiravir was being developed by Fujifilm in 2014, WHO was able to identify that the same molecule was being developed concurrently by another organisation, but was unable to access preclinical data that might have helped inform the design of favipiravir trials in Ebola patients.¹⁵²

Although the Blueprint and other initiatives can be viewed as a response driven primarily by global health security concerns as opposed to

public health need, it can nevertheless represent an opportunity to satisfy urgent public health demands, while engaging in R&D in a manner in which governments set priorities, coordinate R&D activities and ensure adequate financing, all while ensuring that the efforts of such activities are affordable and suitable to the patients and geographies where such infectious diseases are particularly prevalent.

The Blueprint could be a concrete step in the right direction, if R&D efforts are coordinated by a multilateral organisation such as WHO, accountable to all Member States and which ensures the de-linkage of the cost of R&D from the final product price, ensures open knowledge innovation, encourages sharing of data and ensures access to end products by considering them as 'global public goods'.

MSF and other organisations hope that the R&D Blueprint, in lieu of creating a new R&D approach in competition and separate from the Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG), should instead aim to be as closely aligned as possible to the processes, outcomes and approaches used by the CEWG, including alignment or even integration of incentive, governance and oversight mechanisms that both processes seek to establish.

4. GOVERNMENT ACTION TO MEET THE NEEDS OF PATIENTS IN MSF PROGRAMMES AND BEYOND

Addressing the failures of biomedical innovation is a political choice, and failure to do so is thus an ongoing political failure.

While a WHO observatory can start to identify the gaps and needs that remain, and a Fund can start to finance R&D in ways that promote access, transparency and essential health needs, neither can guarantee that patients in MSF programmes and beyond have access to the medicines they need, regardless of disease and ability to pay.

There is evidence that an outcry over high prices can change the pricing behaviour of companies.¹⁵³ But the public outcry around high prices of medicines felt across many parts of the world today should not just target unaffordability, which is but a symptom of the problem, but seek to address its underlying cause. Only governments can make these changes.

The TRIPS Agreement agreed upon by governments in 1994 was the first collective effort to set out a singular approach for governments to incentivise R&D, but as has been shown in this report, the approach was fatally flawed, setting countries on a two-decade path to creating incentives for R&D primarily through monopolies and high prices. Just seven years after the Agreement was signed, MSF, in the midst of the crises we faced to treat HIV and AIDS and a range of neglected diseases, called for the establishment of a global R&D treaty to address neglected diseases.

Subsequently, governments have taken concrete steps to make such an R&D treaty a reality, and in particular at

WHO through discussions that have now lasted for more than a decade, and which seek to achieve some outcomes through the establishment of a WHO Health R&D Observatory and a Pooled R&D Fund. In the landmark report authored by a WHO-mandated Consultative Expert Working Group on Research and Development, Financing and Coordination in 2012, the expert group supported the launch of formal inter-governmental negotiations for a binding global agreement for R&D and innovation for health.

Today, MSF continues to face many of the challenges of yesteryear – such as high prices for new antiretroviral medicines, and ineffective, toxic or non-existent treatments for neglected tropical diseases. Despite some successes, our challenges continue to multiply – including the ongoing lack of medical tools to prevent and treat Ebola virus disease, the high cost of new medicines to treat hepatitis C, or the toxic, lengthy and only partially effective treatment for drug-resistant TB.

Yet these are not our challenges alone. Governments and patients around the world, in rich and poor countries, face the challenge of high prices for new medicines (and even for older products). The failures of the innovation pipeline affect people around the world, as distances have shrunk due to transportation and globalisation, and because certain R&D failures, like antibiotic resistance, affect all people.

These failures are leading governments to take steps that MSF would not have thought possible in 2001. The UN Secretary General's High Level Panel on

Access to Medicines,¹⁵⁴ which convenes a range of eminent technical experts and leaders of government, civil society and industry, represents a further opportunity to discuss and eventually launch a process of change. In March 2016, the President of France called for the G7 and G20 to take up the issue of high medicine prices, and to deliver solutions to address high medicines prices around the world. Incremental changes are within reach, but it is for governments to consider and push for transformational change.

For MSF, our measure of 'success' ultimately rests upon whether people in MSF programmes and beyond have access to the medicines they need, regardless of what disease they may face, what they can pay or where they live. Until we reach that goal, we will continue to bear witness to the failings of the current system of medical research and development, and continue to demand justice and change.

“ We have no model which would meet the need for new drugs in a sustainable way...

You can't expect for-profit organisations to do this on a large scale. If you want to establish a system where companies systematically invest in this kind of area, you need a different system.”

Daniel Vasella, CEO Novartis¹⁵⁵

CONCLUSIONS AND RECOMMENDATIONS

DEMAND TRANSPARENCY:

On the costs of R&D

Lifting the veil on real R&D costs would significantly improve understanding of the fairness of companies' intellectual property and pricing strategies and governments' ability to hold the pharmaceutical industry to account. Without being able to adequately assess R&D costs, it is difficult to devise the most effective incentive mechanisms that can estimate financial needs for innovations of public health importance.

- Pharmaceutical companies should engage in voluntary initiatives to share research, development and

manufacturing costs; clinical trial data; and patent, regulatory and price information; and

- Working together, governments should implement mandatory measures requiring transparency on development costs in exchange for public grant funding or other rewards such as existing priority review vouchers, existing tax credits or via prizes, or as a part of licensing agreements in the case of a compound whose early development was led by the public sector prior to development being taken forward by a commercial manufacturer.

On clinical trial results

Publishing clinical trial results would respect the rights of patients, meet the ethical requirements of the Helsinki Declaration, prevent the widespread practice of selective reporting of results, and promote valuable data sharing in the scientific community that would ultimately boost medical innovation and patient care.

- Governments should enforce rules for all clinical trials results to be published (including failed, withdrawn, and successful trials and trial data for medicines already on the market).

CHANGE THE INCENTIVES:

Stop pursuing harmful measures.

Because of its reliance on patent-based monopolies to finance medical innovation, the current system entrenches problems of affordability and rationing of medicines, while failing to stimulate innovation that answers to priority health needs.

- Governments should cease implementing, pushing for, or acceding to demands for TRIPS-plus measures that worsen the problems of the broken system, and should instead fully implement and apply TRIPS safeguards and flexibilities that enable generic competition, which brings prices down and stimulates affordable access; and
- Pharmaceutical companies should stop lobbying for TRIPS-plus measures in free trade agreements or through direct pressure on

national governments, stop filing law suits – whether through national courts or arbitration panels – against governments that are actively seeking to use TRIPS flexibilities, stop supporting industry groups and third parties that advocate for strict intellectual property rules, and stop filing and seeking trivial patents or applying other strategies to extend patent monopolies.

- **Demand more in exchange for public sector investment into innovation.** Governments and other public institutions invest considerably in pharmaceutical research and development through taxpayer-funded research. Governments also implement publicly-funded subsidies or mechanisms that boost rewards or lower the risk of R&D, as well as granting monopolies through

the patent system. This substantial support should be leveraged to address and prevent the current biomedical innovation system's failure to deliver affordable health tools that answer to priority public health needs.

- Governments should ensure initiatives to finance or incentivise pharmaceutical innovation are designed in a way that contributes to a fairer, more effective and more efficient biomedical innovation system better able to answer to public health needs, by ensuring the affordability of end products; initiatives that fail to meet their stated objectives such as the US Priority Review Voucher should be revised; and
- Governments and other public institutions such as universities should put in place

Continued overleaf

❖ *Conclusions and recommendations continued*

and implement measures that authorise them to leverage investments into publicly-funded research, for example, by granting limited and flexible intellectual property rights to inventions licensed out to companies, by setting pricing ceilings, or by granting (and applying) 'march-in' rights themselves to enforce affordable prices or generic competition in the case of drugs developed with public money.

❖ **Embrace new approaches**

Biomedical innovation is today steered and financed by the

promise of drug sales, with high prices backed by patents and monopoly rights. Public policies need to drive industry to embrace new approaches to R&D that break this link and do not rely on exclusivity as the method to incentivise innovation. Non-profit examples, including the Meningitis Vaccine Project and the Drugs for Neglected Diseases *initiative* co-founded by MSF have delivered affordable tools that answer unaddressed medical needs, showing the potential of applying de-linkage norms to biomedical innovation.

- Governments should introduce and fund incentive mechanisms that de-link the financing of research from drug sales and drug prices, in order to ensure biomedical innovation can respond to public health priorities and deliver affordable products, and where necessary, should enable rational use of critical health products such as antibiotics; and
- Governments that fund Product Development Partnerships should encourage them to set priorities effectively, coordinate with other entities, and ensure products are affordable, available and suitable for all countries.

SET PRIORITIES, COORDINATE EFFORTS, AND ENSURE SUSTAINABLE FINANCING:

❖ Efforts need to be pursued at the international level to address the failures of biomedical innovation on a more systematic basis, such as the Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG). The interest to address critical R&D failings for highly-infectious pathogens like Ebola and Zika show that global cooperation is possible, and may hold some lessons that could be replicated for other public health needs.

- Governments should broaden the scope of the WHO R&D Global Observatory on Health R&D so that it covers all areas

of public health importance, including public and private sector investments, and not only identifies needs and gaps but eventually works with other relevant bodies to set priorities for global health R&D;

- Governments should commit to financing a pooled R&D Fund, and design it so that it incentivises projects that satisfy the basic principles of the CEWG, namely de-linkage of the delivery price from R&D costs, the use of open knowledge innovation and licensing for access. Such a Fund should at least finance, set priorities and coordinate R&D projects related to emerging

infectious diseases, neglected tropical diseases and antibiotic resistance, with an eye towards expanding into other therapeutic areas over time; and

- Governments should launch a high-level political process aimed at re-negotiating how countries collectively coordinate, set priorities and finance or incentivise R&D so that it progressively shifts from a reliance on patent monopolies and instead relies upon incentive mechanisms that prioritise the discovery, development, and delivery of affordable innovations of public health importance.

ANNEX 1: HOW MUCH DOES IT REALLY COST TO DEVELOP A DRUG?

This annex compiles the different studies or reporting on R&D costs for average drug development or specific products identified in the literature, and shows to what extent estimates vary. The studies' estimates of costs range from \$30.3 million to \$2.6 billion, in 2013 dollars. The most widely-cited figures of \$802 million (DiMasi et al., 2003)¹² and \$2.6 billion (DiMasi et al., 2016)¹³ are based on industry-funded studies whose methodology has been widely challenged by observers, and even by Big Pharma leaders, for including sizeable, arbitrarily inflated 'time costs' and costs of failure.¹⁴ Comparing estimates of average R&D costs across time and studies is impossible because of wide variations in methods.

When reviewing these estimates it is helpful to consider a number of factors:

Is the data transparent and are the results replicable? Studies should be subjected to reasonable audit and disclosure of the drugs which authors purport to provide cost estimates for. All-too-often, however, the estimates are not replicable and information not verifiable.

What do the data sample? Figures may vary widely depending on the classes of drugs studied, whether the sample includes repurposed drugs or only new chemical entities, whether compounds have been developed by others and 'licensed-in' to a company or 'self-originated'. These factors can bear a considerable influence on the resulting estimate. For example applying the success rates DiMasi et al. calculated for 'licensed-in' compounds instead of 'self-originated' compounds to the 2003 results would have resulted in a \$640 million estimate (at 2003 prices), instead of \$802 million (adjusted to 2014 dollars, \$1,096 million, in table below).⁹⁷

Does the figure account for public support? The majority of early research is publicly funded and tax breaks along the process of development as well as other public incentives can be significant, but some estimates, including DiMasi et al. do not account for public funding and measure only private contributions to drug development.

What is classified as 'R&D'? What expenses can be classified as R&D costs and how to account for them is debated. For example, how are basic research and discovery costs, which are difficult to track and assign, accounted for? There are also questions about whether and how to account for land or buildings used not exclusively for R&D; legal expenses for acquiring and defending IP; fees paid to doctors to participate in clinical trials; costs of authoring and publishing research results; promotional activities targeted to physicians and payments to doctors for promotional activities; etc.³⁶

What adjustments have been made? In addition to cash outlays, some sources adjust their estimate for attrition rates/ risk of failure/likelihood of success, to account for drug candidates that aren't ultimately approved for market, with various studies estimating probability of success between 7% and 70% for varying samples and time periods. Some studies further adjust for the "cost of capital," to reflect the money a company could have earned in interest by investing elsewhere instead of spending money on R&D, assuming a return of up to 11.5% on that investment over the period of R&D activities – a practice *The Economist* describes as 'padding'.¹⁴ Again, the rate of adjustment varies across studies.

How is the estimate presented?

Consideration of averages/means versus medians/midpoints yield important differences. The 2003 DiMasi study had an estimated median of \$593 million per drug developed, compared to a mean \$802 million, for example.³⁶

Who is making the estimate? The possibility of conflicts of interest due to industry affiliations or funding needs to be taken into account as it may lead to biased figures. For example, both Tufts (DiMasi et al.) and Office of Health Economics (Mestre-Ferrandiz et al.) accepted funding from the pharmaceutical industry and the authors of "How to improve R&D productivity: the pharmaceutical industry's grand challenge" (Paul et al.) are all employed by pharmaceutical firm Eli Lilly.

Alternative methodologies applied to the same data can yield dramatically different results. Instead of the \$500 million figure publicised by the 1991 DiMasi et al. study, an alternate methodology developed by Public Citizen yielded a pre-tax average \$108 million per new drug from 1994 to 2000,¹⁵⁶ which when adjusted for tax breaks comes to \$57 million-\$71 million. A review of the 2003 Tufts study gave a result of \$80.3 million as a mean cost of developing a drug, or a non-capitalised cost of \$43.4 million³⁶ instead of \$802 million.

Estimated or reported R&D costs					
Source	Sample (time period)	Data source	Have the data been adjusted?	Cost of R&D in millions	
				Clinical trials	Total (preclinical & clinical)
Hansen & Chien 1979. **,157	Sample of unspecified number of firm-originated compounds by an undisclosed sample of firms (1963-1975)	Confidential survey	Cash estimate	\$49.9	\$99.9
			Adjusted for risk & cost of capital at 8%	\$79.3	\$174.8
Wiggins 1987. **,158	All types of new pharmaceutical compounds (1970-1985)	Annual survey of the PMA, US FDA, & Hansen (1971)	Cash estimate	xx	\$123.1
			Adjusted for cost of capital at 8%		\$236.9
DiMasi et al. 1991. **,159	Sample of 93 firm-originated compounds first tested in humans by an undisclosed sample of firms (1970-1982)	Confidential survey & proprietary database at Tufts CSDD	Cash estimate	\$88.5	\$209
			Adjusted for risk & cost of capital at 9%	\$138.4	\$424.8
Garber et al. 1992. ¹⁶⁰	R&D investments by Genzyme to develop Alglucerase, a treatment for Goucher disease (1981-1991)	Genzyme data, as reported by OTA	Cash estimate	xx	\$65.6
DiMasi et al. 1995. **,160	Anti-infective subsample of DiMasi's 1991 study (1970-1982)	Confidential survey & proprietary database at Tufts CSDD	Cash estimate	\$74.6	xx
			Adjusted for risk & cost of capital at 9%	\$106.6	
	Cardiovascular subsample of DiMasi's 1991 study		Cash estimate	\$94.7	xx
			Adjusted for risk & cost of capital at 9%	\$149.2	
	Neuropharmacological subsample of DiMasi's 1991 study (1970-1982)		Cash estimate	\$93.1	xx
			Adjusted for risk & cost of capital at 9%	\$156.9	
	NSAID subsample of DiMasi 1991 study (1970-1982)		Cash estimate	\$151.6	xx
			Adjusted for risk & cost of capital at 9%	\$248.2	
DiMasi et al. 1995. **,162	Small firm originating subsample of DiMasi 1991 study (1970-1982)	Confidential survey & proprietary database at Tufts CSDD	Cash estimate	\$73.4	\$272.8
			Adjusted for risk & cost of capital at 9%	\$124	\$630.3
	Medium firm originating subsample of DiMasi 1991 study (1970-1982)		Cash estimate	\$130.1	\$258.9
			Adjusted for risk & cost of capital at 9%	\$206.9	\$509.7
	Large firm originating subsample of DiMasi 1991 study (1970-1982)		Cash estimate	\$90.8	\$219.8
			Adjusted for risk & cost of capital at 9%	\$134.3	\$421.5
DiMasi et al. 2003. **,12	Sample of 68 firm-originated compounds first tested in humans by an undisclosed sample of firms (1983-1994)	Confidential survey & proprietary database at Tufts CSDD	Cash estimate	\$379	\$541.6
			Adjusted for risk & cost of capital at 11%	\$627.6	\$1,077.8
DiMasi et al. 2004. **,165	CNS subsample of DiMasi et al. 2004 study (1983-1984)	Confidential survey & proprietary database at Tufts CSDD	Cash estimate	\$366.9	xx
			Adjusted for risk & cost of capital at 11%	\$623.6	
	Anti-infective subsample of DiMasi et al. 2004 study (1983-1984)		Cash estimate	\$486.5	xx
			Adjusted for risk & cost of capital at 11%	\$661.2	
	Cardiovascular subsample of DiMasi et al. 2004 study (1983-1984)		Cash estimate	\$372.2	xx
			Adjusted for risk & cost of capital at 11%	\$618.2	
	Analgesic/anaesthetic subsample of DiMasi et al. 2004 study (1983-1984)		Cash estimate	\$338.7	xx
			Adjusted for risk & cost of capital at 11%	\$623.6	

Definitions

- Unadjusted outlay is the actual dollar amount spent on R&D activities related to the product(s) for which the R&D costs are being estimated.
- Adjusted for risk (of failure) means that the estimate essentially accounts for R&D expenditures related to other projects that failed (or were abandoned) before reaching the market.
- Cost of capital is an adjustment some argue is necessary to account for the amount of money the company could have earned had they taken the money they spent on R&D and instead invested it and earned a return of the rate indicated. Cost of capital is also referred to as the opportunity cost of investing in R&D.

Notes

All figures adjusted to US dollar 2013 values from: <http://www.usinflationcalculator.com/>

DNDi data converted from euros April 2016.

* DNDi cost estimates do not account for in-kind contributions, which can represent up to 20% of operating costs.

Table adapted from Morgan et al. 2010¹⁰³

Figures from Morgan et al. were previously adjusted for 2009 inflation using GDP deflator.

** Indicates where data has been updated from Morgan et al.

Cash estimate may or may not include an adjustment for risk.

Adjusted for cost of capital figures are also adjusted for risk

Estimated or reported R&D costs					
Source	Sample (time period)	Data source	Have the data been adjusted?	Cost of R&D in millions	
				Clinical trials	Total (preclinical & clinical)
DiMasi & Grabowski 2007. **, 164	13 therapeutic recombinant proteins & monoclonal antibodies first entering clinical trials (1990-2003)	Confidential data from biotech firms & Tufts CSDD data	Cash estimate	\$401	\$666.3
	And 4 biotech compounds first entering clinical trials (1983-1994)		Adjusted for risk & cost of capital at 11.5%	\$736.4	\$1,479.2
	"Time-adjusted" costing data from DiMasi et al. 2003	"Time-adjusted" costing data from DiMasi et al. 2003	Cash estimate	\$622.2	\$801
			Adjusted for risk & cost of capital at 11.5%	\$1,047.7	\$1,571
Young & Surrusco 2001. 165	All drug approvals by the US FDA (1990-2000)	R&D data from PhRMA reports & drug approval data from US FDA	Cash estimate	xx	\$224.4
			Adjusted for risk & cost of capital at 9%		\$458.2
TB Alliance 2001. **, 166	"Low-cost" scenario based on prospective estimate of cost of developing a TB treatment, including cost of failures (circa 2000)	A variety of sources including survey of contract research orgs	Adjusted for risk & cost of capital between 0-3%	\$99.9	\$151.2
	"High-cost" scenario based on prospective estimate of cost of developing a TB treatment, including cost of failures (circa 2000)		Adjusted for risk & cost of capital between 0-3%	\$151.2	\$315.6
Adams & Brantner 2006. **, 167	A sample of 3,181 drugs (1989-2002)	Pharmaprojects database, & cost-per-phase estimates from DiMasi et al. 2003	Cash estimate	\$416.6	\$595.4
			Adjusted for risk & cost of capital at 11%	\$654.4	\$1,166.5
	A sample of anti-parasitic drugs (1989-2002)		Adjusted for risk & cost of capital at 11%	xx	\$610.1
	A sample of repository drugs (1989-2002)		Adjusted for risk & cost of capital at 11%	xx	\$1,524
	A sample of drugs developed by "Firm E" (1989-2002)		Adjusted for risk & cost of capital at 11%	xx	\$700.2
	A sample of drugs developed by "Firm C" (1989-2002)		Adjusted for risk & cost of capital at 11%	xx	\$2,894
Light et al. 2009. 168	Estimated costs to develop Merck's rotavirus vaccine, RotaTeq (1987-2001)	U.S. Patent & Trademark Office, the U.S. SEC EDGAR database, Medline, periodicals, corporate websites & interviews with principal figures	Cash estimate	\$180.4-\$549.2	xx
			Adjusted for risk & cost of capital at 7%	\$290.5-\$949.8	xx
	Estimated costs to develop GlaxoSmithKline's rotavirus vaccine, Rotarix (1995-2003)		Cash estimate	\$162.5-\$504.5	xx
			Adjusted for risk & cost of capital at 7%	\$225.6-\$744	xx

Definitions

- Unadjusted outlay is the actual dollar amount spent on R&D activities related to the product(s) for which the R&D costs are being estimated.
- Adjusted for risk (of failure) means that the estimate essentially accounts for R&D expenditures related to other projects that failed (or were abandoned) before reaching the market.
- Cost of capital is an adjustment some argue is necessary to account for the amount of money the company could have earned had they taken the money they spent on R&D and instead invested it and earned a return of the rate indicated. Cost of capital is also referred to as the opportunity cost of investing in R&D.

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Table adapted from Morgan et al. 2010¹⁹³

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** Indicates where data has been updated from Morgan et al.

Cash estimate may or may not include an adjustment for risk.

Adjusted for cost of capital figures are also adjusted for risk

Continued overleaf ➤

Estimated or reported R&D costs					
Source	Sample (time period)	Data source	Have the data been adjusted?	Cost of R&D in millions	
				Clinical trials	Total (preclinical & clinical)
Adams & Brantner 2010. **,169	A sample of 2,245 drugs (1989-2001)	Pharmaprojects database, & data that Danzon et al. 2004 ¹⁷⁰ compiled from CompuStat & Global Vantage	Adjusted for risk & cost of capital at 11%	xx	\$1,666.6
Paul et al. 2010. **,171	An unspecified sample of products developed by Eli Lilly & undisclosed firms participating in the Pharmaceutical Benchmarking Forum (1995-2010)	Eli Lilly & Company, & KMR Group Pharmaceutical Benchmarking Forum	Cash estimate	\$650.6	\$959.5
			Adjusted for risk & cost of capital at 11%	\$1,048.5	\$1,954.1
WHO 2010. ¹⁷²	Reported costs to develop MenAfriVac, an adapted vaccine for Meningitis A	WHO-reported	Cash estimate	xx	\$53.4
Mestre-Ferrandiz et al. 2012. ⁹⁷	Confidential data from 16 pharmaceutical firms regarding 97 projects completing key development “intervals”, estimating costs & risks to market launch. Preclin excludes discovery. Total includes discovery & from registration to marketing (1998-2002)	Previously unpublished information collected by CMRI in confidential surveys	Cash estimate	xx	\$1,035.6
			Adjusted for risk & cost of capital at 11%	xx	\$1,559.7
DNDi 2013. ¹⁵	Estimated costs to develop SCYX-7158, a new chemical entity for sleeping sickness (2003-2018)	DNDi	Cash estimate*	xx	\$43.7
	Estimated costs to develop fexinidazole, a rediscovered new chemical entity for late-stage sleeping sickness (2005-2016)		Cash estimate*	xx	\$30.3
	Estimated costs to develop a new chemical entity		Adjusted for risk*	xx	\$114.2-171.3
DiMasi et al. 2016. ¹³	Sample of 106 firm-originated compounds first tested in humans by an undisclosed sample of firms (1995-2007)	Confidential survey & proprietary database at Tufts CSDD	Cash estimate	\$965	\$1,395
			Adjusted for cost of capital at 10.5%	\$1,460	\$2,588

Definitions

- Unadjusted outlay is the actual dollar amount spent on R&D activities related to the product(s) for which the R&D costs are being estimated.
- Adjusted for risk (of failure) means that the estimate essentially accounts for R&D expenditures related to other projects that failed (or were abandoned) before reaching the market.
- Cost of capital is an adjustment some argue is necessary to account for the amount of money the company could have earned had they taken the money they spent on R&D and instead invested it and earned a return of the rate indicated. Cost of capital is also referred to as the opportunity cost of investing in R&D.

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DNDi data converted from euros April 2016.

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Table adapted from Morgan et al. 2010

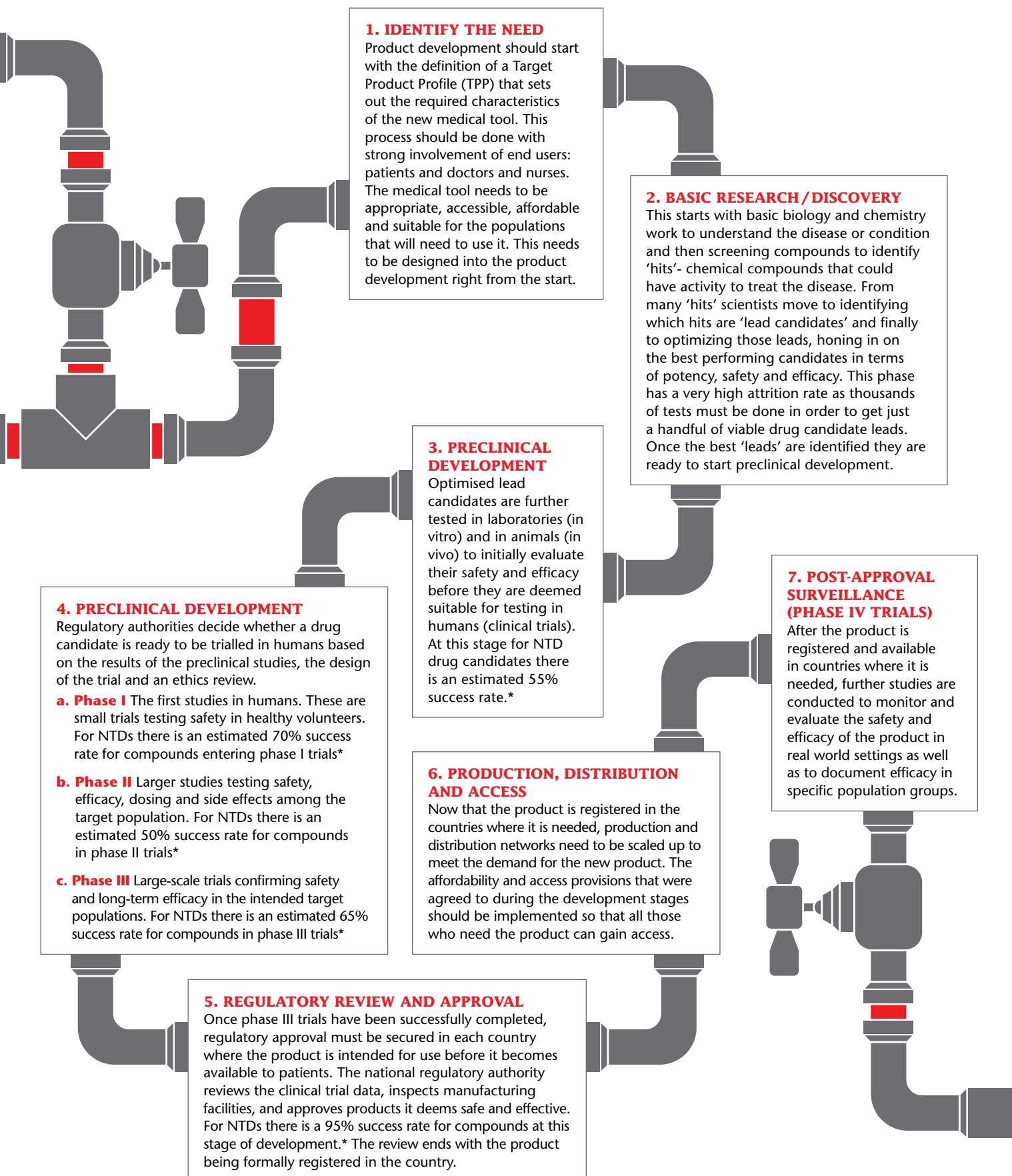
Figures from Morgan et al. were previously adjusted for 2009 inflation using GDP deflator.

** Indicates where data has been updated from Morgan et al.¹⁰³

Cash estimate may or may not include an adjustment for risk.

Adjusted for cost of capital figures are also adjusted for risk

ANNEX 2: DRUG DEVELOPMENT PIPELINE



* Source for attrition rates: 'Virtual drug discovery and development for neglected diseases through public-private partnerships'. By N. Solomon and R.G. Ridley, Nature Reviews, Drug Discovery, Volume 2, 919-928, Nov 2003, pp 5-15. doi:10.1038/nrd1230



GLOSSARY

Access: Access to medicines means that suitable products are available at affordable, sustainable prices to meet patient needs. This means priced at levels affordable to Ministries of Health and other treatment providers, without necessitating sustained donor intervention. It also means ensuring that products are suitable for use in contexts where infrastructure and human resources are limited.

Antibiotic resistance: Resistance to drugs used to treat infections that occurs in bacteria as well as other microbes, such as parasites, viruses and fungi.

Antimicrobial resistance: Resistance to drugs used to treat infections that occurs in bacteria as well as other microbes, such as parasites, viruses and fungi.

Biologics: A class of systemic therapies that contain proteins derived from living cells, as opposed to traditional pharmaceutical drugs that are made up of non-living chemicals. Examples include vaccines, blood and other blood products, as well as genetic therapies.

Biomedical innovation: The basic research, applied research, or translational research conducted to aid and advance the body of knowledge in the field of medicine, particularly as it relates to medical tools: diagnostics, devices, drugs and vaccines.

Bioterrorism: A bioterrorism attack is the deliberate release of viruses, bacteria, or other germs (agents) used to cause illness or death in people, animals or plants. These agents are typically found in nature, but it is possible that they could be changed to increase their ability to cause disease, make them resistant to current medicines, or to increase their ability to be spread into the environment.

Chronic disease: Also known as non-communicable diseases (NCDs), including cardiovascular disease, cancer, chronic respiratory diseases, diabetes,

mental disorders, vision and hearing impairment, oral diseases, bone and joint disorders and genetic disorders.

Clinical trials: An important kind of biomedical research which is distinguished by the involvement of patients. Phase I determines the safety of a product under development in a small group of healthy volunteers. Phase II determines the safety and efficacy of a product in a group of volunteers with the profile of the targeted treatment group. Phase III are large-scale trials to determine continued safety and efficacy and detect less common side effects in a group of volunteers with the profile of the targeted treatment group.

Cold chain: A global network of equipment and services to make sure that vaccines and medicines stay at the right temperature at every step of their journey.

Cost of capital: also referred to as “time costs” or “opportunity costs”, this is the amount of money that a company could have earned, had the company taken the money spent on R&D, invested it elsewhere, and earned a specified rate of return.

De-linkage: Model of innovation that separates or “de-links” the financing of R&D from the sales of the end product, in contrast to the current innovation system where the R&D funding is linked to sales, as the potential money to be made by charging high prices for the product is what determines levels of investment into R&D.

Differential pricing: The practice of setting different prices for different markets, typically higher prices in richer markets and lower prices in poorer markets.

Disease outbreak: The occurrence of cases of disease in excess of what would normally be expected in a defined community, geographical area or season. An outbreak may occur in a restricted geographical area, or may

extend over several countries. It may last for a few days or weeks, or for several years.

Drug discovery: Process by which potential new medicines are identified, including screening, and lead optimisation prior to additional preclinical testing.

Drug-resistant TB: When a drug used to treat TB is ineffective against a strain of *M. tuberculosis*, the bacteria is said to be resistant to the drug (as opposed to drug-susceptible or drug-sensitive).

First-line: The drugs used as a first resort to treat a disease.

Fixed-dose combination (FDC): A fixed-dose combination, or FDC, contains two or more medicines combined into one pill, greatly simplifying treatment for people and treatment providers alike. They also help people better adhere to their treatment, reduce the risk of resistance, and simplify supply chains. FDCs for HIV were largely pioneered by Indian generic manufacturers, and have played a key role in helping simplify treatment, facilitating the scale-up treatment to millions of people living with HIV/AIDS in developing countries.

Generic drugs: A generic medicine refers to a drug that is therapeutically equivalent to an originator product, but is produced by an entity that does not hold the patent for the medicine in question. Competition among generic producers was instrumental in bringing down the price of the first generation of antiretrovirals and other drugs.

Intellectual property (IP): Intellectual property rights are usually exclusive rights, often temporary, granted by the state for the exploitation of intellectual creations. When an IP rights holder enforces these exclusive rights, generic competitors cannot enter the market and the rights holder retains the ability to set any price for the product under protection.

Market exclusivity: Exclusive marketing rights granted by regulatory authorities in some countries upon approval of a drug, separate from patent protection. During a period of exclusivity, a generic or biosimilar drug cannot be approved for marketing by the drug regulatory authority.

Medical tool: Drugs, diagnostics, devices and vaccines. Also described as a medical product.

Multidrug-resistant TB (MDR-TB): Patients infected with strains of TB that are resistant to (at least) the two most powerful first-line antibiotics used to treat TB, namely rifampicin and isoniazid, are said to have MDR-TB.

Neglected disease: A diverse group of diseases and conditions affecting more than a billion people worldwide, but few in wealthy markets. In addition to lacking programmatic support, most neglected diseases lack sufficient tools and R&D resources because patient populations are too poor or too few to incentivise R&D under a system of innovation that rewards companies for developing products by allowing them to charge high prices.

New chemical entity: a drug or chemical that is without precedent among regulated and approved drug products. The NCE designation indicates that a drug in development is not a version or derivative of an existing and previously investigated, trialled and approved substance. Being labelled as entirely 'new' or first-in-class molecule dictates that certain types of clinical trials must be run, and that particular attention must be paid to proving a drug's safety.

Orphan drug: A drug that has been developed specifically to treat a rare medical condition. They may be defined as drugs that are not developed by the pharmaceutical industry for economic reasons but which respond to public health needs. The US Orphan Drug Designation

programme, for example, gives a tax credit of 50% on qualifying clinical R&D expenditure on drugs the US FDA qualifies as 'orphan' (i.e. for diseases that affect fewer than 200,000 people in the country), as well as exclusive marketing rights for seven years.

Patent: A patent is the right to prevent anyone else from making, using or selling the patented invention. It is granted by a government or regional authority. A patent term typically lasts for 20 years, which means that during that period of time, the patent holder has a monopoly on the invention (e.g. a medicine) and can charge the highest price the market will bear.

Pre-clinical research and development: Non-human testing of a medical product candidate to collect safety data, including safe doses, and determine whether a compound will be suitable for human subject testing.

Prize fund: Pre-designated pot of money to be awarded to the developer of a particular product that meets a specified target product profile or milestone target. Prize funds are considered a type of pull mechanism because they incentivise R&D through the promise of a reward based on the delivery of results.

Product development partnership: A not-for-profit product development organisation that partners with the public, philanthropic, and private sectors to develop technologies—diagnostics, drugs, devices, vaccines, and microbicides—targeted at neglected diseases and conditions of high morbidity and mortality in low- and middle-income countries. PDPs are a specific type of public-private partnership (see below).

Priority Review Voucher (PRV): The US FDA's Priority Review Voucher (PRV) programme for neglected diseases is designed to stimulate research into neglected diseases. The mechanism rewards any company that successfully

registers a product for eligible neglected diseases with the US FDA with a voucher. The voucher fast-tracks the review process for a subsequent drug candidate needing FDA approval in the recipient's portfolio (and that would not qualify for priority review on its own merit). Vouchers issued under the PRV program for neglected diseases and a similar programme for rare paediatric diseases can be used or sold to third parties.

Public-private partnership: An informal or formal arrangement between one or more public-sector entities and one or more private-sector entities created in order to achieve a public health objective or to produce a health-related product or service for the public good.

Pull mechanism: Mechanism that induces innovation by rewarding successful development or milestone progress based on the delivery of results. Examples of pull mechanisms include the patent system, prize funds and advance market commitments.

Push mechanism: Mechanism that drives innovation by funding or subsidising R&D phases ex-ante or 'up front'. Push mechanisms mainly come in the form of grants.

Research and development (R&D): Work which is designed to provide new knowledge, the findings of which are potentially of value to those facing similar problems elsewhere. In the field of medicine, the term R&D is used interchangeably with 'biomedical innovation' to refer to the basic research, applied research, or translational research conducted to aid and advance the body of knowledge in the field of medicine - particularly as it relates to medical tools: diagnostics, devices, drugs and vaccines.

Risk of failure/attrition rate: Percentage of drugs entering clinical testing that are not ultimately approved by a regulatory authority.

Continued overleaf ❖

Salvage regimen: A salvage regimen of antiretroviral treatment is needed for people who have developed resistance to first- and second-line treatments.

Second-line: A second-line drug regimen is given to people who have developed drug resistance to their first set of medications – the first-line regimen.

Success rate: The percentage of drugs entering clinical testing that are ultimately approved by a regulatory authority.

Tax credit: An incentive for R&D, whereby the government reduces the amount of tax a company has to pay in order to reduce R&D costs to companies and increase the public share of these costs.

TRIPS: The 1994 World Trade Organization (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) sets minimum standards for the protection of intellectual property, such as patents, for all WTO Members (162 countries as of November 2015). All members of the WTO must comply with the standards set by the TRIPS Agreement. TRIPS required many developing

countries to begin granting patents on medicines. For example, India introduced pharmaceutical product patents in 2005 to comply with TRIPS.

TRIPS flexibilities: As expressly recognised in the Doha Declaration of 2001, the TRIPS Agreement contains several flexibilities that countries may use in order to, among other things, safeguard public health. Flexibilities relate to legal measures that give countries the right to overcome IP barriers where they hinder access to medicines, or undermine public health. The Doha Declaration affirms that “the TRIPS Agreement does not and should not prevent Members from taking measures to protect public health.”

TRIPS-plus provisions: In recent years many developing countries have been coming under pressure to enact or implement even tougher or more restrictive conditions in their patent laws than are required by the TRIPS Agreement, known as TRIPS-plus provisions.

Vaccine: A biological preparation that improves immunity to a particular disease.

Viral load test: A viral load test is a laboratory test that measures the number of virus particles in a millilitre (mL) of blood. These particles are called “copies.” An HIV viral load test should consistently detect and measure virus levels down to 50 copies/mL, have a high specificity and provide reproducible results. The technologies used are advanced and very sensitive for measuring the amount of HIV genetic material present in the blood. For clinicians and people living with HIV, viral load testing helps provide information on the health status of a person living with HIV and how well antiretroviral therapy (ART – treatment with HIV medicines) is controlling the virus.

Voluntary licence (VL): A voluntary agreement reached between the patent-holder (licensor) and another party (licensee) (usually a generic company) which allows the licensee to make, use, and/or sell the invention. Terms and conditions can specify in which countries a medicine can be sold and what the royalty will be. The Medicines Patent Pool is a mechanism that manages voluntary licences between multiple licensors and licensees.

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