GLOBAL MEDICINES COUNCIL

Briefing Paper No 1

INAUGURAL MEETING
APRIL 2017

FLORIDA USA

Global Medicines Council Briefing Paper No 1

Inaugural Meeting April 2017

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Table of Contents

About this document

This Briefing Paper No 1 was compiled and edited by Frederick M. Abbott based on presentations and other contributions from participants at the inaugural meeting of the Global Medicines Council in Tallahassee, Florida, USA on April 14-15, 2017. Additional contributions were made by individual participants in respect to the presentations associated with them, and the document was reviewed by the participants.

April 14-15, 2017
Florida Meeting Participants

Bottom Row: Jamie Love, Dilip Shah, Fred Abbott, Jicui Dong

Middle Row: Xavier Seuba, Nick Drager, Joe Fortunak, Jerry Reichman

Top Row: Ryan Abbott, Jorge Bermudez, Erin O'Connor

Global Medicines Council First Briefing Paper

1. Introduction

On April 14-15, 2017, a small group with expertise in the pharmaceutical sector met in Tallahassee, Florida. A result of this meeting was a decision to constitute a group of experts as the Global Medicines Council. The idea behind the Global Medicines Council ("Council") is to provide research and support for initiatives to improve the provision of safe and effective medicines to individuals around the world, and to promote patient-centric development of innovative therapies.

An important characteristic of the Council is the multidisciplinary background of its member-advisors, including public health specialists, physicians, pharmacists, pharmaceutical engineers, business leaders, lawyers and academic researchers. Each of the advisors has substantial experience involving the pharmaceutical sector, and the group shares the goal of universal access to medicines.

There are two principal objectives of a well-functioning system for the development and supply of medicines. First, scientific research must be promoted so that vaccines and treatments taking advantage of the latest technologies are developed. Second, the medicines resulting from these efforts must be made available to the individuals who need them regardless of their economic status. Governments have an obligation to provide adequate healthcare to those residing within their countries. Accessible medicines are necessary to fulfill that obligation.

The principal mechanism presently used to develop and provide new medicines relies on grants of market exclusivity to innovators while allowing prices to be set in a non-competitive manner. Although the predominant model allows for the aggregation of capital for investment in R&D, non-competitive pricing for products creates distortions that are contrary to the objective of providing universal access to medicines.

It is critical to move toward improved mechanisms for R&D and supply of medicines. Among approaches is separating or "delinking" R&D from medicines production and supply. If production and supply are undertaken on a competitive market basis, the price of medicines should be low. However, alternative mechanisms for aggregating and allocating R&D capital will be needed. This is the principal challenge to deployment of the delinkage model.

Today, perhaps US$150 billion total is spent worldwide on new pharmaceutical product R&D, through a combination of private sector and public sector investment. Perhaps two thirds of the total comes from private sector funding, largely based on investments by heavily capitalized publicly traded companies. Of the approximately $1.2 trillion annual global revenues from sales of pharmaceutical products, about $900 million is returned to those heavily capitalized publicly traded companies, in aggregate. The remainder goes to the generics.

Inaugural Meeting:

The meeting included presentations and discussion on various issues, including:

1. The results of the work of the UN Secretary General's High Level Panel on Access to Medicines (HLP) and the Lancet Commission on Essential Medicines.

2. Discussion of barriers to effective use of defensive measures such as government use and compulsory licensing.

3. The basis for and potential mechanics of delinkage models.

4. The use of local production as a means to promote public health objectives.

5. A new models for R&D based on the concept of a neutral fund-allocating hub.

6. The possibilities for creating repositories of biological resource materials for access by researchers.

7. Challenges presented by a new wave of regulatory barriers, in particular those directed toward biologic medicines.

8. Using private causes of action within administrative processes to challenge improvident approvals and grants of exclusivity.

9. Use of competition law to prevent and redress abuses of market power.

Dr. Jorge Bermudez introduces the work of the United Nations Secretary General's High Level Panel on Access to Medicines and the Lancet Commission on Essential Medicines

The pharmaceutical R&D model relying on grants of exclusivity is inherently problematic. A major effort to provide a conceptual basis for addressing the drawbacks of the exclusivity-based system was through the formation and work of the UN Secretary General's High Level Panel on Access to Medicines (HLP). Jorge Bermudez was a member of that Panel. The HLP convened London and Johannesburg in closed and opened dialogue sessions.

The HLP received a substantial number of submissions from various groups and individuals. On the innovation side, the HLP heard from a number of public-private partnerships, such as DNDi and GHIT, as well as from new organizations attempting to tackle issues surrounding antimicrobial resistance (AMR).

The Report of the HLP included important recommendations in terms of discouraging the application of undue pressure in the context of international negotiations on trade and investment, encouraging the use of TRIPS flexibilities, and strongly promoting transparency with respect to R&D costs and patent status.

The Report of the HLP was cautious in addressing alternatives to the exclusivity-based R&D model, principally on grounds that an alternative basis for aggregating capital has yet to be demonstrated.

Participant Comments and Recommendations:

1. There is a tendency of reports such as that coming from the HLP to have a short-term impact in terms of focusing the global dialogue, but for the impetus to dissipate without concrete action being taken. If the HLP Report is to have a significant impact, individuals and groups must be encouraged to advocate follow-up action. One approach is to identify and focus on particular action items and to press for concrete steps on those.

2. While applauding the call by the HLP for use of TRIPS flexibilities such as compulsory licensing, the political resistance to such actions should not be underestimated. It has proven extraordinarily difficult in practice to persuade governments to issue compulsory licenses in the face of express or implied threats of political and economic retaliation. The HLP strongly condemned the use of undue political pressure, but changing the political economy dynamic will be difficult.

3. If product development partnerships such as CARB-X and GARDP are successful in developing new antibiotics that solve the antimicrobial resistance (AMR) riddle, this may encourage other alternative approaches to new drug development.

4. HLP recommendations regarding increased transparency tie into a number of related proposals for improving R&D models and access to medicines, and this group may consider a research paper and development of a position on transparency as a first action item.

HIGH-LEVEL PANEL ON ACCESS TO MEDICINES

2016: two striking reports:

United Nations Secretary-General's High-Level Panel on Access to Medicines;

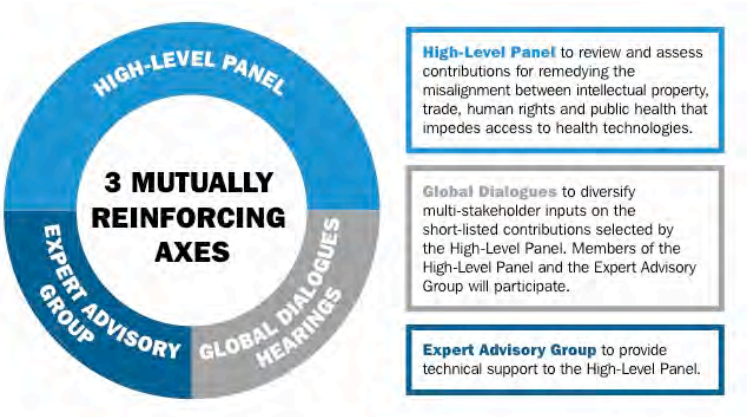
Lancet Commission on Essential Medicines

Dr. Jorge Bermudez

The 2030 Agenda for Sustainable Development

On 25 September 2015, 193 UN Member States unanimously adopted the 2030 Agenda for Sustainable Development, which emphasizes leaving no one behind

Methodology for the UNSG HLP



HIGH-LEVEL PANEL ON ACCESS TO MEDICINES

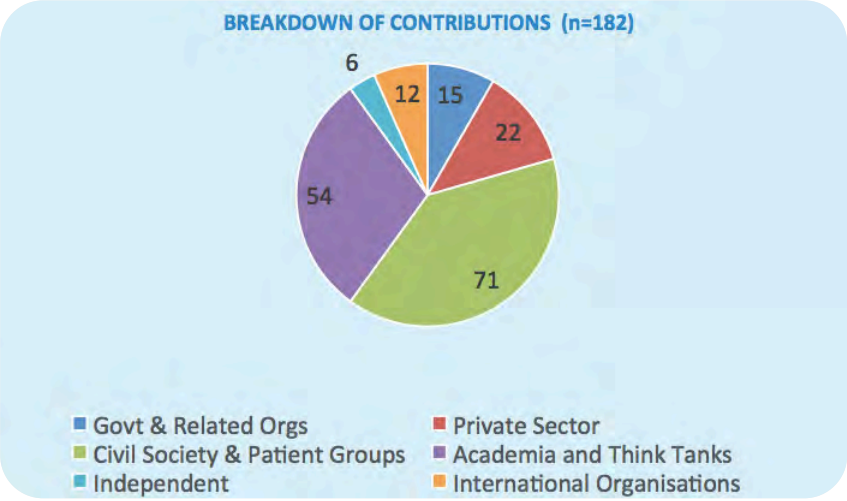
3

Regarding the process

- In line with the recommendations of the 'Global Commission on HIV and the Law', 2012
- In the context of the Post-2015 Agenda and the SDGs
- *"to review and assess proposals and recommend solutions for remedying the policy incoherence between the justifiable rights of inventors, international human rights law, trade rules and public health in the context of health technologies".*

HIGH-LEVEL PANEL ON ACCESS TO MEDICINES

Contributions



HIGH-LEVEL PANEL ON ACCESS TO MEDICINES

5

Report Released on 14 September 2016

- Health technology innovation and access
- Intellectual property laws and access to health technologies
- New incentives for health technology R&D
- Governance, accountability and transparency

HIGH-LEVEL PANEL ON ACCESS TO MEDICINES

6

Key Findings: Barriers to Accessing Treatment

- Access is a global issue, not restricted to LICs
- For hepatitis C, direct acting antivirals, such as Sofosbuvir, are successful in curing hepatitis C
- Sofosbuvir marketed at US$ 84K per patient in the United States
- Gilead signed 5 year voluntary licenses covering 112 lower middle-income countries
- 50 middle-income countries with 49 million people living with Hep C were not included in these licenses (43% of all people living with Hep C)
- 2.6 million people in Brazil, 1.5 million people in Thailand and 30 million people in China live with Hep C

HIGH-LEVEL PANEL ON ACCESS TO MEDICINES 7

Recommendations: IP and Access

- WTO Members must make full use of policy space available in Article 27(1) of TRIPS to curtail ever-greening and reward genuine innovation
- Governments should adopt and implement legislation that facilitates the quick, fair and predictable issuance of compulsory licenses
- WTO Members must revise the paragraph 6 decision to find a solution that enables swift and expedient export of pharmaceutical products

HIGH-LEVEL PANEL ON ACCESS TO MEDICINES 8

Recommendations: IP and Access

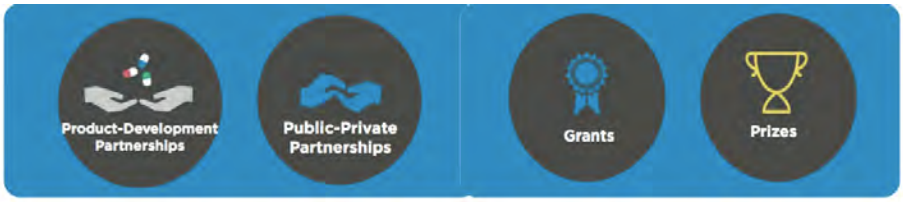
- Governments and the private sector must refrain from explicit or implicit threats, tactics or strategies that undermine the right of WTO Members to use TRIPS flexibilities
- Governments involved in trade negotiations should not compromise right to health by adopting TRIPS plus measures
- Governments should undertake public health impact assessments before entering into trade and investment agreements

HIGH-LEVEL PANEL ON ACCESS TO MEDICINES

9

Recommendations: New Incentives for R&D

- Coordinated and collaborative efforts of public-private partnerships and product development partnerships have brought together the resources and strengths of the private, philanthropic and public sectors to innovate and deliver several important health technologies
- Innovative mechanisms to address unmet needs have enabled policymakers to invest according to public health priorities



HIGH-LEVEL PANEL ON ACCESS TO MEDICINES

10

Recommendations: Binding R&D Treaty

- The UN Secretary-General should initiate negotiations for a binding R&D Convention that delinks R&D costs from end prices
- As a preparatory step to negotiating the Convention, governments should implement a code of principles that would apply to public R&D funds and should be adopted by private and philanthropic funders, product development partnerships, universities, and the biomedical industry
- This recommendation was made to address the gridlock at WHO on a binding R&D treaty

HIGH-LEVEL PANEL ON ACCESS TO MEDICINES 11

HLP: our vision (personal) of what was missing

- Recognize that the current R&D and Access system has failed.
- Concrete and feasible proposals for the short, medium and long-term to remedy a failed system.
- To propose a new IP system for pharmaceuticals, consistent with international codes of human rights and public health, safeguarding the rights of the inventors or individual rights (reaffirming previous recommendations [Global Commission on HIV and the Law, 2012]).
- Countries must be free of pressures when using TRIPS flexibilities, including patenting criteria decisions (litigation of pharmaceutical companies against Argentina and Brasil)

HIGH-LEVEL PANEL ON ACCESS TO MEDICINES

HLP: our vision (personal) of what was missing

- TRIPS-plus on FTAs immediately halted, reverted and banned.
- Too much emphasis on Voluntary; much less on Compulsory measures.
- Essential medicines (WHO Model List for Essential Medicines) excluded from patent protection (Global Health Law Committee of the International Law Association: **effectively automatic compulsory licensing for essential medicines**).
- Extension of the "waiver" for the LDCs.
- Strengthening legal and advocacy roles of civil society.
- Further discussion of the Colombia case (Imatinib Novartis).

HIGH-LEVEL PANEL ON ACCESS TO MEDICINES

Next steps?

- Clarify and make public legal implications, consistency of proposals with the TRIPS Agreement and the "unintended consequences" of the proposed approach.
- Dialogue with WTO for making effective proposals.
- Maintain the debate high in all possible forums.
- Addressing regional approaches, local production capacity and linking with the Lancet Commission on Essential Medicines (expand the LC indicators to a global approach to cover issues raised on the HLP).

HIGH-LEVEL PANEL ON ACCESS TO MEDICINES

Jamie Love addresses alternative research and development (R&D) models for new medicines, with focus on delinkage

Jamie Love introduced the subject of alternative R&D models by reference to the exorbitant prices of new cancer treatments, and the fact that for many of these expensive drugs the basic research was conducted in government-subsidized programs. In the United States, even when drugs are not specifically developed under National Institutes of Health (NIH) grants, they are frequently recipients of the orphan tax credit which amounts to a 50% subsidy on R&D. The US Department of Defense developed a vaccine for the Zika virus and funded clinical trials, but has not included in its development, production and distribution license with Sanofi a provision to regulate the price of the vaccine. In the United Kingdom, cancer treatments are rationed or denied by the National Health Service because of high prices.

Although there has been a good deal of talk regarding compulsory licensing of medicines to achieve lower prices, it has proven extraordinarily difficult for governments to use this mechanism in practice. The NGO headed by Jamie Love, Knowledge Ecology International (KEI), has worked with a substantial number of the governments that have considered using compulsory licensing, but it is very difficult to persuade those governments to act because of fear of economic and political retaliation by the home countries of the Pharma companies. The main obstacle to compulsory licensing is not legal rules, it is political pressure.

Jamie Love explained the concept of delinkage in the context of revising the predominant model for development and distribution of new drugs. The basic concept is straightforward: the costs of R&D are funded in ways that do not rely on market exclusivity and high prices for the resulting medicines to recover R&D costs. The drug technology is licensed or otherwise provided to manufacturers and distributors supplying at competitive market prices.

R&D funding can be provided through direct payments, alternative forms of subsidy such as tax incentives, and "pull" incentives such as guaranteed off-take agreements with fixed pricing. The process of introducing delinkage could be gradual and progressive.

Reference was made to the introduction of proposals for delinkage, including with respect to cancer drugs, in the World Health Assembly.

A group of countries could pursue a delinkage system together (e.g., Brazil, Chile, Greece and India).

Forms of delinkage are already associated with R&D for neglected diseases and research to overcome antimicrobial resistance (AMR).

Another area where major effort is needed is to improve transparency of R&D costs. For example, major Pharma companies book asset acquisition costs as R&D expenditures. The acquired companies or assets may include compound libraries that may eventually prove useful in testing. But, the acquiring company has not undertaken R&D when the expenditures are booked.

There is a good deal of non-transparency with respect to clinical trial costs. Orphan drug designations are currently applied to 75% of new cancer drugs. It is difficult to determine how to fund R&D if we do not have accurate data regarding R&D.

The number of patients in clinical trials can vary substantially, from 1300-1400 up to 6000-9000. Pharma data indicates that each patient enrolled in a cancer clinical trial represents a $60,000 expenditure. It is these numbers that create the expenditure totals referenced in Pharma literature.

Participant Comments and Recommendations:

1. For the originator pharmaceutical industry, 10-to 12% of annual expenses go to R&D, 25% to marketing and 30% to manufacturing; then there is general and administrative, and capital investment. Wall Street expects 10% profit increases each year. If profit margins are projected at 65%, and come in at 40%, the stock takes a big hit. This is what is motivating the industry to increase prices.

2. Unless and until alternative models are developed, Big Pharma is the "only game in town" for companies wanting to introduce new drugs into the marketplace. While smaller R&D enterprises may successfully develop new drugs, they cannot market on the scale of the Big Pharma companies, which is why they typically sell their innovations.

3. $24 billion was spent on HIV drugs in 2015, yet only one new treatment for HIV is introduced each year. HIV R&D accounts for 10% of the NIH annual budget (around $3 billion per annum). It might make more sense for PEPFAR to directly fund HIV-AIDS research and enter into fixed-price off-take agreements for the resulting products.

4. The US government strongly defends the predominant model based on patents and regulatory exclusivity, to the extent that it champions the interests of a Swiss company,, Novartis, in Colombia.

5. In California during the political campaign for medicines pricing transparency, the industry gave up trying to persuade the public that pharmaceutical prices were justified, and argued that California jobs depend on high prices.

6. Jerry Reichman emphasized that key questions regarding delinkage involve identifying the parties that will pay for R&D, and how decisions will be made regarding the projects on which R&D funds will be spent. He also suggested that more attention be given to the use of liability rules and remedies such that third parties (e.g., generics producers)making use of technologies protected by market exclusivity (e.g., patents) may be obligated to compensate exclusivity holders through reasonable royalties, but are not blocked from entering the market.

Delinkage.Org

Benefits

Delinkage has many benefits.

Low prices and expanded access. For many, the most important benefit will be the elimination of high prices on products. Most drugs can be manufactured and distributed at low prices, as commodities benefiting from competition among suppliers of generic alternatives. The high prices for new drugs are enabled by the creation of legal monopolies as the incentive to invest in R&D. As we create new funding mechanisms for R&D, including new cash incentives to reward successful developers of new products, we can eliminate both the monopolies and the high prices associated with the monopolies.

Elimination of price sensitive formularies and high co-payments. When drugs and other products are priced closer to the marginal costs of production, we can expand access and eliminate price-sensitive formularies and high co-payments for drugs.

More efficient incentives. The current system of rewarding innovation through the grant of monopolies is inefficient, for several reasons. For example, companies are rewarded for matching health care outcomes, even when the new products do not improve health outcomes, leading to costly, excessive, and wasteful investments in the development and marketing of products that are relatively unimportant from a medical standpoint. Companies also have incentives to invest in the marketing and inappropriate promotion of products to patients who do not benefit from the drugs. Companies do not have adequate incentives to invest in research that advances science but does not product a monopoly on a commercial product. Under delinkage models, governments can more effectively target incentives to reward products that improve health outcomes (see discussion of end product prizes), and also design incentives for researchers to advance science, and share and provide for royalty-free and non-discriminatory access to data, inventions, and materials (see discussion of the open source dividend and interim results prizes).

Fairness. Under delinkage, prices can be low everywhere, without adverse impacts on innovation, in order to reduce the gaps between the rich and the poor, and making "access to medicine for all" feasible.

Policy coherence. Delinkage aligns the interests of consumers and drug developers, and eliminates the trade-offs between access and innovation. High prices are the enemy of access, the enemy of fairness, and present a fundamental conflict between access and fairness on the one hand, and innovation on the other. Delinkage fixes

Mechanics of Delinkage

Because delinkage is defined in the negative, policymakers have the option of considering any policy option that does not rely upon high prices. Among the many proponents of delinkage, there are diverse views on how delinkage should be implemented. The freedom to design R&D funding methods has both positive and negative aspects. On the one hand, there is the freedom to choose among countless alternatives, including those that can be described as direct funding (through intramural projects, or intermural grants or contracts), subsidies (such as the orphan drug tax credit), and incentives (including most importantly cash rewards). On the other hand, a lack of consensus among delinkage proponents can be unnerving for policy makers, who need to focus on the implementation of specific proposals.

Some delinkage proponents have proposed the elimination of R&D incentives in favor of mostly direct funding, through government research grants and contracts. Others, including KEI, have advocated combinations of direct funding, subsidies, and incentives based upon cash rewards. There are no advocates for eliminating direct funding of research by governments.

The international aspects of delinkage are as important as the international aspects of the intellectual property system. The intellectual property system involves a multitude of treaties, trade and other agreements, and informal norms that collectively establish obligations on governments to grant and enforce legal monopolies and tolerate high prices on products. These involve norms on patents, test data for new drugs, and sui generis regulatory monopolies relating to the development of orphan drugs and research for pediatric populations, as well as other measures. The international aspects of delinkage include efforts to establish global norms for funding R&D, such as through R&D funding agreements or treaties, cross-border collaboration on innovation inducement prizes or prize funds, and proposals for agreements on the supply of public goods.

There is also the challenge of managing the transition from the current system of monopolies and high prices to the delinkage alternative. The policies to navigate this transition are referred to as progressive delinkage.

Among the various proposals for delinkage, some take a voluntary approach, and others make delinkage mandatory. The voluntary approaches have a role, particularly in a transition to full delinkage, for certain cross border implementations, and to address some specific innovation objectives, such as to induce investments in R&D in areas of significant market failure. Over the longer run, however, and to address other policy objectives, mandatory approaches should be preferred or required.

The relationship between intellectual property rights and delinkage depends upon how delinkage is implemented. For example, under a series of legislative proposals in the United States by Senator Bernie Sanders, delinkage would be implemented by eliminating exclusive rights to make and sell products, but patents would still pay a role in determining the owners of the innovations and the claims on billions of dollars in cash rewards.

Savings

Research and development is expensive, but so are drug monopolies. In 2015, the trade association Pharmaceutical Research and Manufacturers of America (PhRMA) claimed that its members spent $58.8 billion on R&D, and that non-PhRMA member spent tens of billions more. But, those same companies also earned significant revenues. In 2015, prescription drugs generated an estimated $413 billion in sales from the United States market alone[1], and more than one trillion dollars worldwide. In the U.S. market, sole source patented medicines are on average 19 times more expensive than generic medicines[2]. For 2015, the cost of the monopoly on drugs could be estimated at $283 billion, just in the United States.[3] Globally, the cost of the monopoly is far more. If the United States had already switched to delinkage, and spent $100 billion in that year to reward researchers and drug developers, it would have saved $183 billion and eliminated restrictive formularies, high co-payments and other access barriers. Moreover, even these calculations under-estimate the savings, since generic drug prices are undoubtedly higher than they should be because of the many inefficiencies in markets for generic drugs that are related to the system of monopolies.

Would $100 billion have been enough for the United States? Yes. $100 billion is nearly twice the PhRMA member reported R&D outlays for that year. $100 billion is more than $2 billion per new drug approved in 2015, a record year for approvals, and $4.8 billion per drug approved in 2010. The $100 billion would also be in addition to the money for biomedical R&D funded through U.S. government agencies. Moreover, the United States is only one country, and the costs of R&D would be shared with others. In 2015, the United States represented 24 percent of global GDP, and 38 percent of GDP in countries the World Bank defines as high income.

The estimated savings are even more impressive when you consider how much of the current R&D budget is wasted on developing drugs that match, but do not improve health outcomes, and on clinical trials that have little scientific merit, but are used to advance marketing objectives.

The amount of money needed to finance incentives is also related to R&D spending involving other mechanisms. If governments expand direct funding and/or subsidies for drug development, the amount needed for incentives would be less.[4]

While R&D is expensive, it makes no sense to spend over one trillion on drugs to finance tens of billions in industry R&D.

[1] IMS Health.

[2] In 2016, GhPA estimated that generic drugs represented 88 percent of all prescriptions filled, but only 28 percent of all revenue). The generic prescriptions were just [(28/88)/(72/12)] = 5 percent as expensive.

[3] 95 percent of 413 x .72 = $283 billion.

[4] For example, if the U.S. Orphan Drug tax credit, which covers 50 percent of the cost of qualifying clinical trials, was expanded to cover more trials or at a higher percentage, and supported by more countries, the costs of conducting clinical trials would be lower, and consequently, the amount needed for an incentive to companies to invest in a trial would be less.

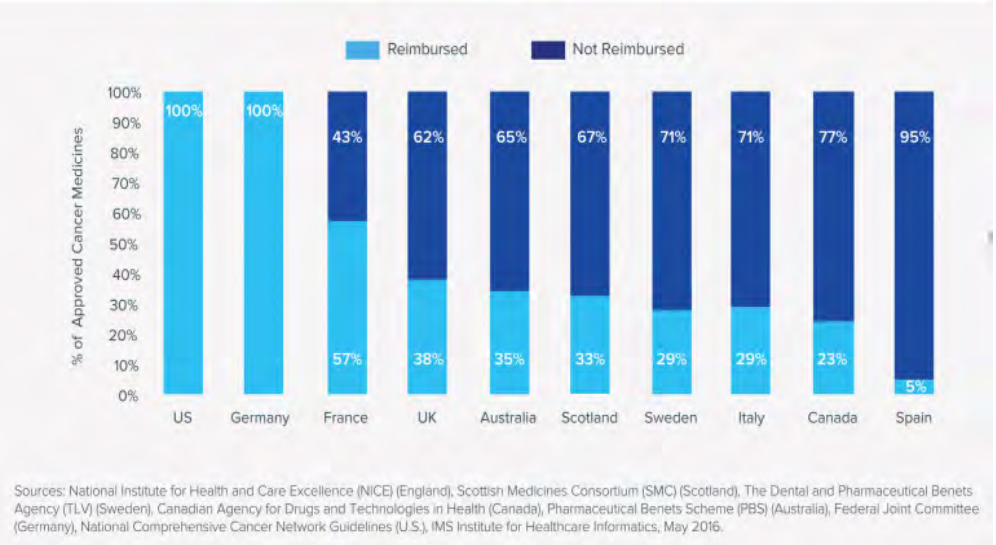
The Impact of High Prices on Access

High prices for drugs, vaccines, and diagnostic tests limit access.

When drugs are expensive, they may be excluded from reimbursement programs, have restrictions on how they can be used, or be subject to high co-payments. Patients may also avoid purchasing expensive (to the patient) prescriptions.

In developing countries, high prices can have devastating impacts on access. A 2011 study by Paul Miano found no patented cancer drugs on the World Health Organization (WHO) list of essential medicines. [1] The exclusion of virtually all drugs newer than 15 years old was powerful evidence that high prices create barriers to access and unfair outcomes. But even in high income countries, high prices create access barriers. A May 2016 study by IMS Global illustrates the uneven reimbursement states for new cancer medicines approved in 2014 and 2015.

Figure 1: Reimbursement Status of Cancer Medicines Approved in 2014 and 2015



According to IMS:

Access to new cancer drugs is not universal even in developed countries, where national health systems' priorities may result in declining to reimburse some products.

Countries employing a formal cost-effectiveness methodology based upon cost per quality life year gained are much less likely to reimburse new cancer medicines than countries using other assessment approaches.

By the end of 2015, 78% of the new oncology medicines launched between 2010 and 2014 were available within the greater EU.

Patients in six European countries gained access to NAS within all 6 therapy categories.

Only one-third of the former Eastern Bloc countries have access to at least one of the new targeted immunotherapies.

Dr. Jicui Dong, Dilip Shah and Joe Fortunak address the challenges of local production

Jicui Dong introduced WHO's work with respect to local production of medical products. She noted that WHO's key leadership expertise in local production is in strengthening regulatory systems and setting international quality assurance standards, such as GxP's and regulatory guidelines. The WHO Department of Essential Medicines and Health Products, which has absorbed the former division on Public Health, Innovation and Intellectual Property (PHI), is seeking to refine its future strategy for strengthening local production to improve quality and access globally.

Jicui Dong referred to three recent country reports regarding China, Cuba and India. The reports are a resource for other developing countries looking to promote local production to learn various strategies taken by the 3 countries that helped strengthen their respective pharmaceutical industry. As an active UN agency, WHO is collaborating with the AUC in implementing the Pharmaceutical Manufacturing Plan for Africa (PMPA). Jicui Dong also introduced the National Strategy and Plan of Action for Pharmaceutical Manufacturing Development in Ethiopia, which was developed and launched by the Government of Ethiopia with support from WHO upon the Government's request. Now WHO, under the leadership of Ethiopia and in collaboration with other partners, is part of the strategy implementation process.

WHO is not an industrial policy organization, and it may not be best suited to devising tax strategies and infrastructure support. But, WHO could serve as an important nexus for information-sharing that might help developing countries avoid problems.

The question of local production ties in closely to issues concerning innovation and transfer of technology. Building a successful local production platform requires addressing a variety of elements, including capital, infrastructure, human resources and so forth. Yet, a pharmaceutical product that is covered by some form of market exclusivity cannot be produced without permission to use the relevant technology, or some way to overcome the need for that permission. In some cases the Medicines Patent Pool (MPP) is serving to provide permission for the relevant technology, and some other voluntary licensing programs outside MPP are functioning.

It is difficult for local production to compete on a cost/price basis in the short run. How do you balance long-term benefits to the country versus short run procurement costs?

Dilip Shah said that Indian manufacturers would establish plants in Africa if provided with power, infrastructure and guaranteed pathways toward regulatory approvals. Companies are dependent on government approvals. The lack of transparency is a big problem. 100%

foreign-owned firms do not appear to be welcome. That said, there is a $40 billion futuremarket in Africa that is attractive, so industry cannot just sit by. Some question was raised concerning the commitment of local producers in Africa to developing projects that can compete on the basis of price with foreign suppliers. There may be overreliance on government procurement preferences and other subsidies that will not be sustainable over the longer-term.

Dilip Shah said that manufacturing is not the most difficult aspect of medicine supply. R&D is the most difficult part, then marketing and distribution, and finally manufacturing. This is the situation for Africa, as elsewhere.

Joe Fortunak suggested that local production in Africa is important as a matter of national self-determination. WHO has put together a good program in Ethiopia based on the concept of moving from the most accessible technologies such as packaging, with a goal toward moving up the value chain, eventually toward API production. He thinks that production of APIs in Africa is a decade away. He recalled, however that 45 years ago there were API producers in Africa. They were put out of business by strict GMPs.

Ethiopia was a good place for WHO to start since the government was supportive from the outset. There is a 12 to 16% delivery cost for drugs from Hyderabad to Ethiopia, and that this makes a 25% price preference for locally produced drugs in Ethiopia reasonable.

Joe Fortunak discussed the possibilities for reducing need for chemical inputs through new technologies, with a case in point being the transition from TDF to TAF. This brings down costs, reduces the environmental footprint, and dramatically reduces the quantity of medicines the patient takes.

The cost of HIV treatment should be $50 per person per year.

The manufacturing cost of sofosbuvir is quite low. While the end-user price is $84,000 for a 12 week course of treatment in the United States, the price is $260 in low and middle income countries.

Joe Fortunak suggested that we need to create a virtual organization to get through all aspects of medicines R&D and production without relying on Pharma.

We need to learn from history, from people who know how to develop the industry. Eventually tthere will be movement toward drug discovery. The main thing is to improve health outcomes in a country.

For local production to succeed, it is important to stimulatel local demand for medicines. This is lacking in some countries because of historic inaccessibility. Nigeria has 200 million people, twice the population of Ethiopia, but there is less demand for medicines than in Ethiopia.

Participant Comments and Recommendations:

1. Jorge Bermudez referred to some of the difficulties that Fiocruz faced in building capacity in Mozambique. After individuals were trained and gained experience, they moved to South Africa for higher wages. He does not see a solution to getting people to stay in place. Jorge Bermudez talked about the possibility of using regional compulsory licensing.

2. Jerry Reichman referred to the possibilities for pooled procurement.

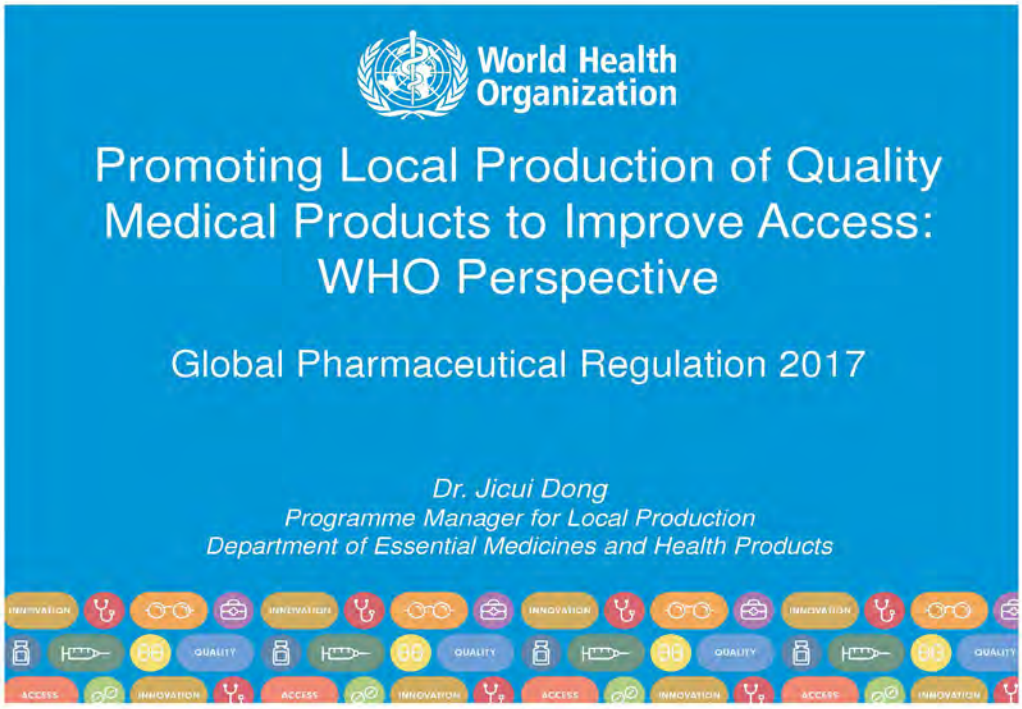
3. Fred Abbott, referring to the issue of personnel and employment, observed that this is common in attempts to create regional regulatory infrastructure. No regulatory office wants to see itself displaced. He referred to the detailed work Andre Kudlinski had done on the subject of pricing preferences in South Africa, which nonetheless did not persuade the Health Department to support local price preferences because of the need to focus on immediate budget concerns. This is a general problem. While a particular course of action may benefit the country as a whole, absent strong central government direction this does not translate into policy for individual departments that must work within their own budgets.

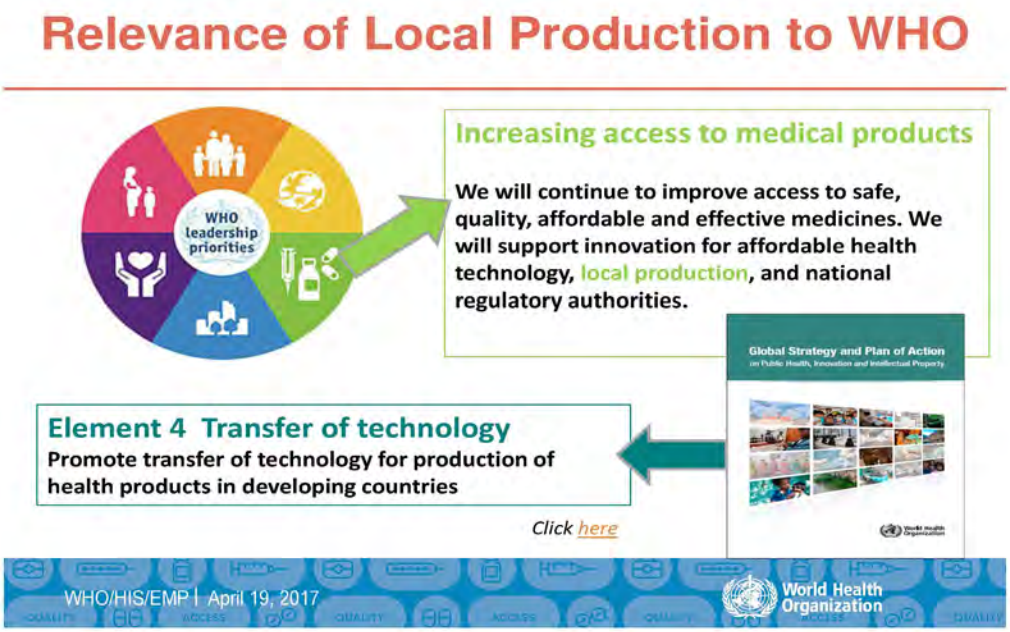
Fred Abbott referred to his experience preparing a report on the Indian local production situation where there was no centralized repository of information needed by foreign investors, and even the ministries involved in different aspects did not appear to know what was going on elsewhere. Dilip Shah confirmed that there is a lack of transparency of information. Major consulting firms such as PWC may have worked to compile information, but these firms are expensive to use.

4. Xavier Seuba suggested that the GMP standards adopted by the International Conference on Harmonization (ICH) are too high for Brazil. He said that WHO must play a more active leadership role in the standards-setting, a role it has largely ceded to the Pharma industry.

5. Jamie Love said that technology transfer programs are needed. Although patents may teach fairly adequately with respect to small molecules, with biologics you need to pay for information, sign nondisclosure agreements, etc. Each agreement needs to be specifically tailored. All of the new cancer drugs are high-priced. You need to increase the speed of technology transfer, and improve transparency. Jamie Love reiterated that compulsory licensing is not working. Even though the law permits, political reality does not. That is why it is preferable to move to a delinkage system.

6. Several participants observed that voluntary locensing programs impose their own types of regulatory barriers, such as a need to compliance with international GMP standards. This latter requirement is intended to serve the valid purpose of assuring products of adequate quality, but at the same time it makes geographic distribution of production functions difficult. Is there some type of technology transfer or regulatory program that could assist address this type of issue? What about the cases where voluntary licensing is not available? Is or will compulsory licensing become a viable part of the pharmaceutical production landscape? Is there some way to depoliticize this tool?


World Health Organization
Promoting Local Production of Quality Medical Products to Improve Access: WHO Perspective
Global Pharmaceutical Regulation 2017
Dr. Jicui Dong
Programme Manager for Local Production
Department of Essential Medicines and Health Products


Relevance of Local Production to WHO
WHO leadership priorities
Increasing access to medical products
We will continue to improve access to safe, quality, affordable and effective medicines. We will support innovation for affordable health technology, local production, and national regulatory authorities.
Global Strategy and Plan of Action
Element 4 Transfer of technology
Promote transfer of technology for production of health products in developing countries
Click here
WHO/HIS/EMP | April 19, 2017
World Health Organization

Why Local Production

Local production can contribute to long-term socio-economic development by:

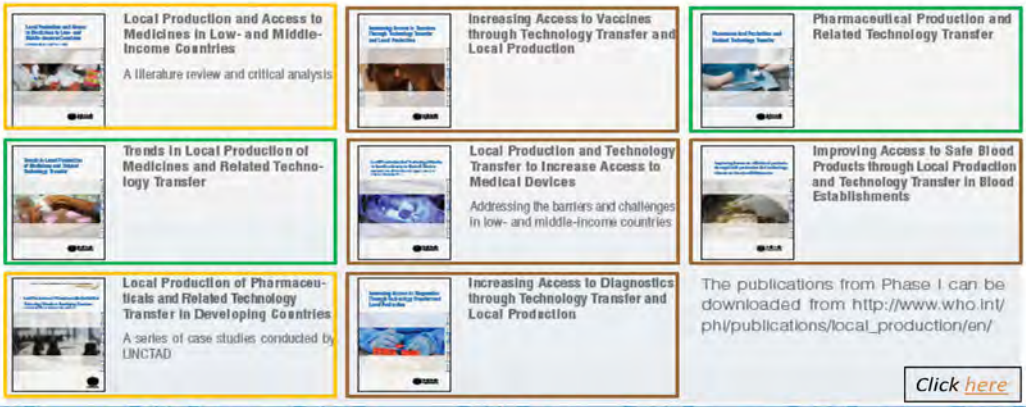
- *improving access to and providing uninterrupted supply of quality-assured medical products*
- *saving resources through less expensive, locally produced medical products, if the production scale is sufficiently large*
- *creating employment, increasing purchasing power and stimulating investments*
- *stimulating increased local innovation capacity and improving health workforce capacities & technical skills*

"Improving access to medical products in developing countries through building capacity for local production and related technology transfer"

- EC Project (Phase 1)
  - Laid down groundwork about local production and technology transfer
    - Studied landscape & trends surrounding local production (LP) & technology transfer (TT)
    - Identified related challenges & obstacles
    - Provided evidence-based recommendations for supporting/strengthening LP

"Improving access to medical products in developing countries through building capacity for local production and related technology transfer"

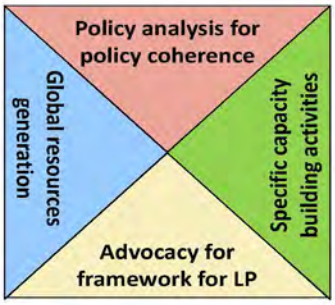
EC Project (Phase 1)



Framework for Local Production to Improve Quality and Access

"Improving access to medical products in developing countries through building capacity for local production and related technology transfer"

EC Project (Phase 2)



Some examples:

- Development of resources
  - WHO Model List of Essential Medicines risk analysis for local production
  - Country experiences with strengthening local production & technology transfer
  - Report on the role of IP in local production and its challenges/obstacles
- Policy analyses for policy coherence
- Technical assistance for manufacturers

WHO/HIS/EMP | April 19, 2017 World Health Organization

"Improving access to medical products in developing countries through building capacity for local production and related technology transfer"

- EC Project (Phase 2)
  - Country experiences in promoting local production to improve access & public health
    - Cuba, China and India
    - Look into different government policies that contributed to promoting LP

      e.g. for Cuba, education policies were put in place for necessary knowledge & skills to support biopharmaceutical industry

Click here

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"Improving access to medical products in developing countries through building capacity for local production and related technology transfer"

- EC Project (Phase 2)
  - Report on role of intellectual property (IP) in local production in developing countries
    - Gives guidance to policy-makers on designing an IP system conducive to LP & public health
    - Examples of different situations:
      - LP through agreements
      - Landscape of patents for select medicines in select countries/regions

Click here

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NSPA-Pharma

The Ethiopian Deputy Prime Minister, while officially launching the strategy, called it a "flagship programme" for Ethiopia's next 5-year National Development Plan (GTP-II, 2015-2020). WHO has been working with the government as a development & technical partner, with the launch & implementation supported financially by Gates Foundation. Click

WHO/HIS/EMP | April 19, 2017 World Health Organization

NSPA-Pharma Implementation

Key achievements in 2016:

WHO supporting the Ethiopian Government

- Set up project governance structures
- Strengthen the national regulatory system
- Revitalize the national GMP road map
- Develop a method to prioritize the local production of essential medicines
- Assess the readiness and feasibility for local API manufacturing
- Assess the feasibility for local production of *entecavir* (anti-Hep B)
- Develop a post graduate curriculum on regulatory affairs
- Provide technical assistance to local and foreign projects (2 local, 4 foreign)
- Exploit Ethiopia's LDC status to locally produce patented products
- Develop the draft national incentive packages for local manufacturers and foreign investors

WHO Activities on Local Production

Collaboration with Development Partners

Under the context of the PMPA (endorsed in 2007)

- Development of a collaboration framework for the PMPA-BP Consortium
- Development of Vaccine Manufacturing and Procurement in Africa (VMPA) study *(an inter-agency collaboration)*
  - VPMA White Paper & Case Studies (South Africa, other)
- Revitalization of the PMPA's Technical Committee
  - the 6th TC meeting
- Development of the abridged version of the PMPA-BP

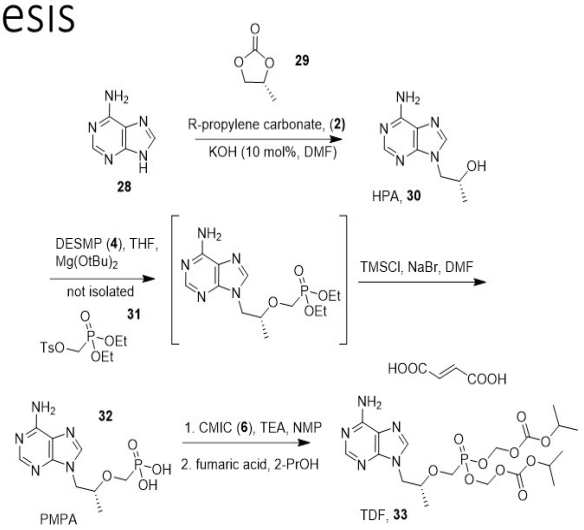

Let's Discuss
1. WHO's roles on Local Production?
Examples: Strengthen quality and the regulatory system; Enable evidence-based decision-making to address priority global challenges
Want to listen to you…
2. How to coordinate the interagency partnerships, and how to collaborate with various stakeholders?
WHO/HIS/EMP | April 19, 2017
World Health Organization

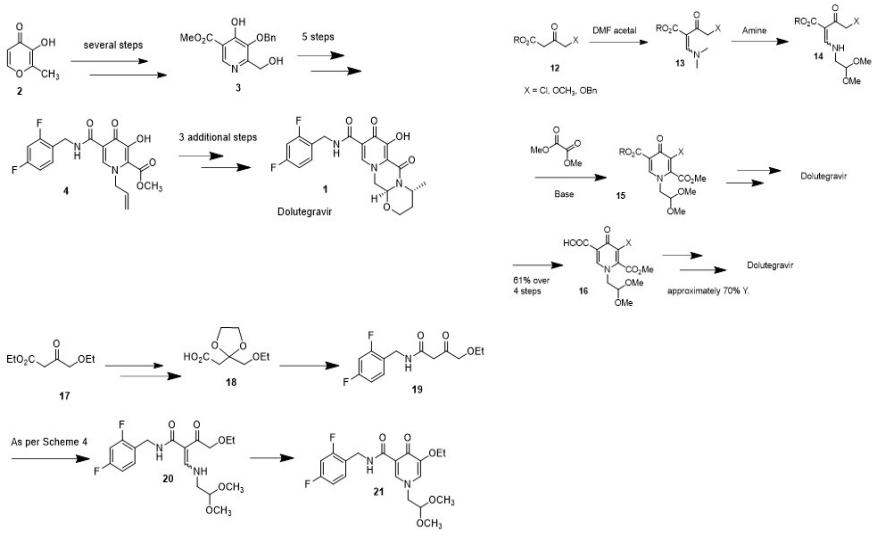
Global Production, Regulatory, and Trade Environment

Joseph Fortunak
jfortunak@howard.edu
jfortunak@Comcast.net

APIs and Finished Pharmaceutical Products (FPPs)

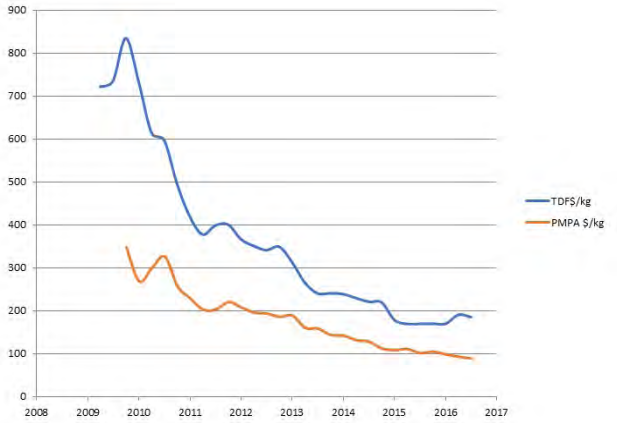
API Synthesis





API and FPP pricing

API	FPP Pricing, US	FPP Pricing , LMICs	API pricing/kg, India/China	Generic API pricing PPPY or per treatment
Sofosbuvir	$84,000	$200 - $650	$800	$27
Daclatasvir	$63,000	$45	$850	$4.25
Tenofovir disoproxil fumarate (TDF)	$15,000	$66	$140	$15.40
Efavirenz	$2,600	$48	$105	$24
Lamivudine (3TC)		$42	$135	$15
TLE (TDF/3TC/EFV)		$95	$95	$55
Imatinib	$125,000		$140	<$40
Cyclophosphamide	$27,000		$270 - $310	<$20
Cholic Acid	$312,000	N/A	$370/kg (MP Biomedical)	$33 - $57



Drug (indication)	Dose	Pricing/dose, US	Pricing /dose, LMICs
Cefuroxime (anti-infective)	500 mg, 20 count	$1.815 - $2.15	$0.368
Atazanavir (AIDS)	300 mg, 30 count	$29.74 - $52.77	$0.5213
Atenolol (cardiovascular)	50 mg/30 count	$0.133 - $0.3787	$0.0059
Atorvastatin (lipid-lowering)	20 mg/30 count	$0.3327 - $2.933	$0.0714

Representative pricing of medicines in the US versus median pricing in LMICs.

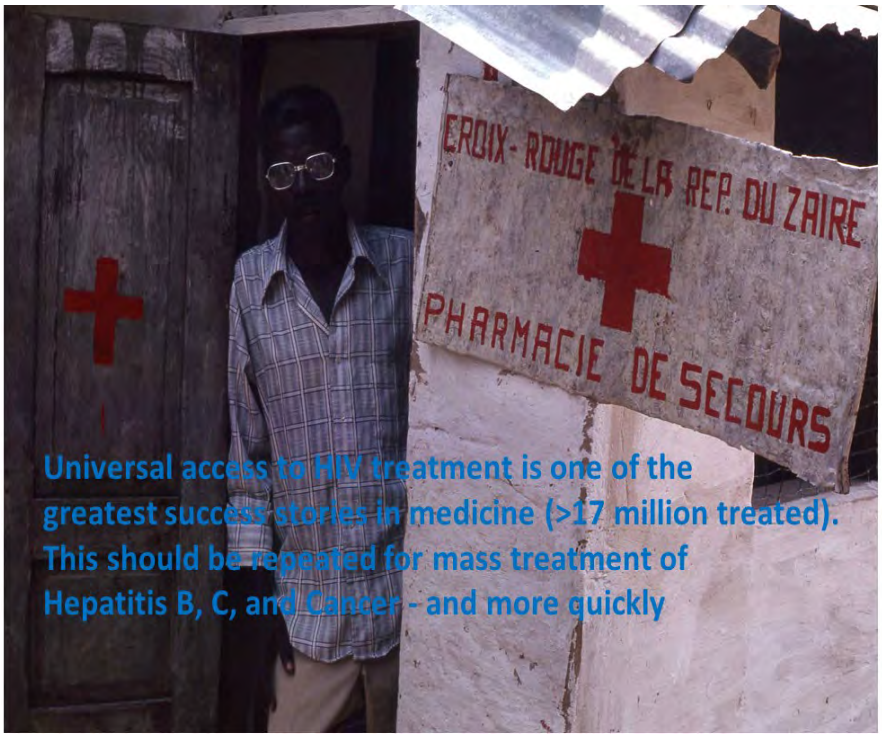
Full Disclosure

Journal of Virus Eradication 2015; 1:000–000 ORIGINAL RESEARCH

Analysis of minimum target prices for production of entecavir to treat hepatitis B in high- and low-income countries

Andrew Hill*[1], Dzintars Cotham[2], Graham Cooke[2], Sanjay Bhagani[3], Isabelle Andrieux-Meyer[4], Jennifer Cohn[5], Joseph Fortunak[6]

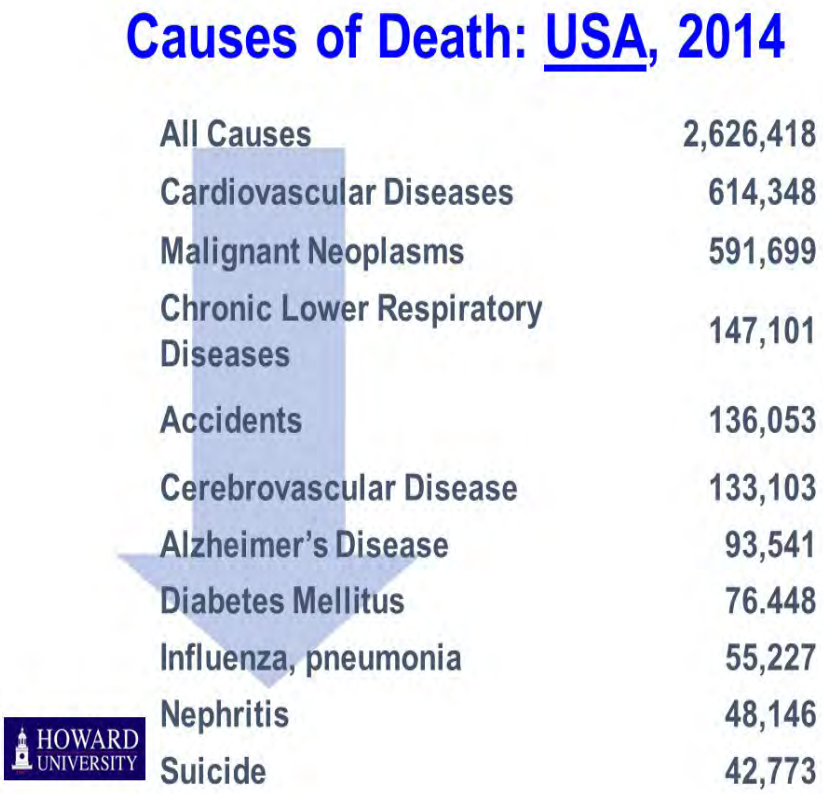
[1]Department of Pharmacology and Therapeutics, Liverpool University, UK, [2]Faculty of Medicine, Imperial College London, London, UK
[3]Department of Infectious Diseases/HIV Medicine, Royal Free Hospital, London, UK, [4]Division of Infectious Diseases, Geneva University Hospital, Switzerland
[5]Division of Infectious Diseases, University of Pennsylvania, Philadelphia, US, [6]Chemistry and Pharmaceutical Sciences, Howard University, Washington DC, US

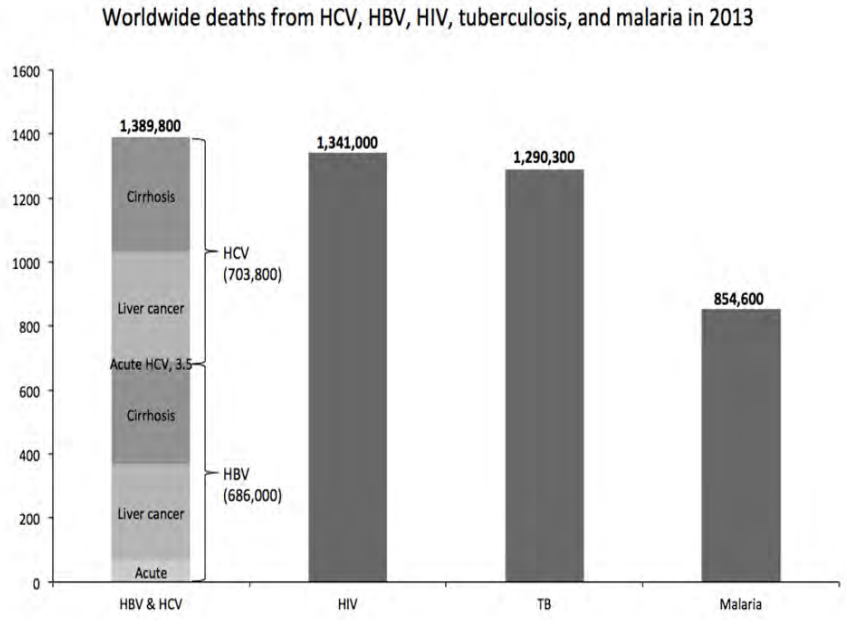


Universal access to HIV treatment is one of the greatest success stories in medicine (>17 million treated). This should be repeated for mass treatment of Hepatitis B, C, and Cancer - and more quickly

Impact of Global Access Campaigns Upon the Indian and Chinese Pharma Industries

Priorities in LMICs?





32

Global Burden of Disease report, Lancet 2014, 385: 117-171

Causes of Death - Africa

- ***BUT: This does not even count the incalculable burden of cardiovascular diseases and diabetes…***
- (Rob Ridley) Approximately 14 million deaths per year occur in sub-Saharan Africa because of ***preventable or easily treatable diseases***:
  - Diarrheal diseases
  - Simple Infections
  - Malaria
  - Tuberculosis
  - HIV/AIDS
  - Hepatitis B and C

	LE Sales Rank	Units MAT/02/2012 (Absolute)	Units MAT/02/2013 (Absolute)	G%	Units MAT/02/2014 (Absolute)	G%	Units MAT/02/2015 (Absolute)	G%	LE Sales MAT/02/2012 (Absolute)	LE Sales MAT/02/2013 (Absolute)	G%	LE Sales MAT/02/2014 (Absolute)	G%	LE Sales MAT/02/2015 (Absolute)	G
Pharma market		1,678,724,286	1,879,809,426	12%	1,889,000,369	0%	2,025,931,360	7%	19,321,766,510	23,018,465,849	19%	24,655,001,290	0	28,464,898,532	15
AUGMENTIN	1	5,672,894	7,139,103	7%	7,646,917	7%	8,446,074	10%	234,255,131.00	301,282,679.00	29%	331,396,377.00	10%	383,364,252.00	16
CEFOTAX	2	15,535,228	18,712,976	6%	18,648,982	0%	22,617,438	21%	176,698,648.00	211,882,976.00	20%	214,656,672.00	1%	261,212,400.00	22
CATAFLAM	3	10,741,137	11,993,641	15%	13,833,146	15%	15,741,697	14%	157,189,424.00	185,895,360.00	18%	215,429,936.00	16%	254,218,608.00	18
FLUMOX	4	19,083,946	20,621,558	-3%	20,064,919	-3%	22,830,405	14%	180,519,632.00	197,372,840.00	9%	196,242,248.00	-1%	229,488,160.00	18
AMARYL	5	6,062,052	5,959,519	-18%	4,878,933	-18%	5,278,000	8%	162,915,164.00	150,649,312.00	17%	186,991,104.00	-2%	203,736,896.00	9
CONCOR	6	7,883,438	10,109,245	8%	10,891,693	8%	10,297,149	-5%	108,741,360.00	138,177,744.00	28%	149,290,416.00	7%	192,026,640.00	29
VOLTAREN	7	8,901,812	10,914,665	8%	11,826,481	8%	13,657,880	15%	124,834,576.00	146,992,320.00	18%	160,319,888.00	9%	190,911,344.00	19
CATAFAST	8	4,735,016	6,368,183	17%	7,460,022	17%	9,860,638	32%	85,230,288.00	114,987,296.00	35%	134,280,480.00	17%	177,489,680.00	32
CURAM	9	4,377,980	4,879,127	11%	5,916,986	11%	6,130,988	11%	105,729,092.00	126,038,737.00	19%	154,147,296.00	22%	175,983,148.00	14
INS MIXTARD 30 HM	10	5,295,024	5,396,533	3%	5,697,747	3%	6,435,462	16%	125,099,852.00	133,149,632.00	6%	145,106,266.00	9%	164,029,744.00	13
CONTROLOC	11	982,467	1,161,646	77%	1,984,033	77%	2,512,696	29%	65,896,246.00	87,071,952.00	32%	127,483,448.00	46%	161,073,320.00	27
PLAVIX	12	451,232	564,462	12%	632,065	12%	783,655	24%	92,592,560.00	115,712,656.00	25%	129,573,328.00	12%	160,649,280.00	24
DIAMICRON	13	7,201,537	7,766,258	-5%	7,416,760	-5%	7,633,418	3%	132,712,864.00	148,033,856.00	12%	146,825,440.00	-1%	166,200,592.00	6
BRUFEN	14	9,693,193	11,748,957	19%	14,035,053	19%	14,811,014	6%	92,090,067.00	118,885,812.00	29%	145,667,440.00	23%	150,049,280.00	3
VIRECTA	15	6,295,725	7,029,428	7%	7,553,141	7%	7,803,024	3%	113,022,486.00	127,130,944.00	12%	139,038,176.00	9%	149,185,104.00	7
ZANTAC	16	5,133,917	6,783,327	14%	7,744,629	14%	7,619,694	-2%	97,256,144.00	127,889,912.00	31%	146,319,280.00	14%	145,126,480.00	0
BREC	17	8,846,291	7,965,115	-27%	5,169,673	-27%	3,891,269	-25%	118,825,040.00	175,339,612.00	48%	182,899,520.00	4%	136,359,696.00	-2
HIBIOTIC	18	2,646,420	2,656,489	2%	2,721,637	2%	2,717,476	0%	113,994,472.00	125,004,560.00	10%	130,366,880.00	4%	130,549,152.00	0
FERROTRON	19	1,374,927	2,345,157	28%	3,006,912	28%	3,638,299	21%	45,372,592.00	77,390,184.00	71%	99,228,096.00	28%	120,096,864.00	21
DEPOVIT B12	20	12,612,744	19,886,356	-17%	16,482,672	-17%	18,821,424	14%	77,666,984.00	114,904,072.00	48%	103,416,104.00	-10%	119,696,480.00	16
CLEXANE	21	1,116,682	1,198,849	20%	1,439,410	20%	2,164,116	50%	58,730,912.00	66,434,560.00	13%	77,285,512.00	16%	118,435,464.00	53
CEFAXONE	22	3,727,432	5,458,467	-11%	4,879,786	-11%	6,978,384	43%	60,680,380.00	94,673,224.00	55%	82,508,928.00	-13%	115,548,640.00	40
PANADOL	23	3,890,605	6,293,269	26%	7,887,318	26%	10,139,507	29%	44,152,352.00	70,761,552.00	60%	87,033,520.00	23%	115,071,984.00	32
GYNERA	24	3,036,951	3,568,049	7%	3,800,329	7%	4,454,488	17%	51,628,168.00	60,496,832.00	17%	90,339,312.00	49%	111,362,448.00	23
EPICIPHIN	25	0	2,408,524	50%	3,611,777	50%	5,729,026	59%	0	43,637,724.00	#DIV/0!	87,164,712.00	64%	106,489,632.00	55
VIAGRA	26	226,618	1,381,773	4%	1,437,434	4%	2,256,557	57%	25,076,988.00	57,296,600.00	128%	60,714,018.00	6%	103,180,352.00	70
														4,331,557,61	13

Do we compare/contrast India and China?

Local Pharmaceutical Manufacturing – Africa


INDUSTRY
CLASSROOM AND LABORATORY TRAINING
Regulatory
ACADEMIA
HOWARD UNIVERSITY
29

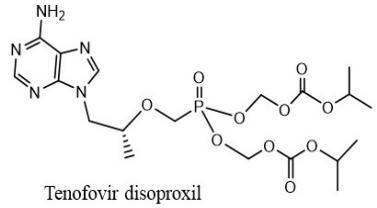
Patents

The Patent Estate - Evergreening

- Pharmaceutical companies represent nearly every aspect of drug development and delivery as containing patentable innovation:
  - Composition of matter
  - Method of use
  - Combinations with other drugs
  - Pharmaceutical compositions (formulations)
  - Processes and Intermediates (not listed in the Orange Book)
  - Crystalline forms (salts, polymorphs, hydrates, solvates, co-crystals, dispersions)
  - Latter-day "improvements"

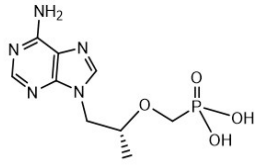
Tenofovir Alafenamide – Patent Applications

Tenofovir, Tenofovir Disoproxil, Tenofovir Alafenamide



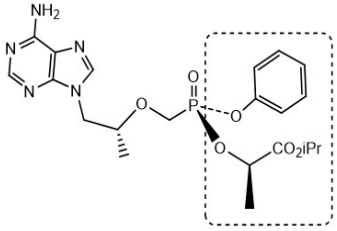
Tenofovir disoproxil

Prodrug selected by Gilead Sciences (John Martin)



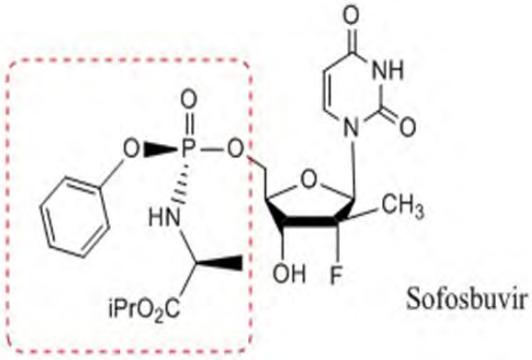
Tenofovir (API)

Synthesized by Antonin Holy and tested by Eric de Clerq



First published by McGuigan et. al., (1989) and applied to hundreds of antiviral compounds

Sofosbuvir



Sofosbuvir

Emerging Issues

- Alternative salts of tenofovir disoproxil fumarate (citrate, phosphate) from Indian generics have been approved by the EMA (March, 2017) and the tartrate is expected to be approved this month
- This provides a means for getting around originator patents, but it also creates new patent issues... (DTG, TDF, solvates and new crystal forms of important APIs (aripiprazole/abilify)
- Tenofovir disoproxil fumarate is presently taken by an estimated 12MM people in LMICs
  - Patent coverage on the drug molecule theoretically expires in 2017/2018
  - Gilead Sciences seeking to extend this to 2020 in US and Europe with a 2015 application covering solid state forms of tenofovir disoproxil, preventing generic companies from entering market

Dr. Nick Drager presents an R&D hub platform

Nick Drager discussed the model of TBVi, the non-profit that he is leading in Europe. The basic idea is that the European Union and other funders rely on TBVi and its experts as "honest brokers" to evaluate proposals and award funding, with the parties agreeing to share data. TBVi does not take or own IP, or equity stakes in any of its partners. While the R&D partners are expected to follow access and affordability guidelines, this is not established contractually. TBVi's value-added is as a knowledge platform, sharing pre-market data, with 150 groups involved. The basic function is to mobilize funding. To specify "gateway criteria". Would this work outside of Europe without EU funding? The other major funder is the Gates Foundation. Would it work in India? South Africa? They are establishing an African network.

Nick Drager said that there is a "market" for TB treatments, and in general a good deal is going on.

Participant Comments and Recommendations:

1. Jorge Bermudez asked how this interacts with AMR research. Also, the 5 BRICS countries account for 50% of TB infections. How are they represented? As to why there is such a prevalence of TB in the BRICS countries, there has not been a control model so it is difficult to know the real data. One of the problems with TB is the long treatment time.

Accelerating TB Vaccine Research & Development Through Partnership

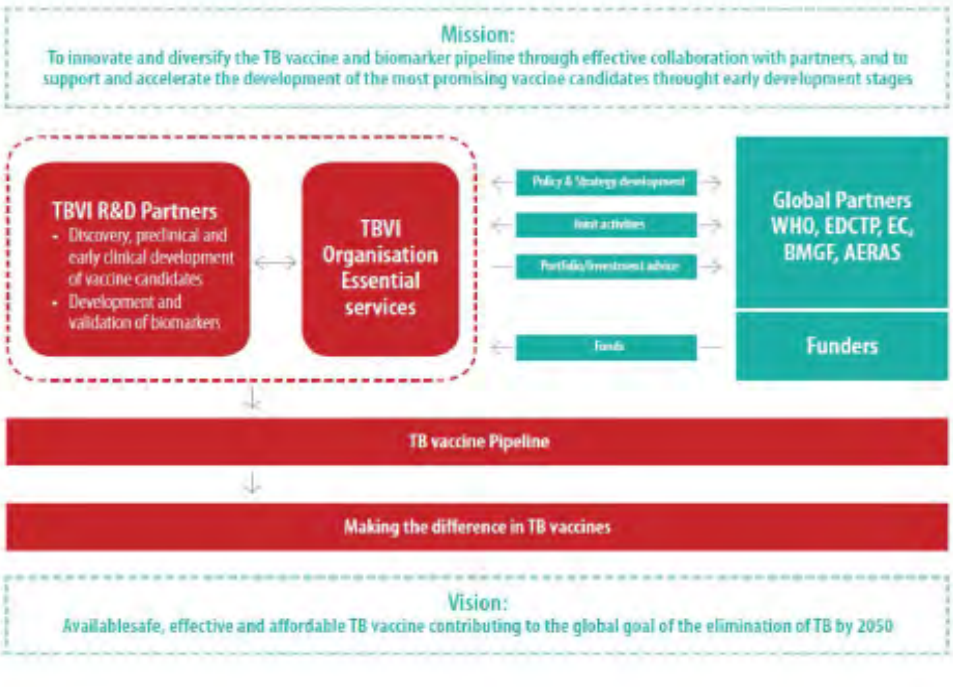
TBVI

TuBerculosis Vaccine Initiative

www.tbvi.eu

Dr. Nick Drager

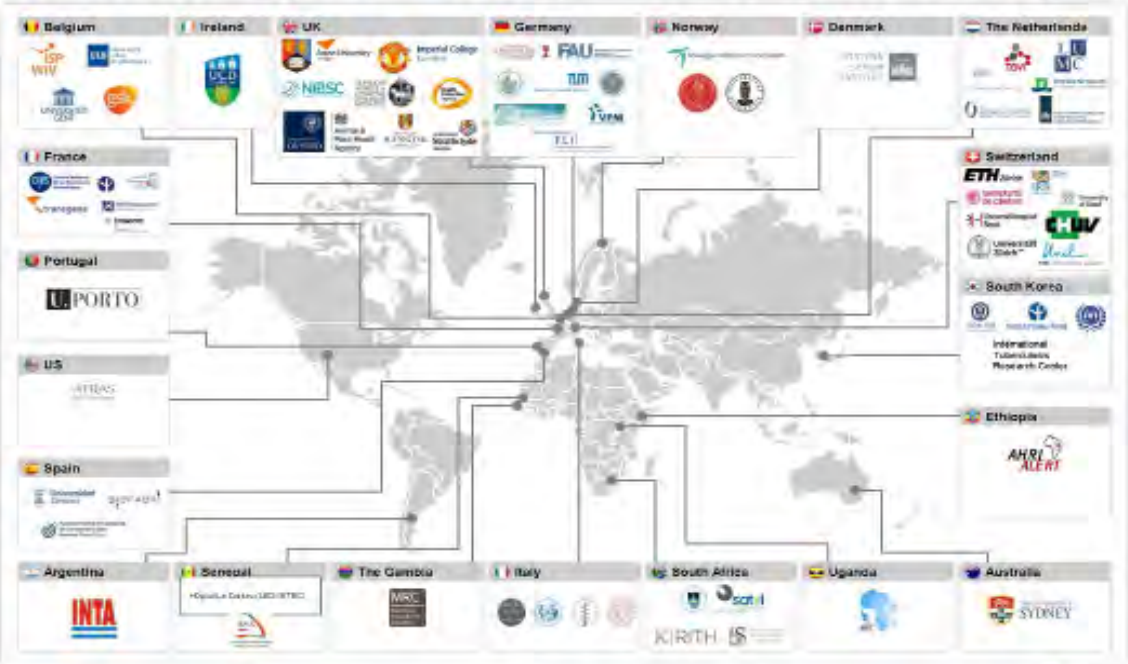
TBVI Business Model



TBVI operating principles

- Vaccine R&D through partnership
- Promoting an enabling R&D environment
- Ownership of vaccine candidates and biomarkers and any IP rights remain with researchers and vaccine developers
- Access and affordability of vaccines a guiding principle and is a commitment that is part of each project grant agreement supported by TBVI

We have worked together with our 72 partners worldwide in the last 10 years



TBVI – Accelerate the discovery and development of new TB vaccines that are safe, effective and affordable.

TBVI organisation

- Pools resources, provides project management and technical support to allow its R&D partners to focus on the science
- Leverages public sector funding to gain private sector investment.
- Provides the knowledge platform which enables its R&D partners to share unpublished data and convenes the brightest minds in TB research, bio-pharma and the public sector to bring a new vaccine to the market.
- Gives cutting edge expert, unbiased scientific advice to both scientists and funders.
- Acts as an "honest broker" between scientists and funders (IP rests with R&D partners; TBVI does not take equity/ownership)
- Provides funders with portfolio and investment advice. It engages with its global partners in developing up-to-date policy, strategy and priority setting in TB vaccine R&D

TBVI – Services to R&D partners

- As a **Product Development Partnership (PDP)**, TBVI integrates, translates and prioritizes Research and Development (R&D) efforts to discover and develop new TB vaccines and biomarkers for global use. The TBVI organization provides essential services that support the efforts of its 50+ R&D partners from academia, research institutes and private industry in the TB vaccine field. These services include:
  - Technical advice and support for product and clinical development
  - Resource mobilisation
  - Knowledge exchange and networking
  - Project identification, design and development
  - Project management
- TBVI provides funders with portfolio and investment advice. It engages with its global partners in developing up-to-date policy, strategy and priority setting in TB vaccine R&D.

4 We are mindful about how to allocate our funds

We manage our projects in a way to reduce any financial risks

General governance principles

TBVI manages ongoing projects to keep them on track

Transparency

- All TBVI's articles, policies, rules, decisions and recommendations are published to show transparency among stakeholders and public

Conflicts of interest

- TBVI uses safeguards to manage possible conflicts. All workers and experts are to declare their conflict of interests and comply with TBVI's conflict interest policy

TBVI acts as the gatekeeper

- Controls the financial status
- Checks if the research milestones are achieved

If there any problems TBVI will help out

Standards and codes of conduct

- All clinical trials participated by TBVI will be performed in a way accepted by ICH guidelines along with ethical and regulatory requirements

Confidentiality

- TBVI treats data received from its collaborators with strict confidentiality. Confidentiality agreements are a standard with handling sensitive information

SOURCE: TBVI

3 Our collaborative partnership model improves the quality of TB research

Partners regularly get together to share their knowledge

In total TBVI has organized over 40 scientific events on TB vaccine R&D[1]

This have led to cross learning, avoiding overlap and building ther on each other's knowledge

Example events	Location	# participants
4 global forums on TB vaccines	• China • South-Africa • Estonia • Switzerland	• Up to 300 participants, including policy makers, pharmaceuticals
22 specific project meetings	• Netherlands • Germany • Switzerland	• With annual 150+ researchers from specific projects — TBVAC — NEWTBVAC — TBVAC 2020 — Les Diablerets

> *It was for me really useful to know what is going on to **avoid overlap** and **build further** on **others' knowledge***

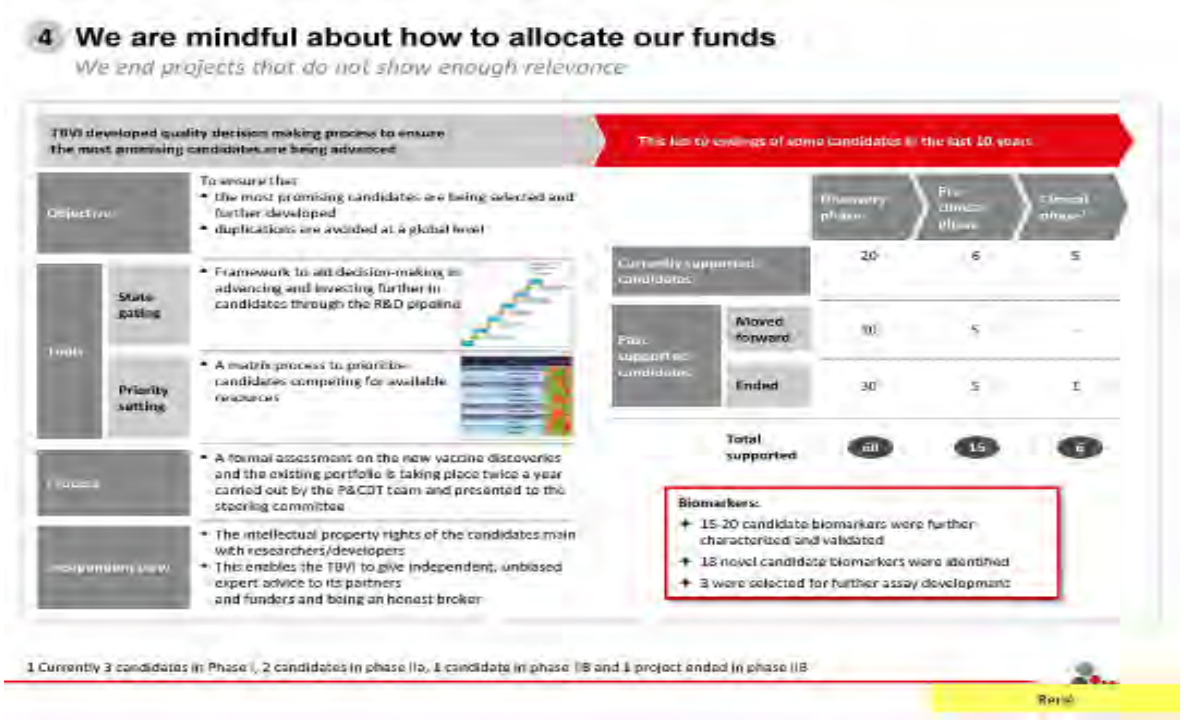
> *After the presentations regarding the latest data and research findings, we had the opportunity to **engage in discussion** and debate about the path forward for this critical research.*

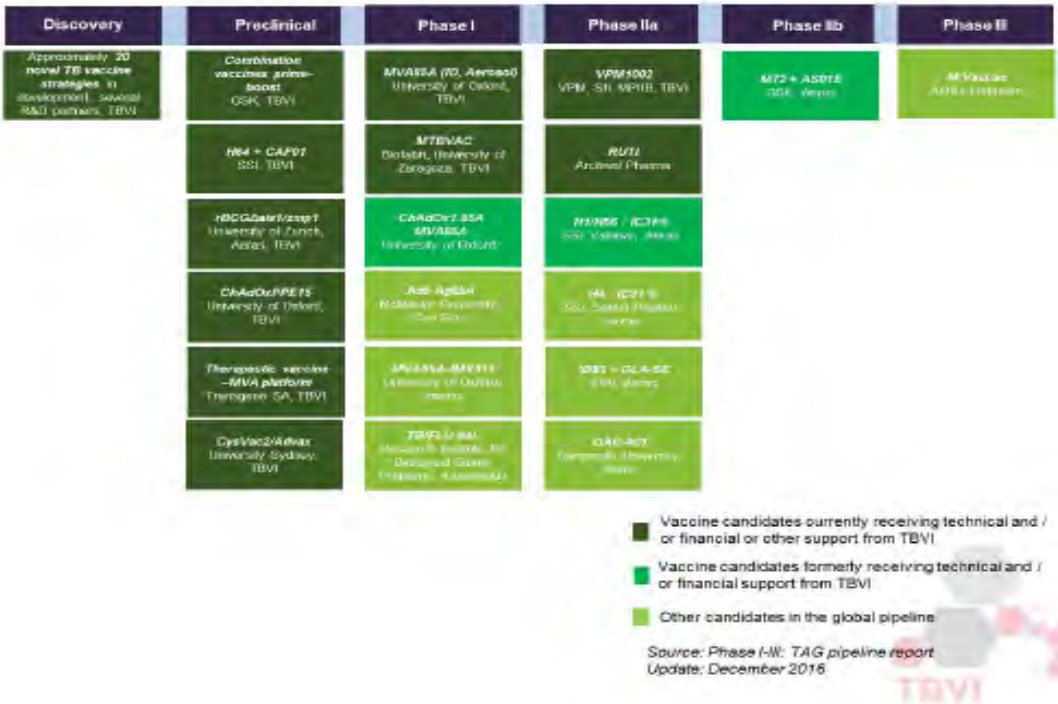
> *For me it is now **easier to connect** with all the stakeholders in the world (the leading researchers, product developers, pharmaceutical companies, government officials, advocates and others).*

TBVI creates an enabling environment for its consortium partners and other relevant stakeholders to promote knowledge sharing on events, but also outside events

1 Since 2004

SOURCE: TBVI


4 We are mindful about how to allocate our funds
We end projects that do not show enough relevance
TBVI developed quality decision making process to ensure the most promising candidates are being advanced
This led to endings of some candidates in the last 10 years
Objective
To ensure that:
the most promising candidates are being selected and further developed
duplications are avoided at a global level
Tools
Stage-gating
Framework to aid decision-making in advancing and investing further in candidates through the R&D pipeline
Priority setting
A matrix process to prioritize candidates competing for available resources
Process
A formal assessment on the new vaccine discoveries and the existing portfolio is taking place twice a year carried out by the P&CDT team and presented to the steering committee
Independent view
The intellectual property rights of the candidates main with researchers/developers
This enables the TBVI to give independent, unbiased expert advice to its partners and funders and being an honest broker
Discovery phase
Pre-clinical phase
Clinical phase
Currently supported candidates
20
6
5
Past support to candidates
Moved forward
10
5
Ended
30
5
1
Total supported
60
15
6
Biomarkers:
15-20 candidate biomarkers were further characterized and validated
18 novel candidate biomarkers were identified
3 were selected for further assay development
1 Currently 3 candidates in Phase I, 2 candidates in phase IIa, 1 candidate in phase IIB and 1 project ended in phase IIB


Discovery
Preclinical
Phase I
Phase IIa
Phase IIb
Phase III
Approximately 20 novel TB vaccine strategies in development, several R&D partners, TBVI
Combination vaccines prime-boost
GSK, TBVI
H4 + CAF01
SSI, TBVI
rBCGDeltaUreC::hly+
University of Zurich, Aeras, TBVI
ChAdOx1/MVA ID
University of Oxford, TBVI
Therapeutic vaccine –MVA platform
Transgene SA, TBVI
CysVac2/Advax
University Sydney, TBVI
MVA85A (ID, Aeras)
University of Oxford, TBVI
M72 + AS01E
GSK, Aeras
Vaccine candidates currently receiving technical and / or financial or other support from TBVI
Vaccine candidates formerly receiving technical and / or financial support from TBVI
Other candidates in the global pipeline
Source: Phase I-III: TAG pipeline report
Update: December 2016
TBVI

Jerry Reichman proposes a commons for biological resource materials

The Propertization of Plant and Microbial Genetic Resources

Consider that plant and microbial genetic resources, together with traditional knowledge concerning their uses by indigenous communities, had long been treated as freely available inputs into scientific research. Both pharmaceutical products to cure diseases and plant varieties to improve food security still remain heavily dependent on unrestricted access to these genetic resources. Obviously, the notion of a vast public domain served the interests of the Great Powers, who presided over biodiversity rich colonies. Nevertheless, it also led to the formation of public seed banks and microbial culture collections, institutions whose ongoing efforts to validate and preserve *ex situ* genetic resources constitute an integral part of the global scientific research infrastructure, with benefits to humanity at large.[1]

In the last quarter of the twentieth century, however, developed countries in the Global North pressed their former colonies–now sovereign and independent nations–to expand and respect patents on both plant and microbial genetic resources under the Agreement on Trade Related Aspects of Intellectual Property Rights of 1994, or at least to recognize plant breeders' rights under the International Convention for the Protection of New Varieties of Plants of 1991(UPOV). In response, developing countries in the Global South demanded and obtained exclusive rights to plant, microbial, and animal genetic resources and related data originating from their national territories under the Convention on Biological Diversity of 1992 (CBD), as reinforced by the Nagoya Protocol to the CBD of 2010.[2] This tug

of war between developed and developing countries threatened the very existence of public seed banks and microbial culture collections on which both agricultural research and the life sciences had long depended.

Strenuous efforts were subsequently undertaken to rescue the public seed banks administered by the Consultative Group on International Agricultural Research (CGIAR). Under the aegis of the United Nations Food and Agricultural Organization (FAO), the CGIAR's public seed banks were entrusted to a global Crop Commons that the International Treaty on Plant Genetic Resources for Food and Agriculture (ITPGRFA) established for this purpose in 2001. Now that the Nagoya Protocol to the CBD has expressly validated this multilateral regime of facilitated access to plant genetic resources for breeding and research purposes, similar efforts are underway to devise a multilateral regime of facilitated access to the public microbial culture collections governed by the World Federation for Culture Collections (WFCC).

[1] See, e.g., Cletus Kurtzman, The Agricultural Research Service Culture Collections: Germplasm Accessions and Research Programs, in DESIGNING THE MICROBIAL RESEARCH COMMONS: PROCEEDINGS OF AN INTERNATIONAL SYMPOSIUM 55 (P.F. Uhlir ed., 2011); World Federation For Culture Collections (WFCC), Guidelines for the Establishment and Operation of Collections of Cultures of Microorganisms, 3rd ed. (Feb. 2010), http://www.wfcc.info/guidelines.

[2] The Nagoya Protocol to the CBD authorizes seizure of imported end products derived from genetic resources without access and benefit-sharing agreements with provider countries

Xavier Seuba addresses trade and marketing barriers for biologic medicines

Xavier Seuba introduced regulatory barriers impacting on medicines, in particular biosimilar products. The discussion revolved around on-going disputes on two crucial topics: abridged regulatory approval processes and regulatory changes that impact on biologic products already in the market. These case-studies were used to reflect upon broader global concerns of both normative and institutional nature. First, in the normative context, it was discussed the potential relevance of the World Trade Agreement on Technical Barriers to Trade when adopting guidelines for the approval of biosimilars. Second, in the institutional field, the role of international norm-setting bodies and international harmonization processes was also introduced.

Biologic products, in particular biotechnological drugs, have become key therapeutic tools to treat a large number of diseases. Presently, more than 70% of deaths are caused by non-communicable diseases, and the majority of them are more and more treated with biologics. Products of biologic nature have also crucial importance to prevent a number of infectious diseases. However, competition is urgently needed in this pharmaceutical sector, in particular in emerging and developing economies. For instance, according to recent studies, the prices of trastuzumab, used to treat breast cancer, should decrease between 70-95% to make trastuzumab accessible in Latin American countries. It comes, therefore, as no surprise that developing economies think how best foster competition in the biosimilars market.

Regulatory approval processes for biosimilars can foster or hinder competition. Comparative pharmaceutical law shows great dynamism of legal frameworks for the approval of biosimilar products, and reveals as well the existence of several possibilities to satisfactorily address quality, safety and efficacy concerns. However, new norms that promote biologic competition by means of abridged market approval processes have prompted criticism of national and international associations of originator industries and some governments. Countries belonging to all levels of development, but in particular developing and emerging economies, have been the object of such criticism. The scientific consistency of arguments putting into question quality assurance guarantees of new approaches have to be treated separately from the legal strategy employed to challenge new bills. More precisely, the World Trade Agreement on Technical Barriers to Trade does not hinder national laws that promote international trade and competition. On the contrary, it would run against those that restrain trade and competition.

A second area of discussion concerns the impact on already existing products of changes introduced into laws regulating biologics. Litigation is currently taking place in several countries. Originator companies challenge the validity of market authorisations for biosimilars when normative changes take place and focus the debate on so-called "intended copies", mostly originating from emerging economies. The basic principle is clear: the most updated versions of regulatory requirements should be followed. The controversy, however, revolves around the specific actions with respect already existing products and the timing of those actions. While innovative biotech producers demand the immediate disposal from the channels of commerce of "old" products not fulfilling new conditions, the action in reality should change depending on the relevance of the changes and depending on the area they impact upon. With this scheme in mind, actions may entail removal, submission of extra information, or just waiting for the renewal of the marketing authorization to supplement the information.

Participant Comments and Recommendations:

1. Dilip Shah referencd the Biocom investigation in India involving Roche and its efforts to impede the entry of biosimilar.

2. Fred Abbott attempted to clarify with Xavi how the TBT agreement might be relevant to biosimilar standards adopted by a country like Colombia. There are some potential theories, but none seem persuasive on their face.

3. Jerry Reichman mentioned the potential value of a biologics material commons.

Global Pharmaceutical Regulation 2017
April 14-15, 2017 Florida State University, Tallahassee

Disputes over Biosimilar Regulations

- Approval of Biosimilars and Changes Impacting Already Approved Products-

Xavier Seuba
Senior Lecturer and Researcher
Academic Coordinator and Judicial Training Manager
Centre for International Intellectual Property Studies (CEIPI)
University of Strasbourg

Relevance of Biologics...

Public health

- NCDs amount to 70% of deaths
- The most sophisticates MABs are used to treat
  - Cancer
  - Autoimmune diseases
  - Alzheimer
- Biologics also for the treatment of
  - Chronic diseases such as diabetes (insulin)
  - Infectious diseases (recombinant vaccines)

Market

- In 2020
  - world market for biotech drugs will amount to USD 250 billions
  - 55% top 100 drugs will be biologic
  - Expiry of US patents of 14 biotech: sales worth up to 67 billions in 2014
- But competition is desperately needed
  - trastuzumab price should reduce from 70% to 95% to be accessible in Latin America

... importance of biosimilars and their market authorisation

I. Abridged regulatory path for the approval of biosimilars? Would it be a trade barrier?

Differences in size and structure of some macromolecules make difficult full characterization and exact copies may be impossible

The challenge is demonstrating that differences between the biosimilar and the reference medicinal product do not have a significant impact on clinical efficacy and/or safety

The economic and social function of fostering competition and access is the same for "biosimilars" and "generics". From that standpoint, they can be called "biogenerics" :

- Fulfil the same medical function
- Promote competition
- Use the same INN (although...)

Abridged approval of biosimilars

- Two commonly accepted principles that rule the marketing approval process for biosimilars:
  - Extended characterization exercise: demonstrate that the physicochemical and functional characteristics are very similar to those of the medicine or standard of reference.
  - Specific tests to assess the identity, purity, potency and immunogenicity of biocompetitors

- Colombian decree on MA of biotechnological medicines includes an "abridged" comparability path for biosimilars
- It proposes that, in some cases, information available in relevant countries and authorities will be used to accelerate entrance and save unnecessary tests
- Negative reaction of industries producing biotechnologicals, and their home countries

Route	Type of product
Complete	New biologic
Comparability	Known biologic
Abridged comparability	Known biologic

Information requested in the three routes

- Description of the process and place of production
- Expression system
- Biological identity tests
- Potency evaluation
- Physicochemical characteristics
- Evaluation of the biologic activity
- Evaluation of purity
- RM plan
- Immunogenicity studies

... continues what others also do

- "**In specific circumstances, a confirmatory clinical trial may not be necessary.** This requires that similar efficacy and safety can clearly be deduced from the similarity of physicochemical characteristics, biological activity/potency, and PK and/or PD profiles of the biosimilar and the reference product. In addition, it requires that the impurity profile and the nature of excipients of the biosimilar itself do not give rise to concern."
  CHMP/ 437/04 Rev 1 (into effect, April 2015)

- Colombian "third" path has not been yet tested. There is a similar regulatory process in Brazil, but products are not considered biosimilars
- The idea is that **scientific advances and increased knowledge on proteins allow going beyond the paradigm of clinical comparability**
- The ultimate goal is promoting generic competition of assured quality

Reaction on two fronts: trade and health

Trade

- Colombia notified draft decree to the **WTO TBT Committee**. US, EU, US stakeholders, and a Colombian patient groups submitted comments expressing concern
- The EU has been addressing this issue in the context of the WTO TBT Committee and the implementation of the EU-Colombia and Peru FTA
- The **EU** claims that the decree may damage health, be detrimental of the interests of EU companies, and **create barriers to trade**
- The **US** also addressed this issue in the context of **trade barriers** regulation (National Trade Estimate Report on Foreign Trade Barriers)

Health

- US Vice President **Biden** said that it was believed by WHO and US experts' "that the biologic[al]s decree could put health and **safety at risk**"
- The Colombia regulation would **violate** the 2009 WHO guidelines and the **"spirit"** of the 2014 WHO guidelines
- "The view of the **industry** is that regulatory approval path should be on a stand-alone basis, as under the '**complete file path**' route."
- **Similar** concerns expressed over **Indian guidelines:** "potential exists for reduced non-clinical and clinical testing programs if there is proof of strong quality comparability and manufacturing process consistency" (Mysler et al 2016)

Is the WTO TBT Agreement relevant at all?

- National **regulations cannot** become unnecessary **barriers to trade**
  - "necessity test": permitted to restrict trade where a legitimate goal is pursued, i.e. Including the protection of public health and it matches with international standards
- **BIO** (and the **US and EU) allege** that Colombian third path is different from WHO standards (which would be the standard of reference), and hence the **TBT Agreement** enters into play
- In this case, **however**, the legal framework adopted does **not run against, but in favour, TBT objectives**
  - It creates a more competitive framework
  - Benefits national and foreign companies –highly possible, foreign
- Relation with **international standardisation and institutional and power** dynamics behind it: ICH growing preponderance

II. What to do with "old" market authorisations when the regulation or product changes? (and *biomimics*)

Topics of discussion

- Disputes over validity of already granted MA when the normative framework changes
  - Broader discussion on procedures and data requirements for changes to approved products & regulation
  - Relevance of international standardisation
  - Use of (unlearned) courts to alter competition
  - Debate around 'intended copies' or 'biomimics'
- Innovative biotech producers demand the immediate disposal from the channels of commerce:
  - "old" products do not fulfil new conditions, in particular with respect PhV requirements and RM plans
  - They argue that the right to health entitles them to demand cancellation of old MA and intervene in the MA process of 3rd parties

- Originators argue that products introduced in the market prior to the implementation of regulatory pathways for the approval of biosimilars are just "intended copies" or "biomimics"
  - Their efficacy, safety and clinical performance are put globally into question

• 23 intended copies would exist in Mexico, + 25 in India (Pfizer)

Table 3 Countries in which intended copies of listed biologics for rheumatic conditions are approved and/or marketed without biosimilar regulations [14, 17, 91, 92]

Year of market introduction	Rituximab	Etanercept
2007	India (Reditux™)	–
2008	Peru (Reditux™)	Colombia (Etanar™)
2010	Chile, Bolivia (Reditux™) Mexico (Kikuzubam®)[a]	–
2011	Jamaica, Ecuador (Reditux™)	China (Yisaipu)
2012	Paraguay (Reditux™)	Mexico (Etart™; Infitam™)
2013	–	India (Etacept™)

[a] Withdrawn in 2014

From general principle to implementation

- Principle: fulfilment of the most updated versions of regulatory requirements. This is the case of comparative pharma-biotech legislations.
- Controversy, however, concerning specific actions with respect already existing products and the timing of those actions
- Majority of courts in Mexico are requesting immediate removal of "old" products from the market... But WHO 2016 take a more nuanced approach
  - WHO Expert Committee on Biological Standardization *Guidelines on procedures and data requirements for changes to approved biotherapeutic products* (draft Nov 2016)

Guidelines on procedures and data requirements for changes to approved biotherapeutic products

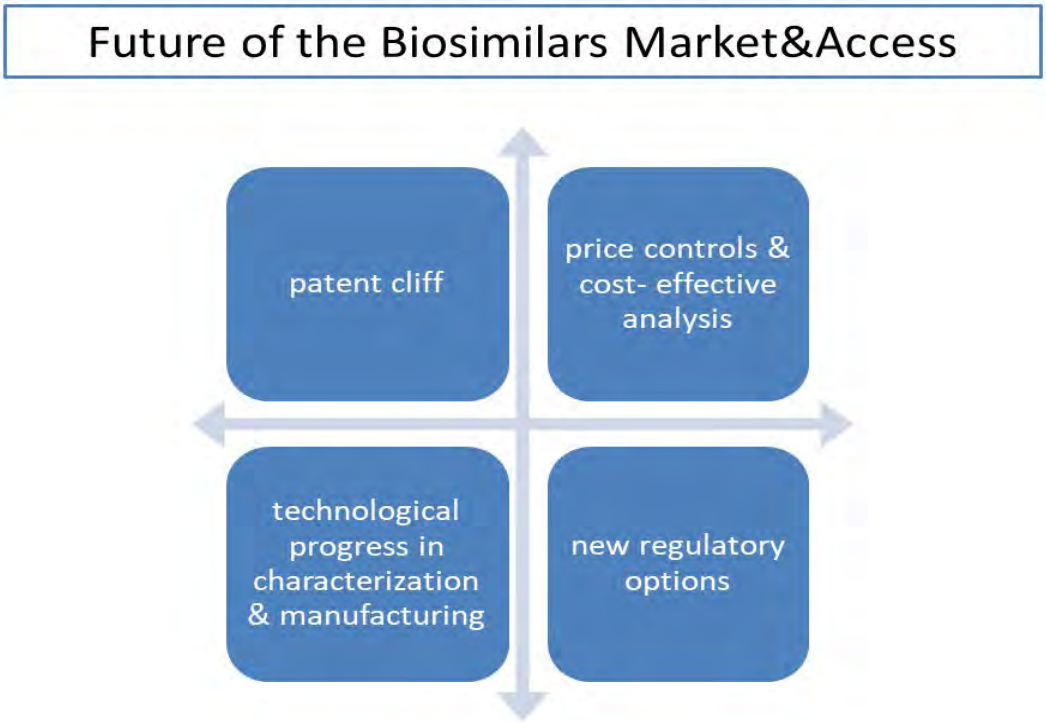
- Inform and support national authorities and producers about changes on already approved products to ensure both QSE and access
- Key aspects
  - Changes refer both to the product and norms
  - Changes (and guidelines) impact both innovators and biosimilars
  - Standards must be changed adopting a risk-management approach that impacts both on competitors and innovators.
- Principles
  - The most updated standards must be demanded in the processes for the renewal of marketing authorizations.
  - Active programs for verification of standards must be put in place by checking products in the market
  - Implementation of new regulations should not impact on provision and access to products

WHO: action will change depending on the area and impact

- WHO guidelines basic scheme, distinguishes...
  1. Assessment
  2. Identify area of concern (Q, S&E, labeling or adtve information) plus relevance of the impact (major, moderate, minor, no impact)
  3. Action
     - Suspend
     - Ad-hoc procedure to supplement the information
     - Wait for the renewal of the marketing authorization to supplement the information
- *vs.* immediate removal requested by originators

Strategic Areas & Combined factors

- **Social**: highly complex debate, difficulties in catching the attention and understanding of broader public
- **Judicial**: courts as "scientific gatekeepers" (*Daubert v. Merrell Dow Pharmaceuticals*)
- **Legal**: IP exclusivities strengthened by means of regulatory exclusivities
- **Governance**: global governance of pharma standards
  - Both the 2009 WHO biosimilar guidelines and the 2016 "changes" guidelines were 'animated' by IFPMA associates (in the first case, linkage was foreseen; in the second, only biosimilar producers were initiallly targeted)
  - The concept of comparability was developed in 1995 by the FDA. In 2004 became ICH Q5E. From there, it made the way to the 2009 WHO guidelines


Future of the Biosimilars Market&Access
patent cliff
price controls & cost- effective analysis
technological progress in characterization & manufacturing
new regulatory options

Dr. Ryan Abbott discusses the role of Big Data in medicines regulation and a proposal for private causes of action challenging regulatory approvals

Post-Market Drug Regulation in the Age of Big Data: What Path to the Promised Land?

INTRODUCTION

Every day 2.5 quintillion bytes of data are created—so much that 90 percent of the world's data has been produced in the last two years alone. This information revolution is transforming education, labor markets, and social relationships, and is creating entirely new industries. Some of the greatest advances have and will come in biotechnology and bioinformatics, where "big data" is altering new drug development, clinical practices, and health care financing. It also has the potential to lead to a new kind of understanding of how drugs work in the real world. In 1991, the Food and Drug Administration ("FDA") based its approval of the cholesterol-lowering drug simvastatin on pre-market controlled clinical studies that included a total of 2423 patients. In 2011 alone, health care providers, just in the United States, wrote almost a hundred million prescriptions for the drug. Imagine the impact of being able to analyze data from every one of those patients to evaluate whether simvastatin is safe and effective. Better yet, imagine analyzing data from every patient who has ever taken the drug in every country in the world. That is the vision of a drug regulatory system powered by big data. Historically, that type of research has been unachievable. But now, for the first time in human history, it is a possibility.

However, it remains just that—a possibility. Although a vision for a new type of post-market regulatory system exists, a plan does not. If the vision is to come to fruition, policymakers must address some operational challenges. First, the right kinds of data will need to be collected. Second, the data will have to be aggregated for analysis. Third, the results of analysis will need to be effectively plugged into the regulatory process. Unfortunately, progress along those three dimensions has been frustratingly slow, and even the data that is already available for analysis is being underutilized. Pharmaceutical companies are not adequately incentivized to use this data to maximize public health. The FDA is mission-driven to improve public health, but it

lacks the resources, information, and entrepreneurial drive of the 1.1 trillion-dollar-a-year private industry it oversees. Third parties, such as insurance companies, academics, and rival firms have some role, but their incentives to police the drug market are relatively weak despite the potential public health benefits.

Maximizing the data's value requires restructuring market participant incentives to enhance third party engagement in post-market surveillance. There are many ways to accomplish this, and the ideal solution may be a mix that offers a variety of incentives. However, I propose a novel mechanism to enhance third party engagement in the form of a new administrative bounty proceeding modeled after the False Claims Act qui tam regime. This would provide petitioners an award if they present the FDA with original data documenting a drug safety or efficacy concern that results in amended product labeling or the withdrawal from market of an approved drug or device. Petitioner rewards, paid by the government, could be structured to award a portion of the money that the federal government will save by avoiding adverse effects and medically ineffective therapies in patients with government health insurance.

POLICY RECOMMENDATIONS

1. Establish an administrative bounty proceeding that will motivate third parties to submit data on drug safety and efficacy to the FDA.

2. Model the administrative bounty proceeding after the Federal Claims Act qui tam regime.

3. The federal government should pay petitioner rewards based on a portion of the money that the government will save by avoiding adverse effects and medically ineffective therapies in patients with government health insurance.

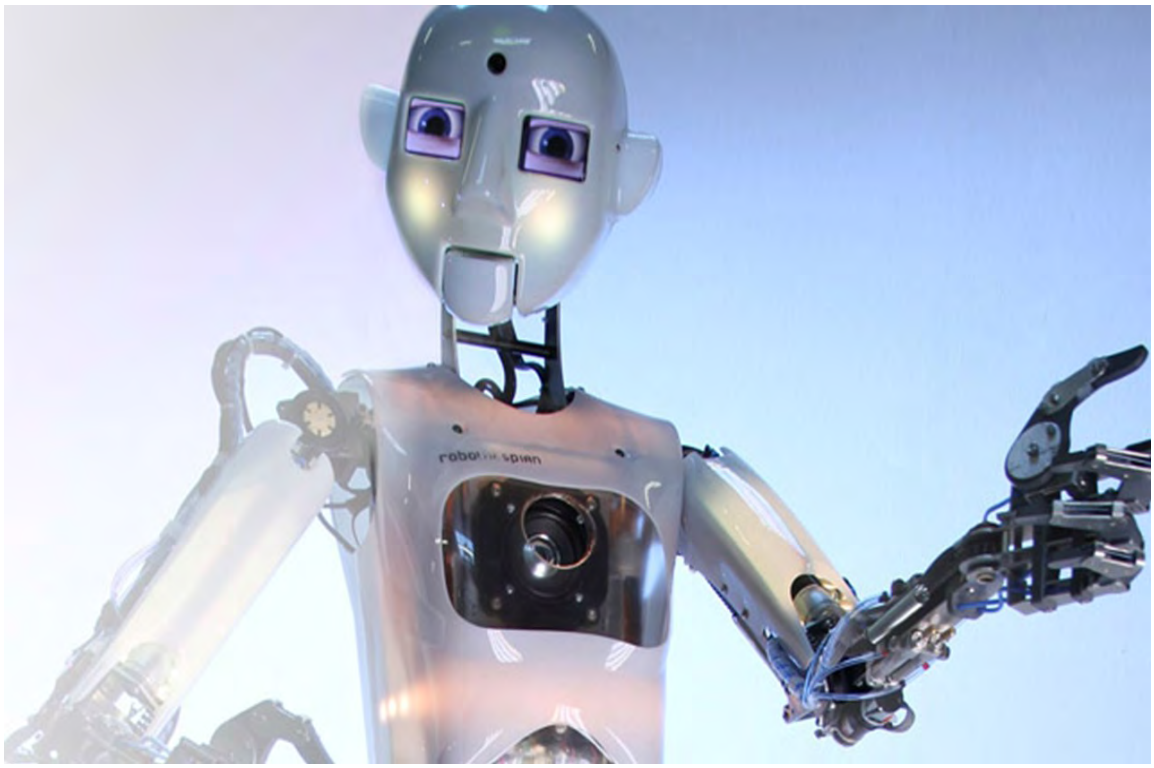
This presentation is based on: Ryan Abbott, *Big Data and Pharmacovigilance: Using Healthcare Information Exchanges to Revolutionize Drug Safety*, 99 Iowa L. Rev. 225 (2013).

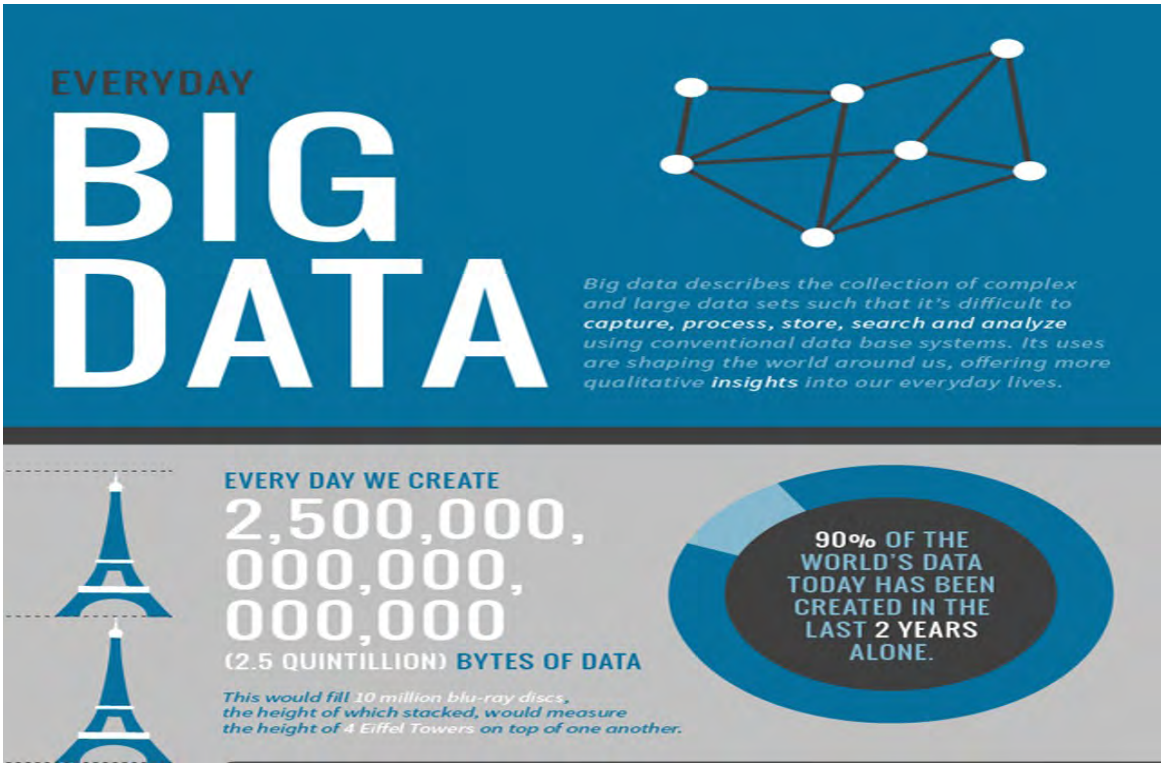
Big Data and the New Regulatory Regime

Ryan Abbott, M.D., J.D., M.T.O.M.

Professor of Law and Health Sciences, University of Surrey School of Law

Adjust Assistant Professor, David Geffen School of Medicine at UCLA





Big Data and Drug Regulation

- Data collection
- Data aggregation
- Data analysis
- Appropriate use

Sentinel System

- September 2007: FDAAA required FDA to develop an active surveillance system—25mm individuals by July 2010; 100mm individuals by July 2012
- Contracting and self-regulation vs. notice-and-comment rulemaking.
- Primarily distributed model, common data format, private operation
- Exclusive safety focus
- Today, access to more than 178mm individuals

Inadequate Third Party Participation

- Insurers
  - No benefits from sharing research results
- Academics
  - Slow, not-targeted to regulators, needs translation
- Plaintiffs' attorneys
  - Slow, recovery for damages not preventing injuries, non-transparent

New Incentives for Third Parties

- An administrative bounty proceeding for third parties to submit data on drug safety/efficacy to the FDA modeled after FCA qui tam regime.
- Qui tam litigation used to combat medical and pharmaceutical fraud and abuse under the False Claims Act (FCA)
- Government lacks the resources or ability to adequately combat false claims by itself, so it permits private qui tam actions that enable private individuals ("relators") to enforce the FCA
- Improper payments under Medicare and Medicaid are estimated at a staggering $70 *billion* annually. The federal government gets about $3 billion annually from FCA cases.

Administrative Bounty Proceeding

- Petitioner award for presenting FDA with original data documenting a drug safety/efficacy concern that results in amended product labeling or the withdrawal from market of an approved drug or device.
- An FDA administrative hearing, which would create an adversarial process where one party seeks to maintain drug approval (or labeling) while the other seeks to have the drug withdrawn (or labeling amended).
- The administrative hearing this proposal envisions would be a sophisticated litigation-type process.

Financing

- If a petitioner submission results in the FDA removing a product from the market or amending labeling, the federal government could pay the petitioner a reward based on the government's estimated cost savings over a determined time period.
- If the product's sponsor was negligent in obtaining or maintaining FDA approval, the sponsor could be responsible for paying the petitioner award instead of the government, based on a percentage of a drug's revenue during the period after the manufacturer should have known of the adverse data.
- If the manufacturer knowingly, recklessly, or with gross negligence withheld evidence of a drug safety problem from the FDA, the product sponsor could be responsible for treble damages, half paid to the petitioner and half to the government.

Vioxx

- 29,000 potentially eligible claimants nationwide alleged heart attacks from Vioxx use, and 17,000 alleged strokes.
- The estimated average costs to Medicare of treating a patient for 180 days after a heart attack or stroke are $16,845 and $16,280 respectively.
- This suggests that the total direct costs for patients from Vioxx use were $765 million. About 95 million Americans, or 31% of the population, are covered by government health insurance.
- 31% of $765 million, or $237 million, is the amount the federal government would have to pay as a result of adverse effects from Vioxx during its market life.

Pre-Clinical & Off-Label Use

- Movement toward deregulation of pre-clinical approval and restrictions on pharma speech

Fred Abbott discusses the use of competition law to prevent and redress pharmaceutical industry abuse of patents and market power

The use of competition law to constrain abuses of market dominance through excessive pricing, patent and regulatory abuse, and collusive undertakings is an increasingly important element of defensive measures. UNDP has been focusing in this area. My work has especially focused on the potential use of excessive pricing doctrine to constrain monopoly power. Investigations into pharmaceutical industry anticompetitive abusive practices are gaining traction. The EU Competition Directorate previously undertook a broad inquiry into abuse of patents in the pharmaceutical sector. Following the lead of the British CMA's levying of fines against Pfizer for excessive pricing, the EU Competition Directorate has also launched an investigation into excessive pricing. This work is highly dependent also on transparency, whether voluntary or mandated.

The recent trend toward more robust pharmaceutical-related action by competition authorities, including in emerging markets like China, India and Africa, is suddenly met with suggestions from multinational trade groups that perhaps new multilateral competition rules are needed. These proposals should be treated with caution as they are intended to constrain the power of competition authorities, not expand them.

The enforcement of competition law relies on independent prosecutorial authorities with adequate power to accomplish their jobs. Those authorities rely on independent judges to assess their actions. This may sound like it can be taken for granted, but interference in the work of competition authorities, and gaps in investigative powers, are a substantial issue in a number of countries. It is important to support the independence of these authorities.

Participant Comments and Recommendations:

1 Jamie Love discussed the investigation by the South African Competition Commission relying on essential facilities doctrine because, *inter alia*, the Commission was concerned about the lack of precedent with respect to excessive pricing. He also discussed the compulsory licensing litigation in India involving Nexavar where the judge was more comfortable acknowledging that pricing was generally left in the hands of the drug supplier, but with the condition that access to patients must not be compromised.

2. Xavi Seuba referred to competition actions initiated in Argentina with respect to distribution. In Colombia both the originator and generics industries are against any form of price controls. In Spain, companies must provide information.

3. Jamie Love suggested that price data regarding clinical trials is relatively easy to obtain or infer, but the real difficulty concerns preclinical research which is a "black box". The DiMasi studies do not reveal pre-clinical data.

USING COMPETITION LAW TO ADDRESS ACCESS AND INNOVATION BARRIERS IN THE PHARMACEUTICAL SECTOR

Prof. Frederick Abbott

Global Pharmaceutical Regulation 2017

FSU College Of Law, Tallahassee, USA

April 14-15, 2017

REASONS FOR USING COMPETITION LAW

- Traditional legislative political process is strongly influenced by financial and other interests that make protection of the public interest difficult
- In principle, competition authorities act independently of executive or legislative direction in specific cases
- Private civil actions may further depoliticize

DIRECT PRICE CONTROLS AN ALTERNATIVE

- Cost-plus disfavored by industry, at least with respect to production
- Corrupt practices problematic
- Political resistance in the US a barrier

DIFFICULTIES WITH CASE-BY-CASE ENFORCEMENT

- Court proceedings, including preparation, typically expensive and lengthy
- Defendants highly capitalized
- Doctrinal uncertainties inhibit
- Triple damages in the United States help to offset barriers

EMBEDDED REGULATORY APPROACHES

- Canadian Patented Medicines Prices Review Board model
- US Hatch-Waxman Act para. iv certification process
- FTC competition enforcement, affirmation in *FTC v. Actavis*

UNDP COMPETITION LAW EFFORTS

- Guidebook on Use of Competition Law to Promote Access to Health Technologies (2014)
- Pharmaceutical Sector Inquiries in ASEAN Region
- Training Programs

EXCESSIVE PRICING DOCTRINE

- Competition authorities and courts traditionally reluctant to address excessive prices "as such"
  - Difficult to determine the reasonable price for a pharmaceutical product based on R&D involving risk, and consequently difficult to determine what is an excessive price over that reasonable price
  - Judicial authorities not well-equipped as price regulators
- Objections not persuasive: addressed in article (Excessive Pharmaceutical Prices and Competition Law: Doctrinal Development to Protect Public Health)
- Transparency implicated in establishing R&D costs

CASE DEVELOPMENTS

- UK Competition and Markets Authority (CMA) in December 2016 imposes fine of £90 million on Pfizer and Flynn for excessive pricing relating to "de-branding" (on appeal)
- *FTC v. Mallinckrodt*, Settlement, fine $100 million and compulsory technology license, January 2017
  - Extraordinary case involving unlawful abuse of monopoly position with respect to vital children's medicine, and charging of excessive prices
  - City of Rockford, Illinois, follow-on to recover excessive payments

TRANSPARENCY

- In ASEAN countries pricing information difficult to obtain because of confidentiality obligations imposed on purchasers
  - Competition authorities can compel, but this is a second-best option
- Pursuing database on patent coverage, market exclusivity and terms

PARALLEL IMPORTS AND REGULATORY TAKINGS

- International exhaustion issue addressed in South Africa Medicines Act proceedings leading ultimately to Doha Declaration
- Currently before US Supreme Court, *Impression Products v. Lexmark*
- Filing of Amicus Brief
- US Import Authorization Legislation
- Surfacing of unconstitutional takings issue by originators
  - Appears taken seriously within congressional branch

The Global Medicines Council and Its Future Work

Jerry Reichman discussed his work regarding the interface between the Marrakesh Treaty for the Visually Impaired and potential use of Article 31bis of TRIPS. He suggests that the Marrakesh Treaty provides very detailed rules (referring to Article 5 regarding Cross-Border Exchange), which could be adapted for use through Articles 31 and 31bis of the TRIPS Agreementt.

Jerry Reichman indicated that royalties awarded by the US Federal Court of Claims are in the range of 4-12%, and that royalties based on government use of patents are awarded all the time. Back to back government use/compulsory licenses are an option for the supply of low cost medicines.

Xavier Seuba indicated we need to look at other barriers, particularly regulatory barriers and market exclusivity.

Nick Drager noted that one reason Canadian generic manufacturers did not have success under the licensing for export legislation is that the Canadian domestic market is too small.

Jerry Reichman referred to the importance of having an intergovernmental committee on IP to resolve policy issues. Jorge Bermudez said that they have that in Brazil but it does not work because the agencies, such as agriculture and health, have completely different perspectives.

On the issue of transparency, Joe Fortunak said that he has a lengthy list of information that he would like to get with respect to biologic medicines. Jorge Bermudez noted the focus of the High Level Panel on transparency.

Nick Drager noted the importance of legitimate and credible positions, such that might be developed and articulated by this group.

Jicui DONG commented that the access to the well-known products like insulin is still a problem. There is a need for more transparency on insulin market data and a need for more public health-focused market research. They are various barriers, such as barriers to biosimilar regulatory approval, that prevent insulin's access. She wondered whether it might be possible for this group to do some efforts to improve the access of these types of products. Jorge Bermudez concurred with this suggestion.

Nick Drager suggested to potentially go after the low hanging fruit, and that transparency might be that low-hanging fruit. Transparency is a cross-cutting issue, and EU authorities take a substantial interest in this.

Jerry Reichman asked whether an organization like Carb-X might be interesting to look at, and how they are handling their access policy. Fred Abbott noted earlier discussions which indicated they had not initially addressed the issue, but would be working on it. He also referred to the related project under the DNDi umbrella, GARDP.

Fred Abbott also reminded that we should keep an eye on what others are or have been doing. For example, a group called Transparency Alliance had a mandate to secure data, and Health Action International has also worked in this area.

Jamie Love concurred that approaching transparency would be a good idea since there are a wide range of parties interested in the subject, including doctors groups and government authorities. He suggested we might be able to scale up work on transparency, including with respect to the cost of clinical trials, conduct of patent landscapes, etc.

Jerry Reichman referred to calls for a failed trial database that would prevent duplication of efforts, and potentially provide research leads.

Xavier Seuba referred to judicial training and standards, as well as advancing work on damages and enforcement rights.

Jicui Dong suggested that perhaps a paper could be published in the WHO Bulletin as an editorial. Then there could be linked papers.

Nick Drager endorsed the idea of looking at transparency. He suggested that the work should be very specific with clear language. The Netherlands is interested in transparency.