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In reply please refer to: HLP 6-3-16

Your reference:

UN Secretary General High-Level Panel
on Access to Medicines
Ruth Dreifuss, Co-Chair
Festus Mogae, Co-Chair

7 March 2016

Dear Madam Dreifuss,
Dear Mr Mogae,

I am pleased to send you this letter and the attached submission in response to your request for a written contribution by the World Health Organization to the UN SG High-Level Panel on Access to Medicines.

The mandate of the High-Level Panel focuses on the current innovation model and its impact on access to health products. It does not include the many other complex challenges countries are facing in designing robust health systems and ensuring delivery of primary care. The Panel is looking both for possibilities for incremental improvements of the current system and for alternative or complementary models through which to research and develop new medical treatments, vaccines and diagnostics.

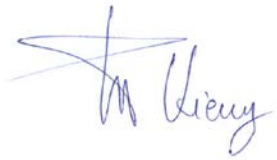
This submission thus briefly summarizes relevant WHO experience in access to medicines that relate to the current innovation system, and presents in more detail a number of WHO-led projects that implement alternative models of innovation. These will foster the development of health products that address priority health needs, to ensure these products will be affordable and available to those who need them.

I hope that this submission proves useful to the work of the High-Level Panel. I would also like to draw your attention to two other submissions in which WHO is implicated:

- "The 3P Project" which aims to rapidly deliver affordable, effective new regimens for the treatment of TB through an open collaborative approach to conducting drug development and through novel approaches to financing and coordinating R&D submitted by Médecins sans Frontières and;
- "Health Product R&D Fund: a proposal for financing and operation" prepared by the Special Programme for Research and Training in Tropical Diseases (TDR) in response to the request by the World Health Assembly in 2014; see Annex 3).

Should you have any questions or should you wish for further information, my team and I would be very glad to provide you with whatever you require. I wish you all success for this endeavour and look forward to continuing to support you in this important process.

Yours sincerely,



Dr Marie-Paule Kieny
Assistant Director-General
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WHO Submission to the UN SG High Level Panel on Access to Medicines

WHO welcomes the launch of the 2030 Agenda for Sustainable Development, and commits to work with partners around the world to achieve the new Sustainable Development Goals (SDGs). Building on the Millennium Development Goals (MDGs), the SDG agenda demonstrates unprecedented scope and ambition. The Goal 3: "Ensure healthy lives and promote well-being for all at all ages", profiles health as a desirable outcome in its own right. Importantly, however, health contributes to the achievement of other sustainable development goals, and is a reliable indicator of how well sustainable development is progressing in general.

The health goal itself includes new targets for key issues on which major progress has been made under the MDGs. The global HIV, TB and malaria epidemics have been turned around. Worldwide, child mortality and maternal mortality have dropped greatly, by 53% and more than 40% respectively since 1990. But much remains to be done. Reports of global progress have often masked discrepancies in progress between and within countries. There is a recognition of the need to focus not only on ensuring that people survive, but that they thrive as well.

WHO looks forward to collaborating with partners to meet all these targets, and welcomes the inclusion of universal health coverage. Universal health coverage expresses the very spirit of the new development agenda, with its emphasis on equity and social inclusion that leaves no one behind[1]. Improving access to medical products, includes medicines, vaccines, diagnostics and medical and assistive devices, is central to the achievement of universal health coverage. Hence, improving access to medicines is core to WHO. Increasing access to essential, quality-assured and affordable medical products is one of the six leadership priorities of WHO and is a key to ensuring equity in public health. In this context, WHO work related to intellectual property (IP) and patents is mandated by the World Health Assembly (WHA) through the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property, which states that:

> "WHO shall play a strategic and central role in the relationship between public health and innovation and intellectual property within its mandates… capacities and constitutional objectives, bearing in mind those of other relevant intergovernmental organizations."

While recognition and protection of intellectual property rights are essential concepts underlying the pharmaceutical industry's current business model, market incentives do not always match public health priorities, as already highlighted by the Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH). Where intellectual property rights lead to dominant market positions and high prices, a number of ethical challenges arise, because medical research should benefit the whole of humanity.

Innovation in medical technologies is characterized by the high costs of research and development (R&D) and a high risk of failure. On the other hand, production costs—in particular for medicines that are small chemical molecules—are often very low. Thus, in the absence of intellectual property protection, competitors can enter the market with cheaper generic versions of new products immediately after the original versions are registered, despite these companies never having had to bear any of the associated R&D costs. It is thus likely that the private sector would not invest at current levels in pharmaceutical R&D were there no legal protection against immediate replication of new medicines—unless the R&D

[1] Modified from -- http://www.who.int/mediacentre/news/statements/2015/healthy-lives/en/

effort was remunerated through a different mechanism. Two WHO expert working groups have explored and assessed alternative or complementary innovation models that the HLP may want to consider in its deliberations (see 4.1).

This submission briefly presents some relevant WHO experience in access to medicines (see 1-2), cooperation between international agencies (see 3), and a number of projects WHO is currently implementing to foster the development of health products that address priority health needs (see 4). This submission leaves out many other aspects of WHO's work and experience that are relevant to access to medicines in general, as we understand that these are outside the mandate of the HLP.

1. Towards increased availability and fair pricing of medicines

1.1. Expansion of the Essential Medicines List

Recently, WHO has added a number of patented medicines to the WHO Model Lists of Essential Medicines (WHO EML). Essential medicines are defined as "those that satisfy the priority health care needs of the population". The selection of specific medicines is based on a comprehensive review of available evidence for benefits and harms. The WHO EML are used by governments and institutions worldwide to guide the development of their essential medicines lists and to make appropriate procurement decisions. In April 2015, the WHO Expert Committee on the Selection and Use of Essential Medicines included in the 19th EML 16 new medicines for cancer, all six newly available innovative oral treatments for hepatitis C, and five tuberculosis treatments. While the vast majority of the medicines on the list remain available as generic versions, this revision adds several medicines that are still patented in major markets (all new oral treatments for hepatitis C, several cancer drugs and two new treatments for multi-drug resistant tuberculosis), and which are largely unaffordable for health systems across the world. By adding these new medicines to the Model List, WHO is underscoring the public health significance of these medicines and the need for strategies to make them affordable worldwide and ensure equitable access, including in low- and middle-income countries.[2] WHO is currently also working on a review of all antibiotics, with a view to identifying those to be considered essential.

The High-Level Panel may wish to highlight the importance of the WHO Model List of Essential Medicines as a tool to advocate for access to priority medicines in all countries.

1.2. More transparency about the patent status of essential medicines

To facilitate access to new treatments, the WHO Secretariat published an analysis of the patent situation for all new hepatitis treatments in August 2014. This is continuously updated[3]. The patent working papers identify the most relevant patents and list the countries in which they have been filed and granted. This information is key to allow countries to assess whether they can procure or locally produce generic copies of these treatments. Likewise, in 2016 the WHO Secretariat will publish a study on the role of intellectual property for local production that will contain more patent information on a number of further essential medicines, including for the treatment of cancer.

The High-Level Panel may wish to consider calling for transparency of the patent status of all essential medicines worldwide, as this information is not presently easy to obtain. This would allow countries to assess whether they can procure generic copies, or produce them locally.

[2] For further information on the EML see: http://www.who.int/medicines/publications/essentialmedicines/en/
[3] http://www.who.int/phi/implementation/ip_trade/ip_patent_landscapes/en/

1.3. Expansion of the Medicines Patent Pool

The creation of the Medicines Patent Pool (MPP), following the CIPIH report and ground-breaking work by a number of non-governmental organizations supported by UNITAID, was a major advancement for access to medicines. The MPP started with a mandate to negotiate licenses on HIV drugs with patent holders, in order to allow generic companies to produce and sell generic copies in low and middle-income countries. The Pool has by now signed license agreements with all originator companies marketing antiretroviral treatments for HIV, and has also signed numerous agreements with generic companies. Recently, supported by WHO, the Pool has expanded its scope to tuberculosis (TB) and hepatitis C. Its first license agreement on a WHO recommended hepatitis C treatment allows the marketing of generic copies in more than 112 countries—that is to say, more than two thirds of all middle-income countries can now procure more affordable generic copies under this agreement.

The High-Level Panel may wish to consider calling for further expansion of the mandate of the Medicines Patent Pool to all disease areas, and for all patented essential medicines on the WHO Essential Medicines List to be licensed into the Pool.

1.4. Towards a fairer pricing model

The current intellectual property system has created situations where new treatments are launched at increasingly high prices, which creates affordability and sustainability issues for health systems even in high-income countries. Launch prices as set by companies are not based on R&D investment or production costs, but on the outcomes of economic calculations that aim to identify the highest possible profit margin the market will tolerate.[4] This finding has recently been confirmed by a US Congress investigation into novel hepatitis C treatments. The investigation found that:

"the company's marketing, pricing, and contracting strategies were focused on maximizing revenue—even as the company's analysis showed a lower price would allow more people to be treated".[5]

Many countries have established complex sets of price regulations and controls and other policy measures to limit costs for payers and insurance systems. These systems vary considerably from one country to another, and have produced varied results. In order to align innovation with public health priorities, the right incentives must be set by price controls, decisions about what to reimburse, and reimbursement limits. The price of a medicine, while allowing for a profit margin, should reflect its public health value to consumers and must be affordable for the respective health system. Setting prices based on the societal value of new medicines allows use of the market system to direct R&D investment toward socially valuable new drugs.

While the High-Level Panel focuses solely on the current innovation system's impact on access to *new* medicines, it is also critical to ensure access to all existing *essential* medicines. While the vast majority of these medicines are available as relatively cheap generic versions, the median availability of essential generic medicines in developing countries has been found to be disturbingly low[6]:

[4] Ed Schoonveld, *The Price of Global Health*, 2011.
[5] *The Price of Sovaldi and its Impact on the U.S Health Care System*. Dec. 2015: http://www.finance.senate.gov/newsroom/ranking/release/?id=3f693c73-0fc2-4a4c-ba92-562723ba5255 – Accessed 24 February 2016.
[6] Global Health Observatory data: http://www.who.int/gho/mdg/medicines/availability_text/en/

Median availability of essential generic medicines in developing countries		
	Public sector	Private sector
Low-income countries	37.7 %	70 %
Middle-income countries	46 %	71.7 %

Furthermore, while generic competition is an efficient way to drive prices down, some off-patent essential medicines and vaccines are now so cheap that it is difficult to find manufacturers willing to maintain sufficient consistent production that satisfies quality standards in order to meet global demand. WHO is working on convening a Fair Pricing Forum in 2016 that will address both the issue of unaffordable prices for certain medicines and the phenomenon of essential medicines disappearing from the market (for further detail see Annex 1).

The High-Level Panel may wish to call for more work to be done to assess which models provide an appropriate balance between affordability and maintaining incentives for investment, including into R&D.

1.5. The case of chronic non-communicable diseases

The rising burden of chronic non-communicable diseases (NCDs) is quickly becoming the largest contributor to disease burdens and premature deaths in all countries. In parallel with preventive efforts, ensuring access to essential and affordable medicines is a key priority. The WHO Global Action Plan for the Prevention and Control of Non-communicable Diseases 2013–2020[7] fixes an objective of achieving 80% availability of the affordable basic technologies and essential medicines, including generics, required to treat major NCDs in both public and private facilities. Around 50% of premature mortality from NCDs can be avoided through equitable and appropriate access to health care, of which continuous supply to medicines is an essential component. The majority (82%) of these premature deaths occur in low- and middle-income countries. Most of the essential medicines for NCD management in primary care are in principle available in generic form; but in reality many of these essential medicines are unavailable in the public sector and are often unaffordable in the private sectors of many countries, in particular low- and middle-income countries. In a 2015 WHO survey, only 21% of Member States reported that they were providing drug therapy in primary care to people at high risk of heart attacks and strokes.

Poor availability and affordability are due to a number of factors, including: systemic weaknesses within health systems; supply chain issues; inequity; lack of insurance coverage; insufficient investment; and high prices (of generic medicines) in the private sector due— inter alia—to high taxes and unregulated mark- ups in the supply chain. A WHO discussion paper addresses the different bottlenecks on the path to attaining 80% availability of affordable basic technologies and essential medicines, along with potential solutions. Intellectual property considerations do not currently play a major role with respect to access, with the exception of a number of cancer treatments (see also 1.1), and in potentially in the future in cases of newly-invented breakthrough treatments.[8]

The High-Level Panel may wish to consider this problem, which is one of the major current challenges in the area of access to medicines, in its review.

[7] Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013–2020: http://www.who.int/nmh/publications/ncd-action-plan/en/.
[8] See http://who.int/nmh/events/ncd-coordination-mechanism-essential-medicines/en/

2. Assessing the line between innovation and lifecycle management

The World Trade Organization (WTO) Agreement on Trade-Related Intellectual Property Rights (TRIPS) leaves countries considerable flexibility in how they translate the TRIPS agreement into national law, something reinforced by the WTO Doha Declaration in 2001. Since then certain WTO Members have used these flexibilities to design national IP systems best suited to their needs and capacities, in particular in the health sector.

The World Intellectual Property organization (WIPO) Database on Flexibilities in the Intellectual Property System assembles resources on the use and implementation of such flexibilities, and shows to what extent and how countries have made use of them.[9] In the area of patent law, two opposing trends can be observed.

On the one hand, a number of high-income countries seek to heighten levels of protection, in particular for inventions in the pharmaceutical sector, through bilateral and regional trade agreements.[10] The features included in these agreements, such as patent term extension, patent linkage and data exclusivity, are impacting generic competition and thus have the potential to delay price reductions linked to competition.

On the other hand, some middle-income countries are redefining what should be considered an invention in the pharmaceutical sector. Following the example of India—which has limited the patentability of pharmaceutical products to new chemical entities—other middle-income countries such as Argentina, the Philippines, Brazil and South Africa have introduced or are considering similar approaches to patentability requirements with respect to pharmaceuticals. For patent examination, the way in which national guidelines for examination are drafted is key to ensuring thorough implementation of patentability criteria. The International Centre for Trade and Sustainable Development (ICTSD), the UN conference on Trade and Development (UNCTAD) and WHO have all published draft guidelines[11] contributing to the improvement of examination of pharmaceutical inventions, particularly in developing countries.

The tightening of patentability standards is a reaction to what industry calls "life cycle management," because

> *"…a key element of life cycle management strategies is to extend patent protection for as long as possible by filing secondary patents to keep generics off the market."*[12]

Secondary patents are follow-on patents filed after the main patent, which usually covers the key active ingredient or protein sequence. Secondary patents typically cover formulations, methods of administration, combinations of different treatments and second or new uses of existing compounds. They can delay the entry of generic copies—for example through patents on specific crystalline forms or combination patents—or allow patients to be switched on to slightly improved patented versions of the same treatment. This can have advantages for the health system (e.g. it can reduce hospitalization time), but it also carries risk.[13] If a patent is granted on

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[9] http://www.wipo.int/ip-development/en/agenda/flexibilities/search.jsp

[10] See for further details: WHO, WIPO, WTO, Promoting access to medical technologies and innovation: Intersections between public health, intellectual property and trade. Geneva: 2013: http://www.who.int/phi/promoting_access_medical_innovation/en/

[11] http://www.who.int/phi/publications/category/en/

[12] Burdon M, Sloper K, The Art of Using Secondary Patents to Improve Protection. *Journal of Medical Marketing, Device, Diagnostic and Pharmaceutical Marketing*, June 2003, vol. 3 no. 3 226-238. doi: 10.1057/palgrave.jmm.5040125

[13] WIPO, Study on pharmaceutical patents in Chile, Geneva 2015: http://www.wipo.int/edocs/mdocs/mdocs/en/cdip_15/cdip_15_inf_2.pdf; WHO, WIPO, WTO, Promoting access to medical technologies and innovation: Intersections between public health, intellectual property and trade. Geneva: 2013: http://www.who.int/phi/promoting_access_medical_innovation/en/ – Page 131; European Commission, Final

a slightly improved version of an existing medicine and patients are switched to the new version, the price reductions linked with generic competition are delayed.

The High-Level Panel may wish to consider the question of how to draw the line between what advancements should be considered patentable and what is part of lifecycle management.

3. Cooperation across the UN family

Based on the mandate provided by the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property, the WHO, WIPO and WTO secretariats have initiated trilateral cooperation to provide more coherent policy advice to their respective Member States, and to avoid creating fragmented programmes with important omissions, ensuring particularly that they consider the repercussions of trade and intellectual property policy frameworks on innovation and access to medicines. For more information, see Annex 2.

WHO has also worked closely with UNCTAD and the UN Industrial Development Organization (UNIDO) on local production of medicines in developing countries, with the goal of improving access. In 2014, WHO carried out a joint mission with the UN Development Programme (UNDP) to provide policy support to the Republic of Moldova, and, with the Joint United Nations Programme on HIV/AIDS (UNAIDS) and UNDP, published a policy brief on the use of WTO TRIPS flexibilities with regard to HIV.[14] There is, however, a need for closer collaboration within the UN system in order to make better use of limited resources, and to provide more comprehensive technical support.

In line with its constitutional mandate "to act as the directing and co-ordinating authority on international health work," WHO organized the first ever meeting of the UNAIDS, UNITAID, UNCTAD, UNDP, WHO, WIPO and WTO secretariats in February 2015 to share information on their respective activities regarding public health and intellectual property.

The High-Level Panel may wish to advocate for closer collaboration, under the leadership of WHO, between the different organizations within the UN system and other relevant organizations working on access to medicine. This enhanced collaboration could facilitate the integration of each organization's respective mandate regarding access to essential medicines.

4. Alternative/new approaches to R&D

4.1. The Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (GSPA-PHI)

This key WHO resolution of GSPA-PHI was the outcome of recommendations relating to the Commission on Intellectual Property Rights (IPR), Innovation and Public Health (CIPIH), set up in May 2003 in pursuance to WHA56.27. WHO Member States set up a time-limited body to consider the relationship between intellectual property rights, innovation and public health. The operative part of the text of the resolution establishing the CIPIH (WHA56.27) reads as follows:

> *"...collect data and proposals from the different actors involved and produce an analysis of intellectual property rights, innovation, and public health, including the question of appropriate funding and incentive mechanisms for the creation of new*

Report on its competition inquiry into the pharmaceutical sector, http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/

[14] http://www.who.int/phi/publications/category/en/

medicines and other products against diseases that disproportionately affect developing countries..." CIPIH concluded that "importance of Intellectual property rights in the promotion of the needed innovation depends on context and circumstance. They are considered a necessary incentive in developed countries where there is both a good technological and scientific infrastructure and a supporting market for new health-care products. But they can do little to stimulate innovation in the absence of a profitable market for the products of innovation, a situation which can clearly apply in the case of products principally for use in developing country markets. The fundamental problem is the lack of effective demand in the market for products that are required to prevent, treat or cure illnesses that affect poorer people in developing countries. The market alone, and the incentives that propel it, such as patent protection, cannot by themselves address the health needs of developing countries. That is the principal reason why new initiatives have sprung up in recent years, such as public–private partnerships".

BOX – WHA Resolutions on Innovation and Access to medical products	
2003	WHA56.27: Intellectual property rights, innovation and public health
2006	WHA59.24: Public health, innovation, essential health research and intellectual property rights: towards a global strategy and plan of action
2006	WHA59.26: International trade and health
2007	WHA60.30: Public health, innovation and intellectual property
2008	WHA61.21: Global strategy and plan of action on public health, innovation and intellectual property
2009	WHA62.16: Global strategy and plan of action on public health, innovation and intellectual property
2012	WHA65.22: Follow-up of the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination
2013	WHA66.22: Follow-up of the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination
2014	WHA67.28: Follow-up of the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination: Meetings of stakeholders for selected health research and development demonstration projects
2015	WHA68.18: Global strategy and plan of action on public health, innovation and intellectual property WHA68.34: Follow-up of the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination, Report by the Director-General

It may be noted that the GSPA identified several deliverables on public health, innovation and intellectual property (IP) to promote innovation, transfer of technology and access to medicines for public health. The GSPA outlined 108 specific actions across eight elements and 25 sub elements. These elements are:

1. Prioritizing research and development needs;
2. Promoting research and development;
3. Building and improving innovative capacity
4. Transfer of technology;
5. Application and management of intellectual property to contribute to innovation and promote public health;
6. Improving delivery and access;
7. Promoting sustainable financing mechanisms; and
8. Establishing and monitoring reporting systems.

Further, WHO Member states in WHA62.16 called upon the public health community to conduct an overall programme review of the global strategy and plan of action on its achievement, remaining challenges and recommendations on the way forward and report to the World Health Assembly through the Executive Board (WHA62.16 para 6). This review, which is ongoing, will eight elements, 25 sub-elements and 108 action points. The Box does not capture all the activities on this subject taken up by WHO.

One of the eight elements of the GSPA-PHI, on which consensus had not yet been achieved in 2008, focuses on financing and coordination of R&D for diseases that mostly affect developing countries. This element was addressed through the convening by WHO of an Expert Working Group (EWG) and a Consultative Expert Working Group (CEWG) on Research and Development, in 2009 and 2011 respectively.

4.2. Recommendations of the Expert Working Group (EWG) and the Consultative Expert Working Group (CEWG) on Research and Development

The EWG assessed more than 90 proposals for the financing of R&D. Overall, WHO Member States were not fully satisfied with the report, and requested the WHO Director-General to establish a CEWG to build on the work of the EWG. The CEWG submitted its report in 2012,[15] recommending that:

- Countries should commit to spend at least 0.01% of GDP on government-funded R&D
- WHO should set up a global health R&D observatory to gather information on investment in R&D and the R&D pipeline
- WHO should start negotiations on a binding global treaty providing effective financing and coordination mechanisms to promote development of health technologies for Type II and Type III diseases, as well as to meet the specific needs of developing countries concerning Type I diseases.

The CEWG also highlighted open approaches to R&D and innovation, pooled funds, direct grants to companies, milestone prizes, end prizes and patent pools and the general principle of de-linking the costs of R&D from the price of the medicine, meaning that the investor does not have to recoup its R&D investment through the sales revenues. WHO Member States discussed the report in an open ended meeting in November 2012 and agreed on a strategic work plan that included the creation of a WHO global health R&D observatory, implementation of a number of health R&D demonstration projects, and exploration of a potential financing mechanism for pooled contributions and coordination. The work plan also addresses available data on funding for health R&D, health products in the pipeline, clinical trials, and research publications. For further detail see Annex 3.

The High-Level Panel may wish to consider the findings of the CEWG report and the separate submission by the Special Programme for Research and Training in Tropical Diseases (TDR) on the possibility of hosting a pooled fund for voluntary contributions toward R&D.

4.3. R&D Blueprint for pathogens likely to cause severe outbreaks in the near future

The 2014-2015 Ebola outbreak in West Africa revealed that the world is largely unprepared for major outbreaks of emerging, highly infectious pathogens. In particular, medicines and vaccines were not available to meet the outbreak and could not be developed in time to control it.

With increasing global interconnectedness, pandemics become more likely. Therefore, according to resolution WHA 68(10), WHO is developing a Blueprint for R&D preparedness and response to emerging pathogens likely to cause severe outbreaks in the near future, and for which few or no medical countermeasures exist. Guided by overarching ethical considerations, the R&D Blueprint will address these issues by clearly mapping activities, roles, responsibilities and budgets to promote strategic research in advance of and during outbreaks. Financing for R&D

[15] *Research and development to meet health needs in developing countries: Strengthening global financing and coordination* – Report of the consultative expert working group on research and development: Financing and coordination. Geneva: World Health Organization; 2012 (http://www.who.int/phi/cewg_report/en/, April 2012)

preparedness could be provided by mechanisms similar to those suggested in the CEWG report. For further information see Annex 4.

The High-Level Panel may wish to consider the R&D blueprint in the elaboration of its final report.

4.4. Antimicrobial resistance: The Global Antibiotic Research and Development Partnership

The R&D pipeline for new antibiotics is largely empty. There is a lack of investment by industry into R&D because of the limited expected return on that investment. The WHO Global Action Plan on Antimicrobial Resistance (GAP-AMR) that was adopted by the WHA in 2015 suggests creating new partnerships to foster the development and conservation of antibiotics. WHO and the Drugs for Neglected Diseases Initiative (DNDi) are currently setting up an international partnership called the 'Global Antibiotic Research and Development Partnership' to develop new antibiotic treatments addressing antimicrobial resistance, while emphasizing the suitability of new tools for resource limited settings. The Partnership will work closely with all stakeholders—including pharmaceutical and biotechnology companies, start-ups, product development partnerships, academia, civil society, and health authorities—from countries of all income levels to develop new antibiotic treatments that address existing needs and gaps.

In the short term, the Partnership will:

- Identify needs, gaps, and top priorities for the development of new antibiotics and antibiotic regimes not addressed by other actors
- Launch innovative short-term projects to deliver needed therapeutic solutions, such as appropriate paediatric formulations or improved regimens of existing antibiotics.

In the long term, the Partnership will identify and support a portfolio of innovative R&D projects through registration of new therapeutic tools, and secure funding sources to sustain long-term activities. Carefully aligned with existing initiatives that focus on fostering investment into new antibiotics, the Partnership's uniqueness lies in addressing global public health needs and placing emphasis on products or projects that industry is unlikely to manufacture or undertake due to expected lack of profitability. For further information, see Annex 5.

The High-Level Panel may wish to consider the use of the product development partnership approach to address the issue of antimicrobial resistance (AMR).

Annex 1:

Fair Pricing Forum

WHO aims to carry out work on high-priced medicines through a series of landscape analyses and a forum in 2016 to provide a global platform for relevant stakeholders to discuss and develop effective strategies towards universal health coverage. Funding is being sought to carry out the analytical work and convene the forum. The underlying approach is to identify the most promising options and strategies to expand access to new medicines while ensuring that sufficient incentives remain for research and innovation, and that generic medicines also remain on the market.

The rallying call of the post-2015 Sustainable Development Goals agenda to 'leave no one behind' must include affordability of treatment. The main barrier to access to many new medicines, including cancer medicines, orphan drugs, and the new options for hepatitis C is unaffordability, including many cases when there is evidence to show that manufacturing is relatively inexpensive. This problem is now touching not only low-income countries, it is increasingly affecting middle- and high-income countries as well.

There is a need to engage in a global discussion on finding new ways to set prices of medicines. It is clear that a purely market-driven model is insufficient to ensure that medicines in general, and new medicines especially, are made readily available and affordable to all who need them. New approaches and new partnerships are needed to refresh the discussion on drug pricing and to find workable solutions. To that end, WHO proposes to convene a global forum to discuss access to high-priced medicines, including new products such as medicines for hepatitis C, cancer and medicines for 'rare diseases', with the aim of supporting countries to develop effective access strategies. At the same time, it is also important to ensure that prices for essential medicines do not become so low that they are non-viable for manufacturers to produce quality products.

The underlying concept of this consultation would be 'fair pricing' – that is, pricing models that ensure greater affordability and access while also providing industry with the necessary incentives for sustaining R&D. The approach should be evidence based as much as possible, and should engage all relevant stakeholders. Ideally, it should result in global agreements on different strategies as well as identifying options that can be implemented at global or regional level. The topics for preparatory research and landscape analyses will include:

- Describing regulatory approaches to market entry of new products and their potential impact on pricing
- Synthesizing existing information on efficacy of new medicines launched over the last decade
- Evaluating potential new methods for pricing new medicines. Such methods need to reconcile the need for fair pricing, with the difficulties of obtaining accurate information on research, development and manufacturing costs.
- Evaluating new methods for setting minimum prices for off-patent 'vulnerable' essential medicines to ensure that they remain available
- Reviewing strategies to mitigate impact of intellectual protection on access.

It is planned to complete the background work by mid-2016 and convene the forum late in 2016.

Annex: 2

Trilateral Cooperation between WHO, WIPO and WTO

Global Challenges Brief on Trilateral Cooperation[16]

Why is trilateral cooperation needed?

Identifying the right mix of policy options on issues relating to public health, innovation, intellectual property (IP), and trade to best advance national objectives is a huge challenge for governments. Coherent, comprehensive and accessible information can help inform decision-making. The complementary and coordinated expertise of WHO, WIPO and WTO can offer real benefits to national policymakers.

What each organization brings to the table

- WHO brings vast expertise in all areas of public health, including medicine and vaccine policy, medical devices, regulatory issues, pricing and procurement, research, development and innovation, and other factors affecting access to medicines.

- WIPO is uniquely positioned to promote a truly global understanding of the value of the IP system and the importance of the right policy mix in encouraging innovation by providing information on patents, including the patent status of key medicines and vaccines in developing countries. WIPO also contributes expertise on patent law.

- WTO works on several aspects of trade policy that have direct relevance to public health, including international IP rules, regulations and flexibilities, and commitments on tariffs and easing trade barriers. These aspects of trade policy can affect both innovation and access to medicines.

Since 2009, collaboration among WHO, WIPO and WTO has intensified, with a marked increase in the sharing of knowledge to promote better understanding of the policy options surrounding public health, IP and trade.

The flagship ***Trilateral study***[17] published in 2013 is available in Arabic, Chinese, English, French, Spanish, and Russian. The study was prepared to serve the needs of policymakers, lawmakers, government officials, NGOs and researchers seeking a comprehensive overview of the full range of related issues.

Since 2010, the trilateral partners have organized a series of **Joint Symposia** in Geneva. These events are designed to improve the flow of practical information and to guide and support technical cooperation.

When implementing international standards at country level, policymakers working on public health, IP and trade look to international organizations for guidance and training. WHO, WIPO and WTO cooperate and coordinate their **capacity in building and training activities** in order to make best use of their respective areas of expertise. These activities include a comprehensive IP and health component, which the three organizations design and implement in close collaboration.

[16] For the full version see: http://www.wipo.int/edocs/pubdocs/en/wipo_pub_gc_10.pdf
[17] http://www.who.int/phi/promoting_access_medical_innovation/en/

Annex 3:

Health Product Research & Development Fund: Financing and Operation

(also submitted to UN High-Level Panel on 27 February 2016)

Research and development (R&D) for health products normally focuses on diseases with a commercial market in high-income countries. R&D is still limited for diseases of poverty. Considering this, in 2014 the World Health Assembly requested the Director-General to investigate potential mechanisms and tools to finance R&D to accelerate product development. The TDR report, *Health Product R&D Fund: a proposal for financing and operation*, to be published on 17 March 2016, describes how a potential pooled fund would operate under the governance of the WHO Member States, and how the tools, some of which will be published later in 2016, could be used for transparent and efficient operation of the proposed framework. The tools described in the Report include:

- The Portfolio-to-Impact model: a new robust financial modelling tool which allows estimating minimum funding scenarios;
- A compendium of Target Product Profiles: a new online resource that would be housed in WHO which collects and maps health product pipelines in a standardized manner;
- Operational mechanisms for efficient and transparent management of the fund as well as the portfolio of health product R&D projects.

The development of a new R&D fund under WHO would create, for the first time, a mechanism to identify and cost out health products for diseases of poverty. The fund would ensure that any products that are developed would be affordable, accessible, acceptable and available to the countries that need them.

TDR is confident that its existing governance mechanisms could establish a transparent and efficient mechanism to manage a proposed fund and portfolio. Disease-endemic and donor countries would form part of this governance structure, opening the door to new funders.

Health Product R&D Fund: a proposal for financing and operation, Special Programme for Research and Training in Tropical Diseases (TDR). To be published on 17 March 2016 and made available at http://www.who.int/tdr/capacity/gap_analysis/en.

Annex 4:

The Blueprint for R&D preparedness and response to emerging pathogens likely to cause severe outbreaks in the near future, and for which few or no medical countermeasures exist

Ebola broke out of rural seclusion and into West African cities in a matter of weeks. The Middle East Respiratory Syndrome (MERS) virus spread to 21 countries in three years and is still on the move. SARS travelled by plane across hemispheres to cause hundreds of deaths and an estimated cost of 13 billion dollars in just six months. With more frequent travel, globalised trade and greater interconnectedness between countries, infectious disease outbreaks of international concern are becoming inevitable, and they remain unpredictable. When faced with diseases for which there are few or no medical countermeasures, massive chaos and loss of life can ensue.

WHO is spearheading a global movement to avert major epidemics by making the world outbreak-ready through R&D preparedness, spotting emerging epidemics to stop them before they spiral out of control. While conventional surveillance, contact tracing and containment measures remain cornerstones of a health emergency response, a repertoire of effective health technologies could be the key to pre-empting full-blown epidemics, and limiting their human, social and economic losses.

At the request of the World Health Assembly[18], WHO has convened a broad coalition of experts to develop a Blueprint for R&D preparedness and response to emerging pathogens likely to cause severe outbreaks in the near future, and for which few or no medical countermeasures exist.

Key elements of the blueprint

1. Prioritise global infectious disease threats
    - Identify top threats. A list of eleven top threat pathogens has been identified to focus initial R&D efforts:

Priority list of diseases defined by workstream 1

- Crimean Congo haemorrhagic fever
- MERS-coronavirus disease
- Ebola virus disease
- Nipah Fever
- Zika fever
- Severe fever with thrombocytopenia syndrome
- Lassa fever
- SARS coronavirus disease
- Marburg haemorrhagic fever
- Rift Valley fever
- Chikungunya fever

    - Develop a review process to reassess priorities in light of changing circumstances
    - Plan for the transition from preparedness to action in the event of an outbreak.

2. Identify research priorities
    - Based on a prototype R&D roadmap for MERS, develop roadmaps for all priority diseases and for cross-cutting issues such as regulatory science and social science research

[18] http://apps.who.int/gb/ebwha/pdf_files/WHA68/A68_DIV3-en.pdf

- Agree on standard and ethical procedures for accelerated testing of new health technologies in emergencies.

3. Global coordination & expansion of capacity
   - Establish organisational frameworks for the coordination of national and international actors and inclusion as equal partners of scientists in low- and middle-income countries
   - Assemble a network of clinical trial sites in low- and middle-income countries where vaccines can be tested against emerging disease threats
   - Agree on the open sharing of data, the fair sharing of biological samples for research, and manufacturing plans for new health products.

4. Continuous monitoring and assessment

5. Mobilise funding
   - Mechanisms to increase coordination and funding for preparedness

Annex 5:

A Proposal for a Global Antibiotic Research and Development Facility to Promote Research, Responsible use, and Access to new Antibiotics [19]

The WHO Global Action Plan on Antimicrobial Resistance (GAP-AMR) calls for the creation of new partnerships to foster the development of new antibiotics. To implement this part of the GAP-AMR, WHO and DND*i* propose the creation of a '**Global Antibiotic Research and Development Facility**', an independent product development partnership, to develop new antibiotic treatments addressing antimicrobial resistance and to promote their responsible use for optimal conservation, while ensuring equitable access for all in need.

The Facility will work closely with all stakeholders in the field of antibiotic research and development (R&D) including pharmaceutical and biotechnology companies, start-ups, other product development partnerships, academia, civil society, and health authorities—from countries of all income levels to develop new antibiotic treatments. It will:

- Address global public health and the specific needs of low- and middle-income countries
- Target products that industry will not develop due to foreseen lack of profitability
- Pilot the use of alternative incentive models that support conservation of and access to new antibiotics based on DND*i*'s experience in implementing alternative R&D models for neglected diseases
- Ensure that new antibiotics are affordable to all in need.

In the short term, the Facility will start by identifying priorities for the development of new antibiotics and antibiotic regimes not addressed by other actors. Based on this analysis, it will launch short-term R&D projects to develop needed new therapeutic solutions, such as missing paediatric formulations, combinations, new formulations, or improved regimens of existing antibiotics. In the long term, the Facility will develop a broader portfolio of new antibiotic treatments and see them through to registration. Carefully aligned with existing initiatives that invest in new antibiotics, the Facility's uniqueness lies in addressing global public health needs and placing emphasis on products or projects in which industry does not invest.

On 1 December 2015, the DND*i* Board of Directors agreed to set up the Facility and host it for the start-up phase (initial two years), and to provide the scientific environment and infrastructure to ensure an effective incubation period. As of February 2016, seed funding from two countries had been secured and the post for a Director of the incubation team had been advertised. Work had started on identifying short- and medium-term development projects.

A Global Antibiotic Research and Development Facility

There is general agreement that no single measure will solve the lack of R&D for new antibiotics. A partnership model for product development based on previous experience with neglected diseases is an important element of the overall strategy. Such a partnership can test alternative incentives that also contribute to conservation of and access to new antibiotics, such as milestone prizes, buy-outs, and staggered end-stage prizes/payments. By doing so, a product development partnership will provide an important alternative to the traditional profit-oriented pharmaceutical approach.

A three-pronged approach

The Facility will pursue three parallel objectives:

[19] The Concept Note was revised to reflect the discussions during the technical consultations held at WHO on 13 November 2015. For more information see: http://www.who.int/phi/implementation/consultation_imnadp/en/

1. **Research and product development**
   - Develop improved formulations or combinations that may prolong the life of existing antibiotics through short-term product development projects
   - Work with partners on rapid and (near) point-of-care diagnostics
   - Support innovative and paradigm-shifting approaches to the development of new antibiotics.
2. **Conservation**
   - Build conservation strategies directly into the R&D process
   - Propose conservation strategies for antibiotic treatments, taking into account issues related to animal husbandry.
3. **Access**
   - Implement and test new incentive models enabling the de-linkage of R&D costs from the price of the product
   - Promote access for all in need while minimizing unnecessary and non-rational use.

GUIDING PRINCIPLES

The work of the Facility will be based on the following principles:

- New antibiotics have to be affordable and should be subject to a global conservation agenda.
- There is a need for a global mechanism to finance and conserve new antibiotics. Public investment into development of new antibiotics should come with appropriate obligations to governments, regulators, producers, and distributors with respect to the marketing and responsible use of these new products to avoid the rapid build-up of drug resistance
- Sustainable investment should be coordinated at country and international level to avoid dispersion of resources
- In order to answer global priority public health needs, R&D should focus on the most significant drug-resistant bacterial infections
- In order to promote highly innovative approaches, science shall be the sole driver, and should determine the fate, of supported projects
- The governance model shall ensure appropriate representation of all relevant stakeholders and preserve the necessary independence of the Facility.

PORTFOLIO APPROACH

The Facility will develop a portfolio approach to:

- Improve and prolong the use of current antibiotics
- Exploit ‘low-hanging fruit’ to improve the management of neglected bacterial infections
- Explore innovative approaches to tackling AMR.

These three objectives can be broken down to short-, medium-, and long-term projects that will be further elaborated below.

INTERVENTIONS

The objectives can be translated into possible interventions. The Facility will endeavour to:

- Develop better paediatric formulations (form, dosage, shelf-life)
- Develop new formulations of existing drugs (appropriate dosage, administration route)
- Review and possibly re-engineer ‘forgotten’ antibiotics
- Develop combinations of existing drugs to address AMR
- Facilitate clinical trials in low and middle-income countries of relevant antibiotics that are in the R&D pipeline
- Explore innovative but risky projects, including adjuvants, anti-virulence, dormancy breakers, biomodulators, or phages that venture capital and industry are not financing
- Promote with partner organizations (such as the foundation for innovative new diagnostics - FIND) the development of diagnostics that can optimize the use of new and current antibiotics
- Jointly with WHO, develop and test new approaches to conservation.

The Facility will ensure its work does not duplicate that of other initiatives and organizations. It will also ensure that relevant research ongoing in existing spheres can be appropriately transferred to meet low- and middle-income country needs and contexts. Active partnerships will play a key role in translating proposed interventions into concrete outcomes.

PROJECTS

Below is a summary of ideas for projects. These ideas are 'placeholders' to demonstrate the potential scope of the Facility, but have not yet undergone thorough scientific review. More work needs to be done to develop a complete rationale for these and additional projects to be examined in the coming months. Projects will be developed according to disease priorities, but also according to gaps and opportunities, especially for already-existing antibiotics.

MEDICINES

- Paediatric/reformulations: improved paediatric formulation of Amoxicillin/clavulanic acid, rectal antibiotic for community-based neonatal sepsis (ceftriaxone)
- Improved paediatric formulation of fusidic acid, streptomycin, or colistin for resource-limited settings.

DISEASES

- Typhoid fever: combination treatments, repurposed drugs
- Melioidosis: accelerate the development of an existing new chemical entity (NCE) outside of bio-threat use for affected developing countries
- Gonorrhoea: accelerate development of an existing NCE for developing country use (formulation), including in HIV-positive patients
- Gram-negative infections: from repurposing to potential innovative approaches.

APPROACHES

- Develop (open access) combination screening platforms
- Develop (open access) in vivo platforms
- Develop (open access) platform for improved formulations
- Support disruptive scientific approaches (e.g. anti-virulence) that are too risky for venture capital and industry
- Promote, with partner organizations, the development of diagnostics that can optimize the use of new and current antibiotics.

While the main focus of the Facility will be on drug development, it will also collaborate with institutions such as FIND to accelerate the development of important diagnostic tests for resource-limited settings. Such examples could include a rapid diagnostic test that can differentiate bacterial and viral infections, a multiplex (fever) test to diagnose important bacterial infections accurately, and tests that can accurately identify resistance to specific antibiotics. Such potential tests already have analogies such as a rapid diagnostic test for malaria or the assay for the simultaneous detection of tuberculosis and rifampicin resistance directly from sputum. WHO, both through one of its demonstration projects[20] and with FIND, is building target product profiles to accelerate development of such AMR-relevant diagnostics. Potential diagnostic tests may also be important for identifying future epidemiological trends and hence needs, and accelerating the clinical testing of new antibiotics.

In summary, from a scientific perspective the Facility will add value by:

- Covering neglected areas, e.g. combination and reformulation work that is unlikely to be undertaken either by industry or by current research programmes

[20] http://www.who.int/phi/implementation/ANDI_ChinaNDI_documents.pdf

- Facilitating clinical trials in low- and middle-income countries of relevant antibiotics that are in the R&D pipeline (e.g. for gonorrhoea)
- Providing open access to platform tools for the research community
- Supporting projects that are lacking sufficient financial incentives, or which are too risky for investors.

CONSERVATION

Developing new antibiotic treatments will only have a lasting impact if we change the way we use them. The fact that traditional market incentives will not guide the development strategies of the Facility will allow for a public health needs focus. It will also allow for taking conservation into account in the design of the R&D pipeline, so that conservation and access are built together into product development. When bringing products to the market, the Facility, with its industry partners, will develop innovative approaches in packaging and labelling that support responsible use.

The Facility will develop an access-driven IP policy for newly developed tools, and support controlled distribution and appropriate use of new antibiotics.