tagline s, viral hepatitis, and tuberculosis

NEWS ON THE FIGHT TO END HIV/AIDS, VIRAL HEPATITIS, AND TUBERCULOSIS

BRINGING DOWN THE HOUSE ON INTELLECTUAL PROPERTY AND ACCESS

WHOSE INTELLECT? WHOSE PROPERTY?

A Blueprint for Bringing Down the Pharma IP House of Cards

By JD Davids, TAGline Guest Editor and Suraj Madoori, U.S. and Global Health Policy Director, TAG

s the Trump administration makes noise about the high price of pharmaceuticals while doubling down on its commitment to "protect the engine of American ingenuity," this issue of TAGline dives deep into the rhetoric and realities of intellectual property (IP) protections and the current wave of political shenanigans on critical drugs, surfacing the fundamental lies and vested interests that deny medication to those in need in the United States and around the world.

While the horrors of the current administration include wrenching actions that strip entire communities of rights and liberty, an honest appraisal of the years of the HIV crisis reveals longstanding practices of both Democratic and Republican leadership who chose to advance pharmaceutical industry interests, rather than look out for the actual needs of the American people and those worldwide who need essential medications.

We all know the game: excessive levels of intellectual property protection-particularly in developing countries-aggravate, rather than help solve, the problem of access to affordable medicines. We know that extensive patent protection for critical and innovative medicines delays the introduction of generic competition that would lower prices. And we've seen the United States use threats of sanctions and more to undercut nations that seek to extend treatment access to their populations.

ntellectual property issues—including patents, profits, public financing of research for private gain, large trade deals, and global medication access—have long been a central facet of the fight for lives and justice in the HIV pandemic. As Richard Jefferys reminds us in his exploration of IP issues in HIV cure and vaccine research (see <u>Cure/</u><u>Prevention</u> page 12), one of the first definitive wins of direct action HIV/AIDS protest came with the New York Stock Exchange disruption that called for a reduction in the price of AZT—a formerly "orphan" drug then patented by Burroughs Wellcome.

This TAGline takes you behind the scenes of effective and

growing advocacy that could change the way the world gets treatment in the years ahead.

ou will find compelling articles that examine recent and future debates and considerations in intellectual property and access to medicines, particularly across HIV, TB, and HCV. You'll emerge with tools and calls to action to help you challenge the use of intellectual property as a strategy to keep affordable medicines out of the hands of those who need them the most, both domestically and globally:

Bryn Gay tells of inspiring and practical tactics from the front lines of the global access to medicine (A2M) movement (see <u>A2M</u> page 8). And she teams up with Claudine Guerra (see <u>Myths</u> page 13) on a tip sheet debunking the top myths of big pharma, arming you to take down the house of cards disguised as President Trump's "blueprint" on drug pricing.

Suraj Madoori and co-author Khairunisa Suleiman of the Global TB Community Advisory Board bring us into the contested corridors of the UN General Assembly at the firstever High-Level Meeting on Tuberculosis, (see <u>Declaration</u> page 3), where the U.S. and South Africa squared off on profit vs. access, laying out what needs to happen now to reap the benefits of South Africa's win.

A2M activists have long argued for delinking the cost of drug development from its ultimate price. Now that one company has tried it, what is there to be learned? Find out more from TAG's TB Project interview with Marc Destito of Otsuka Pharmaceuticals, developer of delamanid.

And turn on the lights with Annette Gaudino (see <u>Boogeyman</u> page 10) as she reveals that there's no monster under the bed that's waiting to pounce on innovation if medication prices are affordable.

Together, these articles serve as a stiff breeze that can take down the intellectual property house of cards. TAG invites you to join us in using these powerful lessons and strategies to win access to medicines for all.

BEYOND DECLARATIONS: LESSONS FROM THE UN HIGH-LEVEL MEETING ON TB ON BUILDING AND TRANSFORMING POLITICAL WILL INTO REAL ACCESS TO MEDICINES

By Khairunisa Suleiman, Co-Technical Lead, Global TB CAB and Suraj Madoori, U.S. and Global Health Policy Director, TAG

n Sept. 26, 2018, the world came together at the United Nations General Assembly in New York for the first-ever High-Level Meeting on Tuberculosis (TB HLM), bringing hope for new political will and resources to jump-start the global response to the world's leading infectious killer. But a draft declaration on TB had been finalized less than two weeks earlier, and the negotiation process had been prolonged and contentious. The fight had brought the global TB community to the brink, with the players nearly going into the TB HLM without a political framework that countries could agree upon. The delay was due to a narrow but deep deadlock between the U.S. government and the government of South Africa: The countries disagreed on paragraphs that supported the rightful use of TRIPS (the Agreement on Trade-Related Aspects of Intellectual Property) flexibilities by governments to promote affordable access to new tools and treatments in the fight against TB.

The negotiations on the declaration provide an ideal backdrop to examine the realities and challenges around global political will to end the world's leading infectious killer, spotlighting the main dynamic and contenders: the obstructionism of the United States government and the bold maneuvering by South Africa in expanding access to lifesaving medicines. As activists take forward the commitments beyond the TB HLM to expand access to medicines for TB, we are well advised to learn lessons from the history and political dynamics that fueled the negotiations.

The U.S. Threat at Every Step

At nearly every step of the negotiations, the U.S. government threatened to nix the TB HLM declaration if language on access to affordable medicines was retained, and U.S. negotiators repeatedly deleted the operative text. These moves frustrated South Africa, which is heavily burdened by TB, and other G77 nations that struggle in expanding treatment and associated tools. In solidarity with the global TB community, U.S. civil society organizations advocating on TB and access to medicines (A2M) sent a letter to their own government appealing for them to "work in good faith to find a political solution" in respecting other nation's rights in exercising TRIPS flexibilities.¹ The letter went unanswered.

The negotiations on the declaration provide an ideal backdrop to examine the realities and challenges around global political will to end the world's leading infectious killer.

Yet, many A2M advocates contend that the disruptive involvement and hard-line stance of the U.S. government in these multilateral negotiations is neither new nor surprising. In fact, the protracted proceedings are part of a larger pattern in which the U.S. prioritizes industry profits over matters of public health. In just the past year, the U.S. government has penetrated multiple policy environments, aiming to rebuke other governments for trying to address their own public health crises (see Table 1). For example, in remarks to the 71st World Health Assembly in May 2018, U.S. Health and Human Services Secretary Alex Azar said, "President Trump has made reducing the cost of prescription medications for Americans a top priority, and we have already begun taking action to improve affordability within our market-based, innovation-friendly system." Azar further condemned nations for "practices by which other countries command unfairly low prices [for] innovative drugs."

This U.S. myopia also means that domestic patients with TB lose out, with the U.S. neglecting to address its own national pricing and policy issues at the TB HLM.

A Deceitful Ideology

The persistence of the U.S. government in narrowly focusing on the access provisions in the TB HLM, risking the whole negotiating process rather than encouraging other nations to end the world's deadliest infectious disease with every tool possible, is consonant with the administration's industry-centric "blueprint" on drug pricing.

While this harmful rhetoric and practice predates Trump, this strategy is laid bare in his administration's May 2018 plan on drug pricing, called American Patients First: The Trump Administration Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs. The largely industry-backed plan contains a strong mandate to the U.S. Trade Representative (USTR) to go after other countries for the "global freeloading" on American taxpayers, ostensibly because other countries often pay substantially lower prices for drugs for which there have been U.S. investments in research and development (R&D).

Table 1: Roadmap to U.S. Government Obstructionism on A2M in 2018

Date	Event and Action
January 2018	11th annual IP Attaché Roundtable, Washington, D.C.: U.S. officials announce they are actively working to prevent international organizations in Geneva from advancing the 2016 United Nations High-Level Panel (HLP) on Access to Medicines recommendations, considering them harmful to U.S. economic interests. The U.S. Chamber of Commerce Global Innovation Policy Center announces the formation of an IP law enforcement network, with 13 attachés in 10 countries, including India, Brazil, and Thailand. ²
April 2018	Office of the U.S. Trade Representative (USTR), Washington, D.C.: USTR releases the 2018 Special 301 Report, identifying "priority watch list" nations that do not "adequately or effectively protect" intellectual property. The list includes 12 countries, such as heavily TB- burdened nations of India, Indonesia, Russia, and Ukraine, and threatens to subject these nations to "intense bilateral engagement during the coming year." ³
May 2018	71st World Health Assembly, Geneva: During drafting of a Roadmap for Access to Medicines and Vaccines, the U.S. representative criticizes the use of compulsory licenses by countries to prioritize affordable access to medicines. The representative further criticized the Roadmap's recommendations made by the HLP in its impact on the U.S. "innovation system." ⁴
August 2018	UN High-Level Meeting on Non- Communicable Diseases, New York City: Directly following the TB HLM, the U.S. government holds up the finalization of the political declaration over language calling for countries to lawfully use TRIPS flexibilities. ⁵

The blueprint postulates that by going after other countries, i.e., reinforcing intellectual property (IP) rights and discouraging compulsory licensing, drug prices will somehow become lower in the U.S.. This truly deceitful ideology underpinned the U.S.'s objectives and engagement in the TB HLM.

TAG and many other organizations submitted public comment on the blueprint noting that such reinforcement of IP is no different from what the U.S. has done in the past, arguing that it is mere spin for demonstrating political will to a polarized electorate by an administration desperately seeking a win on drug pricing.⁶

This U.S. myopia also means that domestic patients with TB lose out, with the U.S. neglecting to address its own national pricing and policy issues at the TB HLM. The TB drug supply is often prone to disruptive stock-outs and vulnerable to fragile market conditions and unexpected price spikes, even in the U.S. In early 2018, manufacturer Sandoz unexpectedly discontinued the U.S. production of isoniazid, a key drug in the treatment of TB. Bedaquiline, one of only two new TB treatments that are approved by the U.S. Food and Drug Administration, continues to experience difficulty in uptake because of high costs in the U.S.–mirroring the issue of exorbitant pricing and limited access to the drug among low-income countries heavily burdened by TB.

South Africa Remains Valiant

Comparatively, South Africa's approach to the TB HLM declaration was diametrically different to the U.S. When the draft declaration went public on July 20, 2018, South Africa broke a procedural silence on negotiations and valiantly advocated in favor of the stronger initial draft language on access to medicines. The nation urged co-facilitators Antigua and Japan to consider including language for countries to exercise TRIPS flexibilities for affordable and accessible medicines and diagnostics. South Africa also advocated for delinking the price of medicines from the cost of R&D in order to increase affordability of TB tools. The next day, the G77 bloc of countries supported South Africa's stance, thereby reopening negotiations on the TB declaration.

But South Africa's valiant efforts are rooted in its political history. In the past, the South African government has weathered repeated attempts from lobbyists aligned with the USTR and pharmaceutical industry in its work to expand access to critical medicines for its residents through a combination of community activism and progressive policy (see Table 2). Table 2: Collective Action by South African CommunityActivists and Government for HIV Treatment Access

Year	
1997	Section 15C is introduced into South African Medicines and Related Substances Control Act to allow parallel importations of cheaper HIV antiretrovirals (ARVs). ⁷
2001	Pharmaceutical companies file lawsuit against South African government, Ministry of Health. Community activists, led by Treatment Action Campaign (TAC), mobilize to drop the lawsuit. ARV prices drop–but the drugs remain unaffordable.
2003	Complaint lodged to South African Competition Commission on the anti- competition tactics of pharmaceutical manufacturers. Commission finds companies GlaxoSmithKline and Boehringer guilty– leading to a further decrease in ARV prices.

Notably in 1997, South Africa passed the Medicines and Related Substances Control Act to allow for the importation of cheap antiretrovirals (ARVs) to treat HIV. In response, the U.S. continued to pressure South Africa to repeal or change the Medicines and Related Substances Control Act. Because of media attention, resulting from strong community activism, the U.S. relented and stopped pressuring South Africa in 1999.

his valor was on full display in the lead-up to the TB HLM. For example, South Africa government negotiated with pharmaceutical giant Johnson & Johnson to reduce the price of bedaquiline to US\$400 for the six-month treatment course, a change that would benefit all countries that procure treatment from the Global Drug Facility. Civil society activism also contributed to this price decrease, threatening compulsory licensing and calling for a price of US\$32 per month before the negotiations were finalized.⁸ Additionally, ahead of the new World Health Organization (WHO) drug-resistant TB (DR-TB) treatment guidelines, South Africa took another significant step by changing its national DR-TB treatment guidelines to include bedaguiline and prohibit the use of the toxic secondline injectables. This display of political will, alongside strong community activism, subsequently spurred the WHO to recommend the use of bedaquiline and prohibit the use of kanamycin and capreomycin in the treatment of DR-TB.

Political Will Beyond Paper Agreements

But ironically, even with this long history of political will and proactive steps to reduce drug prices, South Africa has never issued a compulsory license to challenge the IP for any drug, perhaps in fear of U.S. reprisal.

For example, the repurposed drug linezolid that is now used for TB is still patented and had only one distributor in the country until 2015.^{9,10} And it is still unaffordable for South Africa at US\$ 442 per six month-treatment course.¹¹ Activists contend that it would be life-saving for South Africa to issue a compulsory license for linezolid and import the generic version, especially now that the drug is part of the core regimen in the new WHO DR-TB recommendations.

There is a naiveté in the TB community about industry. We've played nicely, but companies like Pfizer, AstraZeneca, Gilead have abandoned TB anyway.

In conversations with TAGline, activist Marcus Low of South Africa's Treatment Action Campaign points to the dissonance in South Africa's fight for policies to expand access and the government's failure to take the critical step in implementation, particularly for underserved people in areas of the country hit hardest by DR-TB:

That is why I get upset when people say that TRIPS flexibilities are not needed in TB. People with XDR-TB in Khayelitsha who needed linezolid to have a chance at life could not access it for a long time due to the drug's excessively high price, an excessively high price made possible through patent protection. The reason we have TRIPS flexibilities in international law is precisely to help us intervene in such situations.

The Real Work is Only Beginning.

TB advocates should expect the U.S. to remain active in spurning any attempt to expand access to TB medicines well after the TB HLM. Azar doubled down on the U.S. government's position to protect IP in his remarks at the TB HLM on Sept. 26, saying:

But we will not be able to conquer this challenge without new tools. Because we strongly support the development of these new tools, **we cannot cede** ground on intellectual property rights. (emphasis added)

Respect for intellectual property rights is not just an important international legal obligation, but also the very foundation of the innovation economy that we need to fight TB and other deadly diseases.

Unless we are satisfied with today's treatments for TB– and how could we be–we must be vigilant in avoiding any measures that will discourage market actors from developing the therapies of tomorrow.¹²

The TB HLM declaration process reveals how far major international actors will go in the highly contentious policy space of access to medicines. Ultimately, thanks to South Africa's bold resistance, language on access to medicines and TRIPS flexibilities was retained in the final political declaration—a significant win for the global TB community.

But the TB HLM political declaration represents only a single win in the battle with the USTR and U.S. government writ large, on access to medicines for TB. The recent U.S. political dynamic foreshadows the need for strategic, long-term, community-led activism in truly expanding access to medicines in TB.

Now, for TB activists and advocates the real work is only beginning: We must come together to catalyze and sustain the political will to move beyond paper agreements like the TB HLM declaration, pushing governments to use the TRIPS flexibilities to address their own epidemics. But the negotiations between the U.S. and South Africa also revealed stark disagreements among TB advocates on the value of TRIPS for a disease that sees very little innovation and investment in the first place. But it's a fallacy that we can go without provisions to safeguard public health for future TB drugs, vaccines, and diagnostic tools. This is a strategic opportunity for the TB community to work with the A2M activists who have forged political will on these issues for years, rethinking the way we traditionally fund R&D in favor of alternative models that prioritize access from the beginning of drug and regimen development. The U.S. is a critical donor nation in global TB efforts, both in programs and in R&D, forcing many countries to stay silent and concede to the USTR in fear of biting the hand that feeds them. Strengthening our community's understanding about TRIPS flexibilities and access to medicines will enable us to bolster efforts to advance local advocacy, further building the political will necessary to embolden nations to use TRIPS flexibilities, and to better prepare countries to take on U.S. pressure.

TB activists and advocates must remain vigilant, vocal, and proactive. Marcus Low calls on the community, telling TAGline, "In the TB community there are some who think that we shouldn't criticize J&J or Otsuka about unacceptably high prices because that will make them leave the TB field. But companies don't do R&D in TB because we are being nice to them—there are much stronger market forces at play. There is a naiveté in the TB community about industry. We've played nicely, but companies like Pfizer, AstraZeneca, Gilead have abandoned TB anyway."

Under the Trump administration blueprint (and perhaps especially as we head into critical election years), the USTR has made it clear that it will continue to obstruct countries that exercise internationally recognized rights in multiple international policy platforms, many of which will inevitably include TB. TB advocates must be prepared to work with A2M activists to take on the USTR by methodically dismantling the "foreign freeloading" rhetoric, as well as engaging and monitoring future convenings of the World Health Assembly and large trade negotiations. In doing so, we must replace the "innovation" narrative that centers on protecting IP with R&D proposals that catalyze the next generation of tools for TB and prioritize affordable access for the people.

With the TB HLM declaration win as a green light, TB advocates must now hold the South African government accountable to take the critical next step in fully exercising its right to enhance access to affordable TB medicines. The political will must go beyond the HLM; the South African government should also influence other G77 nations to use TRIPS flexibilities and invest in R&D models that prioritize access to TB medicines for their residents. Lastly, country governments must work with community TB activists, already mobilized after the TB HLM, to make Pharma realize and amend its bad behavior. Community activists should further work with governments to explore policy options such as compulsory licenses for TB drugs, vaccines, and diagnostics to secure affordable diagnosis and treatment for their people. Only then will the fight during the TB HLM have been worth it for communities affected by TB.

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FIERCE ACTIVISM FROM THE GLOBAL ACCESS TO MEDICINES (A2M) MOVEMENT: REFLECTIONS ON RECENT SUCCESS

By Bryn Gay, HCV Project Director, TAG

ccess to medicines (A2M) activists have become better coordinated, articulate, and adept in responding to pharmaceutical industry shenanigans that threaten access to affordable medicines since the establishment of harmonized global intellectual property (IP) legislation under the initial 1995 Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), TRIPS-plus free trade

A2M activists, framing grassroots campaigns through a human rights lens, have organized as and with—people living with and affected by infectious diseases.

agreements, and related national policies. Big Pharma's bullying strategies include lobbying and influencing policymakers to adopt stricter IP provisions, threatening countries with lawsuits and trade sanctions for attempting to invoke IP flexibilities, and spouting unfounded propaganda to justify monopolies on medicines. Built on the relentless energy, extensive global networks, and urgent demands of HIV/AIDS activists, the A2M movement has developed and implemented a number of successful strategies to overcome treatment barriers that hold patients hostage to high prices. A2M activists, framing grassroots campaigns through a human rights lens, have organized as—and with—people living with and affected by infectious diseases. Employing a community education and empowerment strategy, A2M activists have strengthened the technical and political knowledge of people at the center of these epidemics on issues such as:

- The technical aspects of filing patent oppositions before or after patents are granted;
- Guidance on what community advisory boards or governments should consider when negotiating medication prices;
- Advocating in favor of compulsory licenses or other mechanisms that promote the generic production of medicines;
- Monitoring the registration and national approvals of medicines under Pharma's voluntary licensing deals; and
- Bringing community perspectives into high-level scientific committees or policy advisory groups.

ranslating this knowledge into action involves the building of allies and partner networks at the national, regional, and international levels. Those efforts gained momentum at two gatherings this year: the <u>Global Summit on</u> <u>Intellectual Property and Access to Medicines</u>¹ in Marrakech, Morocco, and the <u>Community Activist Summit at AIDS 2018</u> in Amsterdam, Netherlands. Participants shared successes of the A2M movement, notably regarding hepatitis C virus (HCV) treatment. Some of the lessons were: Built on the relentless energy, extensive global networks, and urgent demands of HIV/AIDS activists, the A2M movement has implemented successful strategies to overcome barriers that hold patients hostage to high prices.

- Establishing strong, persistent relationships with health and trade officials, and providing them with data and evidence-based policies, contributed to decisions to use IP flexibilities. For example, Malaysian activists conducted a multiyear campaign to urge the Ministry of Health to invoke a compulsory license on sofosbuvir, opening up generic access to the HCV cure.
- Engagement of overlooked stakeholders can open up new treatment access strategies. For instance, activists were involved in sensitizing patent reviewers to public health concerns in patent filings; one Egyptian patent reviewer was responsible for rejecting the patent on sofosbuvir, which resulted in over 1.6 million people in Egypt receiving treatment since 2014.²
- Campaign planning and policy-making can and must include marginalized voices, including women, LGBTQ+ folks, patients, youths, migrants, people of color, and people who use drugs. Fostering the leadership of members of these groups also is crucial. Both summits centered marginalized voices and were structured to foster new leadership.

Participants reflected on potential pathways to overturning Pharma's cartelization and price-gouging of medicines, such as:

 A People's Pharmacy, a community-driven overhaul of how we currently prioritize, finance, develop, price, distribute, and monitor uptake of life-saving medicines. By de-commoditizing medicines, the People's Pharmacy would reclaim them as common goods so that everyone who needs treatment can share and benefit from them.

- NASA for drug development is a model in which a government-led and -funded research and development agenda, responsive to public health needs, reclaims patent ownership and subcontracts aspects of the drug pipeline to private firms, universities, or research collectives.
- International human rights courts could hold Pharma accountable, hearing legal cases of human rights violations when patients are unable to access drugs due to IP barriers.
- Long-term patent reforms could include strengthening the patentability criteria and review process to avoid abuse of the patent system and granting of unmerited patents on "me too" drugs; allowing the public to attend patent granting decisions and expanding the community's role in challenging patents; and shortening the length of patent life.³

The next phase of treatment activism will require sustainable financing for a community-led donor agenda, training and mentoring among a new generation of activists, technical capacity building and political education among advocates across disease areas (including in fields of noncommunicable diseases), and regular opportunities to exchange lessons and experiences within and between the global South and North.

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GETTING RID OF THE BOOGEYMAN: THE REALITY OF PRESCRIPTION DRUG PRICE CONTROLS

By Annette Gaudino, HCV/HIV Project Co-Director, TAG

Do you remember how old you were when you stopped believing in the monster under your bed? How many times did you have to look and see nothing there before you finally believed the danger wasn't real? In the United States, the fear that price controls would irrevocably harm the prescription drug development pipeline is used to frighten Americans away from systemic change. But once you look under the bed—at the assumptions underlying that belief, up against real-world evidence—there is no rational basis for this fear, and the threat of the boogeyman can be put to rest. Here's why:

Negotiating for your life is a hostage situation, not a free market.

Price Controls Already Exist in the Real World

The specter of price control is framed by the pharmaceutical lobby as an artificial interference in the otherwise natural and smooth functioning of markets. But the power to say no, to walk away from a negotiation, is the most rudimentary form of price control, and it is built into any true market. If we determine that something just isn't worth the asking price, we can walk away. Of course, this is nonsense to anyone who depends on an essential medicine for their very life. Negotiating for your life is a hostage situation, not a free market.

Setting aside the terms of the debate, direct price controls on essential medicines exist in the real world, specifically in all high-income countries, with one exception: The U.S. is the outlier in letting manufacturers set prices, virtually without constraint. The industry campaign to demonize price controls is designed to keep the U.S. an outlier and to block any attempts to grant negotiating power to public payers such as Medicare. The Department of Health and Human Services' drug pricing blueprint, <u>American Patients First</u>,¹ frames the issue exactly as any pharmaceutical industry lobbyist would: "Every time one country demands a lower price, it leads to a lower reference price used by other countries."

In other words, a threat to profits anywhere is a threat to profits everywhere.

But what do price controls actually look like in other countries? Germany provides a fascinating example for the U.S. Similar to the Affordable Care Act (ACA) before the individual mandate penalty was repealed Germans are required to buy health insurance (with 80 percent of Germans choosing the public national health insurance plan), and premiums are subsidized for those with low incomes. And as in the marketplace plans created under the current form of the ACA, coverage for a package of essential benefits is required, with no denials based on pre-existing conditions. Insurance firms compete on customer service, add-on coverage, and to some extent, price. But unlike in the U.S., healthcare plans in Germany are not-for-profit, and their executives have no fiduciary responsibility to deliver returns to investors.

The German system allows pharmaceutical manufacturers to sell any approved product at any price for up to two years without coverage under the national plan. During this period, data on clinical efficacy in the real world is collected and analyzed in comparison with treatments already covered under the national insurance system. At the end of the period, the government offers the manufacturer a price for purchase and coverage by the public system, informed by comparative data and the price of existing treatments for the same condition. The German approach thus solves three real problems: It incentivizes medicine development through both quick return on investment and a guaranteed revenue for truly effective treatments; it generates real-world comparative data to inform clinical decision-making; and it provides distinct, data-based constraints on total health spending.

The Big Lie: Big Pharma Isn't Making Enough Money

Fear of the price-control boogeyman rests on the belief that corporate profits are necessary to fund essential medical and scientific innovation. If unfettered corporate profits are necessary for lifesaving medicines, then why not argue that current profits are too low? Once again, American Patients First does just that:

The loss of patent exclusivity on successful products, new ACA taxes, and requirements to extend higher rebates and discounts to a markedly increased Medicaid and 340B population created an estimated \$200 billion of downward pressure on pharmaceutical industry revenues [emphasis added]-during a five-year period when innovation was decreasing. International price controls and delayed global product launches exacerbated the problem.

This unsourced claim is easily refuted: **Profit margins in the pharmaceutical industry dwarf all other sectors.**

According to the <u>U.S. Government Accountability Office</u>,² the 25 largest pharmaceutical companies have profit margins of 15%-20%, compared with 4%-9% for the global top 500 companies in other industries, with pharmaceutical sector revenues increasing \$241 billion from 2006 to 2015. Sales revenues for a single company (Gilead Sciences) for a single drug class (direct acting antivirals–or DAAs–for hepatitis C) were \$57 billion over the past five years. Total worldwide revenues for all DAAs since 2014 are estimated at over \$66 billion, which has bought us treatment for only <u>5 percent of the estimated 71 million people living with chronic hepatitis</u> <u>C worldwide</u>.³ For the amount we've handed over to DAA brand manufacturers, we could purchase generics to treat those waiting to be cured–twice over.

In 2015, a U.S. Senate Finance Committee investigation on pharmaceutical pricing practices revealed an internal Gilead email discussion on the company's recently acquired DAA sofosbuvir (brand name Sovaldi) in which Gilead executives discussed setting the launch price to establish a new benchmark for this class of treatments (and therefore future products) with no link to already incurred development expenses. These executives demonstrated what access to medicines activists had argued all along: There is little to no link between essential medicine drug pricing and the cost of their actual development and manufacturing.

Demand Drives Development

Demand, as defined by commitment from purchasers to generate revenue sufficient to justify the initial investment, is the true driver of invention, innovation, and access. This is seen most clearly with generic manufacturers: The market must be big enough to generate profit from the investment required to retool manufacturing equipment, purchase active pharmaceutical ingredients, and create a supply chain.



But it can also be seen in the development of new agents. A recent study by Amy Finkelstein, an MIT economist, found an increase in clinical trials for new vaccines in the U.S. after Medicare committed to paying for vaccination, guaranteeing a return on investment for approved vaccines. This shift included a 2.5-fold increase in clinical trials for new flu vaccines since Medicare extended coverage to vaccines in 2005.

Fake Problems, Fake Solutions

Solutions to problems that don't exist aren't solutions. The debate over U.S. prescription drug pricing policy is

KEEPING AN EYE ON INTELLECTUAL PROPERTY ISSUES IN HIV CURE AND PREVENTION RESEARCH

By Richard Jefferys, Basic Science, Vaccines, and Cure Project Director, TAG

The history of antiretroviral (ARV) drug development offers many examples of compounds that were originally discovered and investigated by publicly funded academic researchers, before being acquired and ushered to market by pharmaceutical companies. Among them is azidothymidine (AZT), the first approved ARV, which was synthesized in the 1960s and then shown to have activity against retroviruses in a preclinical mouse study in 1974. The drug was ultimately patented by Burroughs Wellcome, which notoriously attempted to charge an outrageous price when it was green-lit by the U.S. Food and Drug Administration (FDA) as an HIV therapy. It took a nowlegendary ACT UP protest at the New York Stock Exchange to force the company to back down and cut the price by 20 percent.

In HIV cure research, the current prospects for FDA approval –and the pathway toward it–are far less clear than those of ARV candidates. For non-ARV-based biomedical prevention approaches, such as passive immunotherapy with broadly neutralizing antibodies (bNAbs) and vaccines, there is at least clarity regarding what efficacy would look like (a high level of protection against HIV acquisition), but as yet no candidate has shown a level of success sufficient to be considered for approval.

Despite these uncertainties, pharmaceutical and biotech companies have been acquiring rights to some experimental cure and prevention candidates. Examples include several bNAbs, which are being tested for both therapeutic and preventive potential. These types of license acquisitions should not be assumed to be a bad thing; there can be both upsides and downsides. Pharmaceutical and biotech companies are more likely to have the resources and expertise to facilitate large-scale manufacturing and clinical evaluation compared with academic researchers. But, as is seen in ARV drug development, companies can also be reluctant to make their proprietary compounds available for studies in which they would be combined with candidates owned by others. In the event that a candidate achieves sufficient success to gain FDA approval, the price issue will also loom large. As exemplified by the AZT protests, advocates have long pointed out the injustice of excessive, access-limiting profiteering on treatments developed with public support.

or these reasons, it is worth keeping an eye on the ownership of candidates as they progress through the cure and biomedical prevention pipelines. Here are two recent examples:

- PGT121 is a bNAb identified by academic researchers supported by the International AIDS Vaccine Initiative (IAVI) in collaboration with the biotech company Theraclone Sciences. While IAVI's focus is on prevention (and typically involves negotiating agreements designed to secure affordable access if a product is developed), an exclusive license to develop and commercialize PGT121 for therapeutic use-potentially along with other bNAbs discovered using the same technologywas granted to Gilead Sciences in an agreement with Theraclone in 2014. Based on encouraging results in macaques infected with simian immunodeficiency virus, Gilead plans to partner a PGT121 derivative dubbed GS-9722 with vesatolimod, a compound the company developed that modulates immunity by interacting with toll-like receptor 7.
- The bNAb N6 was isolated by researchers from the National Institute of Allergy and Infectious Diseases at the National Institutes of Health (NIH). Commercial licensing of discoveries at NIH follows an established process involving their Office of Technology Transfer; in the case of N6, an announcement was made in the Federal Register in November 2017 explaining that a license to GlaxoSmithKline was being considered. The parties are now negotiating the agreement.

PHARMA LIES, PEOPLE DIE: MYTH-BUSTING FACT SHEET ON MEDICINE DEVELOPMENT AND PRICING

By Bryn Gay, HCV Project Director, TAG and Claudine Guerra, CUNY

The current leaders of the United States manufacture crises, media optics, and catchy sound bites to side step actual responsibility for tackling immensely complex policy issues like extortionately high prescription drug prices. The <u>American</u> <u>Patients First</u> napkin sketch from the Trump administration draws from the Pharmaceutical Research and Manufacturers of America (PhRMA) playbook to spread unfounded myths, deflect blame from companies for price-gouging hijinks, and posit countries that implement price control mechanisms or intellectual property (IP) flexibilities as scapegoats for the U.S.'s dysfunctional pricing schemes. These antics leave patients without access to critical life-saving treatments and diagnostics while bankrupting Americans and payor systems.

Healthcare and treatment activists have become more wellversed and more coordinated in calling out Pharma lies; with coherent messaging, we can continue to expose the flimsy arguments for stronger IP protection on medicines and monopolistic high pricing, building political momentum toward the systemic policy changes we need. The following fact sheet aims to bust the most common myths spouted by Big Pharma:



Myth: Other countries and manufacturers of generics are "free riders" on U.S. Innovation.

Fact: The free rider argument claims that Americans pay more on research and development (R&D) than people in other countries. There is no evidence to support this claim, and other high-income countries (HICs), such as those in the UK and in Europe, show proportionately equal gross domestic expenditure on R&D (GERD) to the U.S. Furthermore, Pharma still makes substantial profits selling the same medicines for much lower prices in other HICs.



Myth: Paying high drug costs in the U.S. translates into a higher quality of life and increased longevity.

Fact: The U.S. pays the highest prices for medicines in the world; in one 2016 study, the U.S. paid an estimated per capita cost of US\$1,443, compared with a range of US\$466-US\$939 per capita in other HICs. Yet we perform worse on many population health outcomes (including life expectancy) than 10 other HICs. Without federal laws and regulations on medicine prices, Pharma can game the patent and pricing systems in the U.S. Alternatively, other HICs such as Germany and the UK use price review mechanisms and a central negotiating authority. European health systems negotiate medicine prices directly, even refusing to pay excessive prices. But U.S. Medicare, accounting for <u>29 percent</u> of all U.S. spending on prescription medications, still lacks the authority to negotiate prices (see "Getting Rid of the Boogeyman: the Reality of Prescription Drug Price Controls," page10).



Myth: Pharmaceutical companies and their industry groups are working with governments to support greater drug access.

Fact: Rather than empowering Medicare Part D to negotiate better prices in the U.S., PhRMA and other lobbyists have shifted focus to countries' lower prices due to use of price controls or policy mechanisms that promote generic competition, such as those enshrined in the TRIPS Agreement. The pharmaceutical lobby has influenced the office of the U.S. Trade Representative (USTR) to <u>bully countries</u> into not using TRIPS flexibilities, such as government use licenses, resulting in USTR's threats to place non-compliant countries on its trade watch list, which brings potential penalties, trade sanctions, and loss of economic incentives.



Myth: The estimated cost to develop a single new drug from laboratory to pharmacy shelves is US\$2.6 billion. Thus, high drug prices are needed to finance R&D and innovation.

Fact: Pharma's prices are chosen to maximize profits and are not based solely, or at all, on R&D costs. By some estimates, U.S. Pharma directs less than 8 percent from sales to R&D.

This oft-cited \$2.6 billion figure comes from a problematic study by the Tufts Center for the Study of Drug Development. In keeping with the lack of transparency in companies' actual expenditures on R&D, it does not provide details on the drugs included in the analysis, nor the sample size, nor the costs per patient included in the trials. It also doesn't include the National Institutes of Health (NIH) funding that went into preclinical drug development. The inflated number is a combination of what Tufts spent on the drug that was approved and money spent on projects that failed.

Median clinical trial costs are more likely US\$19 million. The Drugs for Neglected Diseases Initiative uses an alternative model of drug development that's even lower in cost. It has reduced overhead through in-kind contributions, pro bono work by scientists, pooled data and libraries, and smaller, faster clinical trials. Thus, combination therapies could be developed for US\$10-\$45 million; novel drugs from scratch could require just US\$110-\$170 million in R&D, including the cost of failed therapies.



Myth: Medicines are expensive to develop, so they need to have a high price to cover that investment.

Fact: Medicines are expensive to develop, but R&D costs are exaggerated or undisclosed by Pharma. A concept called delinkage shows the usefulness of separating medicine prices from the cost of manufacturing and investments to R&D, if what we really want to do is ensure affordable access: Calculations for generic production costs of 148 medicines on the World Health Organization Essential Medicines List range between US\$0.01 to US\$1.45 per tablet, versus the tens of thousands of dollars that payors and/or patients currently pay. For example, a 12-week course of sofosbuvir/ledipasvir can be produced for less than US\$100, including a 10 percent profit margin. Medicine prices do not reflect the true cost of R&D.



Myth: Pharma needs long-term patents that exclude generics from the market for decades so they can make back their investments in drug development. Fact: R&D costs, plus substantial profits, are most often recovered from sales within the first few years on the market. From 2012 to 2014, Gilead Sciences's R&D costs for sofosbuvir-based regimens were estimated to be US\$880.3 million. Since 2014, global sales amount to over US\$50 billion, recouping R&D costs 57 times over. In fact, the profits of the largest pharmaceutical corporations are more than double the average of the other Fortune 500 corporations.

Pharma maintains domestic sales profits that exceed R&D costs. For example, in Canada, members of the Innovative Medicines Canada consortium showed domestic profits of US\$15.6 billion–20 times higher than R&D costs (US\$769.9 million, or a 4.9 percent R&D-to-sales ratio).



Myth: Pharma drives innovation through its R&D investments.

Fact: Governments and private philanthropy, not Pharma, drive innovation, particularly in the earlier and riskier stages of R&D. Governments and private philanthropic nonprofit organizations together fund over 40 percent in overall R&D costs, especially in basic science. Pharma then privatizes that work under patent protection, thereby cornering market exclusivity for a medicine for 20 years or longer. In this way, U.S. taxpayers pay twice for patented (originator) medicines: first in the form of government-collected taxes that fund research, and second through payor systems procuring these medicines.

And innovation isn't valuable if it doesn't result in useful treatments. Instead of allocating funds for rare and neglected diseases, Pharma pours profits into marketing, lobbying, legal settlements, stock buybacks, and the creation of "me too" medicines that demonstrate little additional clinical benefit, even if these strategies may innovate how to game capitalism. These practices privatize the benefits of innovation at cost to the public, whereby patients are denied access to affordable medicines and all of society faces higher long-term healthcare costs.



Myth: Stronger patents on medicines protect innovation and prevent the theft of ideas.

Fact: The history of medical progress is filled with examples (like the polio vaccine) of medicines that were developed outside the patent system with the support of public funding. Patents on medicines prevent generic competition, which would dramatically reduce medicine prices. Generic competition dropped the price of HIV antiretrovirals by at least 90 percent.

Moreover, a troubling trend in free-trade agreements, including the renegotiated United States-Mexico-Canada Agreement/North American Free Trade Agreement, is to include TRIPS-plus provisions—those that exceed requirements under the multilateral TRIPS Agreement—that would prolong the monopolies on medicines or undermine countries' ability to set their own patentability criteria.

Data exclusivity under these agreements prevents generic manufacturers from obtaining data on test results for their own studies to show that a medicine is safe and effective. Instead, they must reproduce expensive, time-consuming clinical trials or simply wait longer to introduce their competitor medicine; this delays their ability to bring generic versions to market.

Patent monopolies-defended as incentives for stimulating innovation-actually discourage new ideas because of restrictions on sharing information and the hindrance of access to research. Instead, an open and collaborative approach to biomedical R&D, employing lessons from software development, could accelerate scientific innovation.



Myth: The current drug development model will lead to new medicines for rare and neglected diseases, which are pressing matters in public health.

Fact: Pharma directs very little of its R&D funds to addressing rare and neglected diseases. During 2000-2011, only four percent of new medicines and one percent of R&D dollars were for neglected diseases. One model examined 538 candidates for neglected diseases and found significant annual funding gaps—at least US\$1.5-\$2 billion—over the next five years. Instead, to make a larger profit, Pharma opts to develop "me too" drugs, or identical copies of existing medicines, as well as drugs for non-life-threatening conditions, such as male-pattern baldness, that appeal to consumers in high-income contexts.



Myth: U.S. drug prices may be high, but they don't actually affect access because payors will cover the costs.

Fact: Extortionate prices contribute to decisions by payors (i.e., public health systems, insurance companies) to restrict or ration treatments, such as direct-acting antivirals. States are then forced to ration these drugs to people living with hepatitis C, which could lead to advanced liver disease and liver cancer. In the U.S., most people living with hepatitis C are on Medicaid or uninsured, and the majority of states restrict

treatment according to stage of liver disease, prescriber status, or sobriety requirements. This has resulted in a lack of treatment for 85 percent of people diagnosed with hepatitis C virus in the U.S.



Myth: Pharma rebates will reduce price and lower out-of-pocket costs.

Fact: Pharma rebates are already calculated in the inflated price as a markup. In order to obtain medicines, health systems (through the Centers for Medicare and Medicaid Services and insurance companies) must pay a huge portion of the list prices. Back-end rebates keep pharmacy prices high, and uninsured and insured patients who are vulnerable to high coinsurance rates experience increasing out-of-pocket costs.



Myth: U.S. patient assistance programs cover the price of medicines and address gaps in access.

Fact: Pharma's patient assistance programs enable companies to pass the blame on to insurance companies and do not address root causes of high drug prices. These programs can impose caps, place limits on grants, and require cumbersome application processes. In the case of Truvada for HIV pre-exposure prophylaxis (PrEP), people without healthcare coverage must earn less than 500 percent of the federal poverty level, or US\$60,700 for a single-family household, to be eligible for medication assistance programs. Programs may also exclude out-of-pocket costs, such as blood work, that are necessary for monitoring the treatment itself. In the U.S., people using private insurance may have to pay thousands of dollars out of pocket after the co-pay assistance runs out (see TAGline Spring 2016). Gilead's PrEP co-pay assistance recently increased from US\$4,800 to US\$7,200 per year thanks to community advocacy. It now covers nearly the maximum out-of-pocket cost allowed under the Affordable Care Act for an individual (but not family) plan, potentially mitigating the high cost of Truvada (which averages US\$1,600 per month). However, few patients are aware of the program, and some insurers no longer allow the co-pay card to count toward deductibles. Reducing the price and challenging Truvada's unmerited patents would expand affordable access and avoid treatment disruption, particularly among lower-income patients.

A PHARMA VIEW ON DELINKAGE AND NEW MODELS FOR BIOMEDICAL INNOVATION: AN INTERVIEW WITH MARC DESTITO FROM OTSUKA PHARMACEUTICAL

By Mike Frick and Lindsay McKenna, TB Project Co-Directors, TAG

n an interview with TAG's Tuberculosis (TB) Project, Marc Destito, Senior Director of Public Affairs and Global Alliance Management at Otsuka Pharmaceutical, provides insight into how the development of TB drug delamanid moved the company closer to the principle of delinkage, an approach to biomedical innovation that aspires to separate research and development (R&D) costs from final product prices and volume of sales. Delinkage requires moving beyond traditional approaches of incentivizing R&D that rely on high prices and the temporary monopolies afforded by patents. Although recommended by the 2016 report of the United Nations Secretary-General's High-Level Panel on Access to Medicines and endorsed in several World Health Organization (WHO) and UN declarations and resolutions, delinkage became a flashpoint during negotiations for the recent UN High-Level Meeting on TB. (see <u>Beyond Declarations</u>, page 3) Some countries and blocs of UN member states sought to remove the term from the draft political declaration, and others tried to water down its meaning. Behind these efforts was the influence of the pharmaceutical industry.

The pharmaceutical industry often attempts to justify high drug prices and patent-protected monopolies on medicines by citing the need to recoup investments in R&D. (see Myths, page 13) This narrative is especially indefensible in TB, where innovation is scarce and over 60 percent of funding for R&D comes from the public sector. In this interview with TAGline, Destito reflects on how Otsuka has approached the concept of delinkage with respect to delamanid, first approved for the treatment of multidrug-resistant TB (MDR-TB) in 2014. Destito acknowledges that Otsuka may be using the term delinkage in a way that differs from how its proponents have defined it. This is partly because at the outset of delamanid's development, many of the innovative financing mechanisms and incentives that delinkage requires were not available or had not yet been imagined. Our intent with this interview is to initiate a dialogue with the largest private-sector funder of TB research on the future of financing TB drug and drug regimen development, including the potential for pharmaceutical companies to replace or improve current R&D incentives with needs-driven strategies that promote the availability, affordability, and appropriate use of medicines. We hope this conversation becomes the first of a series on what delinkage means to different stakeholders involved in TB R&D.

This interview, which was conducted over email, has been lightly edited for clarity and length.

TAG: Otsuka is best known for aripiprazole (Abilify), a drug used to treat depression. Delamanid represents Otsuka's first foray into developing a product for the global public health market. Why did Otsuka decide to invest in TB and the compound delamanid, in particular?

MD: The decision to invest in TB was driven almost entirely by the sheer willpower of one person: Otsuka's late Chairman Akihiko Otsuka. He was very passionate about TB, having seen the devastating effects of TB in Asia firsthand. He felt there was a huge unmet medical need for new therapeutic options that were effective with better safety profiles than existing medications. Whereas many companies might have been deterred by the cost of development or the financial risks associated with investing in a neglected disease area like TB, he felt these challenges could be overcome and saw contributing innovation to an area that was underserved by other companies as central to Otsuka's mission and philosophy. "In a way, Otsuka has already demonstrated the concept of delinkage, though perhaps not as it is usually defined. What I mean is that there is no expectation that sales revenues from delamanid could ever recoup the \$522 million that was spent over the life of the project." - Marc Destito

TAG: Did receipt of any public or other financial incentives (e.g., tax breaks, regulatory rewards) play a role in Otsuka's decision to invest in this area?

MD: No. At the time that Mr. Otsuka made the decision to start investing in TB R&D back in the early 1970s, there were very few, if any, public financing or regulatory incentive programs available, and I don't think that was ever a consideration for the company.

TAG: According to data provided to TAG, Otsuka is the largest private-sector funder of TB research, spending \$522 million from 2005 to 2017. How does Otsuka think of these investments in relation to both the volume of delamanid it expects to sell and the price of delamanid?

MD: I don't think the two are related. In a way, Otsuka has already demonstrated the concept of delinkage, though perhaps not as it is usually defined. What I mean is that there is no expectation that sales revenues from delamanid could ever recoup the \$522 million that was spent over the life of the project. I think the goal—and the directive from Otsuka headquarters—is to ensure that efforts moving forward, including R&D for the new [TB] compound OPC-167832, are covered using a combination of delamanid revenues, innovative financing mechanisms, collaborations with public, private, and nonprofit entities, and other potential incentives that were not available when delamanid was being developed. Spending another \$522 million just won't work.

At that time, Mr. Otsuka was willing to invest whatever it took to achieve his dream. Today, the company recognizes funding that level of development without the ability to recoup is highly inefficient and threatens the long-term financial sustainability of the TB project. With increasing regulatory and development costs, the price of following the same approach is probably even higher today. Certainly some of the revenues from delamanid will be re-invested into R&D for OPC-167832 and other TB products including diagnostics, but it will not be enough. Otsuka will need to work much more closely with other partners in the TB community and leverage other financing mechanisms. Collaboration very early in the development process is critical and something that was, frankly, not well utilized by Otsuka during delamanid development.

TAG: Given the above considerations, how did Otsuka determine the current price of delamanid?

MD: As mentioned, Otsuka "delinked" R&D from the price of delamanid quite early on. The current price of delamanid [US\$1,700 for a six-month treatment course in low- and middle-income countries; at least US\$30,900 in high-income countries] was driven by the current cost of goods for the product.

[Note from TAG: this may be true for the price offered to low- and middle-income countries at current volumes, which are low, and with manufacturing taking place in Japan].

Unfortunately, delamanid is rather expensive to manufacture compared to other anti-TB medicines. Without going into too many technical details, it requires utilizing spray-dry technology and is reactive to oxygen, meaning it requires nitrogen compression in double aluminum blisters—all of which drive up the cost.

That said, Otsuka is aware that the cost of delamanid is not in line with global expectations for what the ideal MDR-TB regimen should cost, and several activities have been ongoing for more than a year now to reduce manufacturing costs and thereby price. This has included initiating technology "Otsuka is aware that the cost of delamanid is not in line with global expectations for what the ideal MDR-TB regimen should cost, and several activities have been ongoing for more than a year now to reduce manufacturing costs and thereby price." – Marc Destito

transfer with our license partners, Mylan and R-Pharm, and the possibility of local manufacturing of delamanid in India. This process has started, and we're optimistic that at least part of the tech transfer can be completed in 2019.

TAG: What steps is Otsuka taking to further reduce the price of delamanid in line with calls from civil society for an all-oral regimen to treat drug-resistant TB that costs no more than US\$500? Estimates by Andrew Hill and colleagues indicate that delamanid could be produced for as little as \$5-\$16 per person per month, including a 10 percent profit margin.

MD: The estimations made by Hill and colleagues are not supported by the data or real-world experience, particularly without having access to key technical information and manufacturing processes that only the companies maintain.

[Note from TAG: Evidence-based refutations of Hill's work would require companies such as Otsuka to make transparent drug development and manufacturing costs.]

That said, the current price of delamanid needs to be reduced to encourage scale-up and meet international expectations for an affordable fully oral regimen.

While pricing is an issue that will be addressed, I don't believe that price is the biggest barrier to access right now. We continue to see regulatory challenges in several countries, lack of health system capacity to introduce new innovations, and lack of supportive global and national policy guidance. Even in countries where delamanid is available for free under access programs designed to spur scale-up, uptake is incredibly small and doesn't correspond with actual need. There is also a fair amount of donor funding that is available to high-burden countries, and it's disheartening when some of these funds are left on the table every year. [Note from TAG: To a significant extent, health systems respond to depth and quality of evidence, availability of compassionate use and preapproval access programs, timeliness and geographical reach of regulatory submissions, and other factors when seeking to introduce new interventions. At the same time, many health systems struggle to introduce new technologies for reasons that are outside of pharmaceutical company control.]

TAG: You argue that Otsuka has applied delinkage and is supportive of this principle. Can you further elaborate?

MD: [We've] delinked in the sense that there is no expectation that price or volumes [of delamanid sales] could ever be able to recover the over half a billion dollars that the company has invested in TB R&D over the life of the project. I think this is something very important for other actors in this space to consider moving forward. Even when developing medicines for neglected diseases like TB, which predominantly affect low- and middle-income countries, developers cannot cut corners when it comes to R&D, quality, compliance, pharmacovigilance, and regulatory processes. Developing new medicines that meet the requirements of stringent regulatory authorities still requires costly phase 2 and 3 trials-particularly as these regulatory requirements only seem to increase year after year. Registration fees and regulatory maintenance fees-including for WHO pregualification-are incredibly expensive, particularly when a company is expected to register a medicine in all countries around the world. So if development costs continue increasing but the commercial potential in neglected diseases remains limited, clearly you have an untenable situation which requires a delinked approach that does not rely on traditional marketbased incentive structures for R&D.

TAG: Based on your experience working on Otsuka's delamanid development and access program, what is the role of public and philanthropic funders in incentivizing private-sector involvement in TB research and development?

MD: There is clearly a large role for public and private funders at every stage of the development process. Very often we consider that funding is needed on the R&D side, and it is, but funding is also required to assure appropriate introduction and scale-up of new medicines. Demonstrating a viable market for neglected diseases is critical—otherwise innovator companies have no incentive to develop them in the first place. And unfortunately, what we have seen in TB is that there is often a dysfunctional market where there is not automatic uptake of new innovations the way some companies might expect. That's where I think international funding can play a larger role: to ensure that there is funding and technical support in place for countries to successfully adopt new medicines and demonstrate demand.

TAG: How has the experience developing delamanid changed the way Otsuka is approaching investments in other TB compounds, such as OPC-167832?

MD: Clearly there is an understanding that Otsuka cannot approach the development of OPC-167832 in the same way as delamanid or spend the same amount of in-house financing which is simply not available. The sheer size of the Otsuka investment documented by TAG probably gives other companies pause. It does not incentivize other companies or meet Mr. Otsuka's vision of a self-sustainable public health project. That's why from the very beginning [of OPC-167832's development], we began discussions with partners to see how we could work together. Luckily, there was tremendous interest in exploring development of OPC-167832 in combination with other novel compounds in the hopes of developing a future pan-TB regimen. We have a long way to go but are progressing quickly and have already begun a phase 1b/2a study in South Africa using an innovative approach to speed up the development timeline. In short, I think the biggest lesson learned from delamanid is that Otsuka cannot afford (literally and figuratively) to "go it alone" with the development of its second compound.

TAG: Recent years have seen many calls for "innovative models" for financing and incentivizing R&D for diseases like TB where traditional incentives alone may not be strong enough to attract sufficient, sustained investment from the pharmaceutical industry. Are there any proposals for innovative financing models that you think could work particularly well for TB drug development (e.g., the Life Prize, a product-development partnership model, or something else)?

MD: I think there are a number of interesting approaches that have been discussed, including the Life Prize, which, if it can be implemented, would certainly help attract more innovation. At the same time, I think governments can play a key role to ensure adequate financing and incentives. On the incentive side, the priority review voucher in the U.S. has been important for some companies, and this could be expanded in other regions. Another proposal, called a transferrable exclusivity voucher, gives additional exclusivity on any other product in a company's portfolio and is viewed favorably within the industry.

[Note from TAG: Proponents of delinkage generally do not support incentives based on transferrable exclusivity and have identified serious flaws in the current design of the U.S. Food and Drug Administration priority review voucher program.]

Besides incentives, governments need to work collectively to commit a lot more funding to support health system strengthening, capacity building and other market-shaping activities that support rapid uptake—either through the Global Fund or another type of grant delivery vehicle. The [UN] High-Level Meeting [on TB] presented a great opportunity to spur this kind of creative thinking and multilateral cooperation. The challenge is that, apart from the priority review voucher, we have yet to see a number of these innovative models working in practice with concrete examples to draw from, so I think it's important that the community move beyond the conceptual stage into actual implementation of these incentives. Once it's been demonstrated how developers can benefit from innovative models, the innovations themselves will follow rapidly.

Continued from page 11

constrained by the false belief that direct price controls would threaten the supply of new, effective medicines. This belief rests on the false claim that low revenue is a problem; therefore, only a system that maximizes revenue throughout the supply chain can deliver the essential medicines we need.

In addition to solving the affordability problem that restricts treatment access, we should be working to solve other real problems in medicine development. These include the lack of competitive clinical effectiveness research—head-to-head clinical trials that compare new medicines to existing treatments—and the need to invest in treatment for diseases that affect poor people and poor countries, rather than "me too" medicines chasing proven lucrative markets.

Looking under the bed and seeing there's no monster there allows us to seek bold solutions for pharmaceutical development, rather than being held hostage by the industry's legally sanctioned greed and fear-mongering.

Endnotes

- 1. Department of Health and Human Services (U.S.). American Patients First: the Trump administration's blueprint to lower drug prices and reduce out-of-pocket costs. 2018 May. <u>https://www.hhs.gov/sites/default/files/AmericanPatientsFirst.pdf</u>
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ABOUT TAG

Treatment Action Group (TAG) is an independent, activist and community-based research and policy think tank fighting for better treatment, prevention, a vaccine, and a cure for HIV, tuberculosis, and hepatitis C virus.

TAG works to ensure that all people with HIV, TB, or HCV receive lifesaving treatment, care, and information.

We are science-based treatment activists working to expand and accelerate vital research and effective community engagement with research and policy institutions.

TAG catalyzes open collective action by all affected communities, scientists, and policy makers to end HIV, TB, and HCV.



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