INVESTING IN THE DEVELOPMENT OF NEW ANTIBIOTICS AND THEIR CONSERVATION
A PROPOSAL FOR A GLOBAL ANTIBiotic RESEARCH AND DEVELOPMENT FACILITY\(^1\) TO PROMOTE RESEARCH, RESPONSIBLE USE, AND ACCESS TO NEW ANTIBIOTICS

Expanded Concept Note\(^2\)
2 November 2015

I. INTRODUCTION AND OVERVIEW

The WHO Global Action Plan on Antimicrobial Resistance (GAP-AMR) suggests the creation of new partnerships to foster the development and conservation of antibiotics. To implement this part of the GAP-AMR WHO and DNDi propose the creation of a ‘**Global Antibiotic Research and Development Facility**, an international partnership, to develop new antibiotic treatments addressing antimicrobial resistance and to promote their responsible use for optimal conservation, while ensuring equitable access for all. The Global Antibiotic Research and Development Facility (hereafter referred to ‘the Partnership’) will stimulate innovation for global needs, while emphasizing development of new tools suitable for developing country needs.

The Partnership will work closely with all stakeholders in the field of antibiotic research and development (R&D) – including pharmaceutical and biotechnology companies, startups, Product Development Partnerships, academia, civil society, and health authorities – from countries of all income levels to develop new antibiotic treatments to address the needs and gaps.

Overall, partnership will
- address global public health and specific needs of developing countries, targeting products that industry will not undertake due to lack of profitability;
- pilot the use of alternative incentive models that support conservation of and access to new antibiotics based on DNDi’s experience in implementing alternative R&D models for neglected diseases;
- test proposed new models for the conservation of antibiotics;
- ensure that new antibiotics are affordable to all and are subject to a global conservation agenda.

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;
- establish an international collaborative R&D network;
- launch innovative short-term projects to deliver needed therapeutic solutions, such as appropriate paediatric formulations or improved regimens of existing antibiotics;
- pilot projects to ensure conservation of and access to new antibiotics.

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\(^1\) Hereafter also referred to as ‘the Partnership’.
\(^2\) This paper builds on the shorter initial WHO/DNDi concept paper and provides a more detailed proposal for the Partnership for the development and conservation of new and better-adapted antibiotics.
In the long term, the Partnership will identify and support a portfolio of innovative R&D projects through to registration of new therapeutic tools, provide a framework to support the development and conservation (stewardship) of antibiotics, 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 will most probably not undertake due to lack of profitability (e.g. combinations of existing antibiotics, improved dosing regimens).

I.A. CONTEXT
Antimicrobial resistance (AMR) is a major public health challenge. It compromises global human development, threatens the achievements of modern medicine, and undermines economic development and stability of social systems. AMR affects all countries regardless of their economic classification. The combined result of increased bacterial resistance against current antibiotics and the lack of research to identify new classes of antibiotics threatens human health at a global level. Industry has mostly abandoned the field of antibiotic R&D because of its limited financial attractiveness, the scientific challenges inherent to antibiotic drug discovery, and the complex regulatory framework. This has contributed to the emergence of untreatable, multi-resistant strains of pathogens that are killing an increasing number of people worldwide. The need for new measures and incentives to overcome bottlenecks in the development of new antibiotics has been widely recognized.

I.B. WHY A NEW INITIATIVE?
A number of initiatives have been launched in the past years that aim to reinvigorate the antibiotic R&D pipeline. While this development is positive, even taken together the initiatives still fall short of providing all the necessary tools to cope with the magnitude of the public health challenges faced today. In June 2015, the G7 therefore identified a need to:

‘engage in stimulating basic research, research on epidemiology, infection prevention and control, and the development of new antibiotics, alternative therapies, vaccines and rapid point-of-care diagnostics’. ³

In October 2015, the G7 Ministers of Health declared that they will:

‘explore the feasibility and need of setting up a global antibiotic product development partnership for new and urgently needed antibiotics, vaccine development, alternative therapies and rapid point of care diagnostics and seek collaboration with […] WHO and Drugs for Neglected Disease initiative (DNDi)’.

The Partnership is also a response to many other calls to action that recognize that no single initiative will be enough to address the AMR problem:

- The European Joint Programming Initiative on Antimicrobial Resistance recommends the creation of ‘incentives for the development of new antibiotics, and alternatives for antibiotics such as vaccines’;
- Action on Antibiotic Resistance (ReAct), an independent global network, advocates for increased investment in R&D of new antibiotics;
- The ongoing UK Independent Review on Antimicrobial Resistance chaired by Jim ‘O Neill calls for a global fund to finance research for new antibiotics;

• A 2014 Report to the US President on Combating Antibiotic Resistance recommended the creation of new incentives for the commercial development of new antibiotics through partnerships with industry;

• In 2014, the Lancet Infectious Diseases Commission called for a ‘new sustainable global model for the discovery, development, and distribution of new antibiotics’;

• In the same year, the World Alliance Against Antibiotic Resistance called for ‘new economic business models to support the cost of innovation, while safeguarding public health interests’.

I.C. How does the Partnership relate to the WHO GAP-AMR?

In May 2015, the Sixty-Eighth World Health Assembly adopted the Global Action Plan on Antimicrobial Resistance (GAP-AMR). The GAP-AMR points out that:

‘no major new class of antibiotics has been discovered since 1987 and too few antibacterial agents are in development to meet the challenge of multidrug resistance’.

It calls for new concepts for providing incentives to innovation and promoting cooperation between policy-makers, academia, and the pharmaceutical industry. The Partnership follows precisely such a cooperative approach. More specifically, under Objective 5 the GAP-AMR requests the WHO Secretariat to explore with Member States, intergovernmental organizations, industry associations, and other stakeholders, options for the establishment of a new partnership or partnerships to:

• coordinate the work of many unlinked initiatives aiming to renew investment in research and development of antibiotics;

• identify priorities for new treatments, diagnostics and vaccines on the basis of emergence and prevalence of serious or life-threatening infections caused by resistant pathogens;

• act as the vehicle(s) for securing and managing investment in new medicines, diagnostics, vaccines, and other interventions;

• facilitate affordable and equitable access to existing and new medicines and other products, while ensuring their proper and optimal use;

• establish open collaborative models of research and development in a manner that will support access to the knowledge and products from such research, and provide incentives for investment.

The Partnership addresses a number of these tasks, notably based on the outcome of two expert meetings held in 2014 with a number of representatives from Member States, intergovernmental organizations, NGOs, industry associations, and other stakeholders. This coincided with DNDi’s new Business Plan 2015-2023, which laid the foundations for exploring new disease areas within its own portfolio and/or the possibility of incubating independent initiatives to address unmet, urgent/emerging needs. At the first meeting, hosted by WHO, experts discussed a number of options to further the development of new antibiotics and their conservation. The second meeting was held in conjunction with DNDi to explore more specifically the possibility of using a product development partnership type of model, one of which has proven successful in the area of neglected diseases. The proposed model comprises open, collaborative R&D that enables access to proprietary and non-proprietary knowledge and products in a scheme that ensures affordable access to newly developed medicines, as mentioned under Objective 5 of the WHO GAP-AMR.

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The initial phase is aimed at defining, with the help of Member States, industry, academia, civil society, and other experts and stakeholders:

- the scope of the Partnership;
- its governance model;
- the needs at a global level and specific gap in developing countries;\(^6\)
- a set of short-term projects to be initiated, and the long-term priorities.

This work will be carried out by taking into account the emergence and prevalence of serious or life-threatening infections caused by resistant pathogens in line with the GAP-AMR Objective 5 as well as the specific needs of developing countries. The latter ensures that any new product has the necessary characteristics to respond to unmet needs worldwide and is not restricted to the health systems of some developed countries.

Implementation of the GAP-AMR will require more extensive work in this area, which will both guide and benefit from the Partnership. WHO, under Objective 5, will provide annual updates and reports on the R&D pipeline and current R&D initiatives in the area of antibiotic R&D. The data will feed into the WHO Global Health R&D Observatory.

The Partnership will undertake specific, but not all, actions defined under Objective 5. Other activities will be conducted under the auspices of WHO, including the set-up of a framework for prioritization of specific vaccines (Objective 3.3) and coordinating the work of many unlinked initiatives aiming to renew investment in R&D of antibiotics. The latter must also align with the G7 initiative on coordination of research on antimicrobial resistance, announced by the G7 Ministers of Health in October 2015, mentioned above.

I.c. HOW DOES THE PARTNERSHIP RELATE TO OTHER EXISTING OR ONGOING INITIATIVES?

In recent years, several important programmes have been set up to support antibiotic research in various countries.\(^6\)

**Innovative Medicines Initiative (IMI)** is Europe’s largest public-private initiative aiming to speed up the development of better and safer medicines for patients. IMI supports collaborative research projects and builds networks of industrial and academic experts in order to boost pharmaceutical innovation in Europe. One of its priorities is antimicrobial resistance. IMI’s programme, New Drugs 4 Bad Bugs (ND4BB), focuses on the scientific, regulatory, and business challenges that are hampering the development of new antibiotics. ND4BB include, among others, the creation of a pan-European network of excellence of clinical investigation sites, basic research to tackle in particular gram-negative bacteria, the development of a specific drug discovery platform for antibiotics, and the exploration of new economic models for antibiotic development (DRIVE-AB).\(^7\) It should be noted that these activities fall entirely under the responsibility of the pharmaceutical partners of the consortium.

**Partnership complementarity:** The Partnership will focus on the short and medium term to address certain urgent needs (see ‘The Global Scientific Strategy’ section below) and on the specific needs of developing countries. The work of the Partnership will be coordinated in such a way as to complement the work of IMI. EFPIA, IMI’s industry partner, participated in the expert meeting in December 2014, and DRIVE-AB leaders actively contributed to developing the concept for the Partnership.

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\(^6\) [http://www.cdddep.org/publications/state_worlds_antibiotics_2015_executive_summary](http://www.cdddep.org/publications/state_worlds_antibiotics_2015_executive_summary)

\(^6\) This is not an exhaustive list. An additional evaluation of AMR initiatives in developing countries and emerging economies will be undertaken and brought into this perspective.

\(^7\) [http://www.imi.europa.eu/content/nd4bb](http://www.imi.europa.eu/content/nd4bb)
EU Joint Programme Initiative on Antimicrobial Resistance has been set up to pool national research efforts to spend public R&D resources more efficiently. Joint Programming is used in different areas to overcome the fragmentation of national research programmes in particular where challenges are global in nature. The development of new preventative and therapeutic approaches is only one of many areas that form part of the Joint Programming Initiative on AMR. Research priorities are set out in the Strategic Research Agenda.\(^8\) The latter is implemented through launching joint calls for proposals to facilitate cross-border research projects.

**Partnership complementarity:** The Partnership could be one of the implementers under these EU joint calls for proposals, in particular in two priority areas of the Strategic Research Agenda that are in line with the envisaged Partnership scope: improvement of pharmacokinetics and pharmacodynamics of neglected antibiotics, and development of treatment protocols based on combination therapy using existing and new antibiotics.

**US Biomedical Advanced Research and Development Authority (BARDA)** directly supports companies that develop new antibiotics through its Broad Spectrum Antimicrobials Program. BARDA, for example, launched a Portfolio Partnership with GlaxoSmithKline to support the development of a number of new antibiotics. BARDA actively participated in the meetings held in 2014.

**Partnership complementarity:** similar to the above, the Partnership will explore opportunities for cooperation with BARDA, and with its developing country focus, not only avoid any duplication of scientific efforts but also potentially extend the target geographic areas of the work of BARDA.

The UK independent Review on Antimicrobial Resistance, chaired by Jim O’Neill, was commissioned by the UK Prime Minister to analyse and propose concrete actions to tackle the global problems of antimicrobial resistance. Its final report is due in summer 2016. The Review will assess the extent to which market failure is responsible for the lack of investment in R&D of new antimicrobials and short-, medium-, and long-term interventions, which could be undertaken by governments and other funders to stimulate investment in new antimicrobials for human use.\(^9\) In 2015, the Review published initial proposals to kick-start antibiotic drug discovery efforts at a global level. The proposals include channeling new funds into early-stage research as well as creating a fund for product development to buy out new major breakthroughs. The latter would ensure a predictable and viable market for new antibiotics and, by doing so, provide an incentive for companies to invest.\(^10\)

**Partnership complementarity:** The Partnership fits very well into this new landscape and could become one of the implementers for R&D under the proposed R&D fund.

There is general agreement that no single measure will solve the lack of R&D of new antibiotics. A partnership model for product development is an important element of the overall strategy. New push and pull mechanisms set up with public funding and leadership will provide an important alternative to the traditional profit-oriented pharmaceutical approach.\(^11\) The Partnership will test proposed new models for the conservation of antibiotics, while contributing to and carrying out a number of actions defined in the GAP-AMR.

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\(^8\) [http://www.jpiamr.eu/activities/strategicresearchagenda/](http://www.jpiamr.eu/activities/strategicresearchagenda/)

\(^9\) [http://amr-review.org/node/5](http://amr-review.org/node/5)

\(^10\) [http://amr-review.org/sites/default/files/SECURING%2DNEW%2DDRUGS%2DFOR%2DFUTURE%2DGENERATION5%2DFINAL%2DWEB_0.pdf](http://amr-review.org/sites/default/files/SECURING%2DNEW%2DDRUGS%2DFOR%2DFUTURE%2DGENERATION5%2DFINAL%2DWEB_0.pdf)

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 will most probably not undertake due to lack of profitability (e.g. combinations of existing antibiotics, improved dosing regimens).

Finally, the Partnership aims to go beyond traditional economic models and, by working closely with WHO, pilot and adjust alternative incentives that also contribute to conservation of and access to new antibiotics.

I.D. Why is DNDi the right actor to incubate the Partnership?
Created as a not-for-profit R&D organization headquartered in Switzerland, DNDi was set up by seven founding partners: the Indian Council on Medical Research; the Oswaldo Cruz Foundation, Fiocruz, Brazil; Institut Pasteur, France; the Kenya Medical Research Institute; the Malaysian Ministry of Health; Médecins Sans Frontières; and the Special Programme for Research and Training in Tropical Diseases, WHO-TDR (as permanent observer). What was initially an informal MSF group that began to bring together the then-missing evidence of the lack of appropriate treatments for underprivileged population groups, the ‘Drugs for Neglected Diseases Working Group’, with the Nobel Prize money from MSF, incubated DNDi in 2003.

DNDi has successfully developed a robust pipeline of drugs and treatments for the most neglected diseases, including 15 New Chemical Entities (NCEs) spanning early research phases up to clinical development, and has delivered six treatments. Among the latter are two artemisinin-based combination therapies (ACTs) in fixed-dose formulations for adults and children, both of which aimed at providing much needed fixed-dose combinations that were adapted to the specific needs of the patients, helped to improve patient case management, and delayed the development of resistance. Other treatments delivered include a set of treatments for visceral leishmaniasis in Asia, a combination therapy for visceral leishmaniasis in Africa, a paediatric dosage form of an existing drug for the treatment of Chagas disease, and a combination therapy for the treatment of human African trypanosomiasis. DNDi uses a virtual R&D model, meaning that it does not own laboratories but works with partners who carry out the research on its behalf. DNDi’s cost of development ranges from EUR 6-20 million for an improved treatment, and EUR 30-40 million for a new chemical entity (NCE). With attrition factored in, these estimates are EUR 10-40 million for an improved treatment, and EUR 100-150 million for an NCE to be developed (this does not include the in-kind contribution of pharmaceutical partners). This model has proven effective12 and in its overall Business Plan 2003-2023, DNDi estimates a budget of EUR 650 million to develop 16-18 treatments and ensure a robust pipeline.13

DNDi has given specific focus to patient needs in low and middle-income settings, and through a combination of long-term strategies (building a portfolio with NCEs) and short-term strategies (reformulations, new combinations, and repurposing of existing drugs). The R&D conducted has been made possible by the partnerships developed with 130 entities worldwide, including over 20 pharmaceutical companies and 9 biotechs, and through the set up of three clinical research platforms, which build capacity while conducting clinical research in resource-limited settings.

As part of its business model, DNDi adopted an access-driven IP policy,\(^{14}\) has supported innovative regulatory harmonization and regulatory capacity strengthening efforts notably in Africa,\(^{15}\) and promotes delinkage\(^{16}\) in its agreements with pharmaceutical and academic partners by agreeing that the products resulting from the research and development projects be made available at cost of manufacture plus a small margin to ensure the sustainable production of the products, also known as ‘at cost plus’.

DNDi, has agreed to facilitate the set up and hosting of the Partnership for the first phase (initial two years) and provide the scientific environment, necessary personnel, and infrastructure to ensure an effective incubation period.

II. **OUTLINE OF THE GLOBAL ANTIBIOTIC RESEARCH AND DEVELOPMENT FACILITY**

II.A. VISION
In cooperation with the public and private sectors, develop new antibiotic treatments addressing AMR and promote their responsible use for optimal conservation while ensuring equitable access for all by setting up an international public-private partnership that will focus on global health antibiotic and specific developing country needs.

In recent years, substantial policy work has been conducted on incentives for innovation and conservation of drugs. The Partnership will test and further develop these mechanisms, and work closely with initiatives that are already piloting different concepts to ensure cohesive analysis of the overall effectiveness.

II.B. A THREE-PRONGED APPROACH

1. **Research and product development:**
   - support product development for antibiotics and work with partners on rapid and (near) point-of-care diagnostics;
   - promote innovative and paradigm-shifting approaches to the development of new antibiotics that have a high potential to address patient needs;
   - develop improved formulations/combinations and prolong the life of existing antibiotics through innovative short-term product development projects.

2. **Conservation:**
   - promote appropriate use of new antibiotics in humans, taking into account issues related to veterinary settings;
   - jointly with WHO, develop and test new approaches to contribute to more responsible use of new antibiotics;
   - explore avenues linking guaranteed equitable access in countries with all levels of income with engagements in favour of preservation.

3. **Equitable access:**
   - implement and test – for the newly developed antibiotics – new incentive models enabling the delinkage of the cost of R&D from the price of the product;
   - promote equitable access based on the concept of ensuring access to all in need, while minimizing unnecessary use.


II.c. GUIDING PRINCIPLES
To ensure that the global health needs will be fulfilled, the following principles will guide the activities:

- New antibiotics have to be affordable to all 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.
- R&D should focus on the most significant drug-resistant bacterial infections to answer global priority public health needs.
- Science shall be the sole driver and determine the fate of supported projects in order to promote risky but highly innovative approaches.

II.d. INITIAL SET UP
DNDi will host, for the incubation period, the Partnership’s personnel and provide necessary infrastructure to help set up activities rapidly. An initial start-up team will be constituted at DNDi and will report to the countries and institutions accepting to finance the start-up phase. The team will include professionals with backgrounds in public health, biomedical research, infectious diseases, health economics, antimicrobial research and development, product formulations, business development, financing, drug markets, and drug regulation. One person from WHO will ensure the liaison with WHO and support the initial team.

II.e. WORK STREAMS AND DELIVERABLES
WS 1. SCIENTIFIC
- Global needs identification and TPP definition: identify and agree on global priority patients’ needs and develop a set of priority TPPs (Target Product Profiles), taking into account work already done at national and regional levels. TPPs should prioritize highly relevant infections threatening large populations worldwide and attempt to anticipate AMR evolution. TPPs will provide guidance to the initiative, as well as to other public and private actors in the field of antimicrobial research.
- Analysis of gaps and opportunities: identify the major gaps and opportunities in the current pipeline of anti-infective agents to prioritize the projects capable of fitting the TPPs. A possible focus will be given to approaches often avoided by private investors due to inherently high risks of failure or lack of commercial incentive. Importantly, appropriate diagnostic approaches will be sought to support responsible use of new antibiotics.
- Constitute a working group of key experts: using existing networks, mobilize experts in basic and applied microbiology, clinical microbiology, antibiotic development, diagnostics, and public health to provide advice. Some representatives of this international network will form the steering committee of the Partnership.
- Identify a set of short-, medium-, and long-term projects (see examples below) to address the most urgent needs: in addition to new antibiotics, needs such as appropriate paediatric formulations of existing antibiotics and improved regimens or dosages and combinations of existing antibiotics will be considered in coordination with ongoing work in WHO. Such projects will be initiated as soon as sufficient financing is available.
WS 2. BUSINESS DEVELOPMENT
- Identify key public (academic centres, health departments) and private (start-ups, biotech and pharmaceutical companies, contract research organizations) partners to initiate collaboration on specific projects within the framework provided by the Partnership, and secure initial partnerships to launch specific projects.
- Connect and coordinate with existing scientific networks of antibiotic experts, advocacy groups, such as ReAct, and private-sector networks to identify synergies and collaborations.
- Engage with the private sector to identify major drivers and partnership models suitable to get the sector involved again into antibiotic drug development. The work on potential models and incentives will build upon proposals in this field of R&D.
- Design the partnering and legal framework of the initiative with public and private sectors to ensure responsible use, conservation, and equitable access to any product having benefited financially from the Partnership’s work.
- Define the financial needs and outline strategies for sustainable financing. These projections shall include direct costs to support R&D activities through collaborations, as well as the rewards necessary to create incentives to ensure long-term participation of the private sector. Alternative models of reward such as milestone prizes, buy-outs, and staggered end-stage prizes / payments will be considered for implementation.
- Develop an access-driven intellectual property policy.

WS 3. CONSERVATION
- This work stream will be closely developed in collaboration with WHO, which will lead the work on responsible use and conservation under the GAP-AMR, including on regulatory aspects. Synergies with existing WHO programmes such as Prequalification and the Essential Medicines List are important elements to be explored in this context. The Partnership will work with Member States through the WHO Secretariat to evaluate viable strategies to promote and implement responsible use of new antibiotics, encompassing areas such as quality standardization and assurance, procurement, regulated distribution and use, authorization procedures and requirements, pharmaco-vigilance, and evidence-based selection and use schemes.
- In tandem with the above, launch pilot projects for conservation and access of specific antibiotics of interest, including exploring models such as coordination of pooled procurement for antibiotics to better control their distribution and use.

WS 4. ADVOCACY AND FINANCING
- Define strategic advocacy axes necessary to support conservation, responsible use, new R&D models, and incentives.
- Engage with traditional and non-traditional public and private donors and investors to promote the initiative, and develop and test innovative financing mechanisms to secure financial support required for the business plan proposed.

WS 5. GOVERNANCE STRUCTURE
- Develop a governance model that will ensure independence, prioritize a global health approach, represent patients’ needs, and obtain the support of governments. Such a model shall be based on the experience with existing global and regional initiatives in the area of health and the environment. It will ensure appropriate representation of all relevant stakeholders while preserving the necessary independence of the initiative.
- Identify potential individuals for the Board of Directors and Scientific Advisory Board.
III. **THE GLOBAL SCIENTIFIC STRATEGY**

III.a. **SCIENTIFIC GOAL AND AIM**

The overall goal of the Partnership will ultimately be reducing mortality and morbidity due to important bacterial infections, especially those where drug resistance is an increasing and important problem. Central to this is the concept that patient care must be improved to ensure responsible use through the development of new and optimized existing tools. In the case of malaria, significant improvement in care and delay of emerging resistance has been achieved through drug combination use, fixed-dose combinations, and rapid diagnostic tests. The scale up using such tools was facilitated by the Global Fund for AIDS, TB and Malaria.

Unfortunately, no such scenario exists for antibiotics. Thus, the management of many bacterial infections, often presenting as main syndrome fever, remains empirical. Restricting use alone is not the answer in developing countries where many more children die from lack of access to treatment than drug resistant bacteria. A straightforward scenario of being able to accurately recognize if a sick infant needs an antibiotic is complicated by a lack of a simple diagnostic test and appropriately adapted quality assured formulations. In this context, the Partnership will build on and support the work done on the development of a ‘fever diagnostic’, one of the WHO CEWG Demonstration Projects. In the area of diagnostics, the Partnership will also closely collaborate with Foundation for Innovative New Diagnostics (FIND).

Currently there is a growing risk of drug resistance in important pathogens causing (gram negative) sepsis and diseases such as typhoid and gonorrhoea. In developing countries, neonates and children are particularly vulnerable sub-groups. Insufficient work is done to address all these needs. The Partnership will, therefore, focus on global health needs and address specific barriers to improving patient care, promoting improved use of antibiotics and addressing the threat of drug-resistant bacteria.

III.b. **PORTFOLIO APPROACH**

The Partnership will develop a portfolio approach with key three objectives:

- improve and prolong the use of current antibiotics;
- exploit ‘low-hanging fruits’ 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.

III.c. **INTERVENTIONS**

The objectives can be concretely translated into possible areas of interventions as follows:

- better paediatric formulations (form, dosage, shelf-life);
- new formulations of existing drugs (appropriate dosage, administration route);
- combinations of existing drugs to address AMR;
- facilitation of developing country application of pipeline antibiotics: clinical trials, access strategy, and responsible use;
- exploration of innovative projects (e.g. adjuvants’, anti-virulence, dormancy breakers);
promotion, with partner organizations (such as FIND), of the development of diagnostics that can optimize the use of new and current antibiotics;

- jointly with WHO/EMP (Department of Essential Medicines and Health Products), develop and test new approaches to conservation.

DNDi has concrete experience and success in especially such interventions. In the context of exploring innovative projects, the Partnership will ensure not to duplicate the work of other initiatives and organizations. It will also ensure that any research ongoing in existing spheres can be appropriately transferred to meet developing country needs and contexts. Active partnerships will be important in translating proposed interventions into reality and achieving success.

III.d. Projects
Below is a summary of ideas for projects. These ideas are ‘placeholders’ to demonstrate the potential scope of the Partnership, but have not yet undergone a thorough scientific review. More work needs to be done to develop a complete rationale for these projects, and additional ideas are encouraged. Projects will be developed according to disease priorities, but also according to opportunities, especially for already existing antibiotics, and in terms of approaches. The latter will be developed with a specific aim of ensuring broad benefit that can be capitalized by the wider scientific community.

1. Medicines
   a. Paediatric / reformulations: improved paediatric formulation of Amoxicillin/clavulanic acid, rectal antibiotic for community-based neonatal sepsis (ceftriaxone);
   b. Improve developing country paediatric formulation of fusidic acid, streptomycin, or colistin.

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

3. Approaches
   a. Develop (open access) combination screening platforms;
   b. Develop (open access) in vivo platforms;
   c. Develop (open access) platform for improved formulations;
   d. Support disruptive scientific approaches (e.g. anti-virulence);
   e. Promote, with partner organizations, the development of diagnostics that can optimize the use of new and current antibiotics.

While the main focus of the Partnership will be on drug development, it will also collaborate with institutions such as FIND to accelerate the development of important diagnostic tests for developing country contexts. Such examples could include a rapid diagnostic test that can differentiate bacterial and viral infections, a multiplex (fever) test to accurately diagnose important bacterial infections, and tests that can accurately identify resistance to specific antibiotics. Such potential tests already
have analogies such as a RDT for malaria and Xpert for Tuberculosis. WHO and FIND are already developing target product profiles to accelerate their development. Such potential tests may also be important for identifying future epidemiological trends and hence needs, and accelerating the clinical testing of new antibiotics.

In summary, a clear added value of the Partnership can be rationalized from a scientific perspective, through the following:

- covering neglected areas: e.g. Combination and reformulation work that is unlikely to be undertaken by either companies or current research programmes;
- accelerating R&D for developing countries’ use of pipeline projects (e.g. Gonorrhea);
- providing access to platforms tools for the research community;
- potentially supporting projects that are lacking sufficient financial incentives, or are too risky for investors.

III.e. CONSERVATION
An important aspect of the work of the Partnership will be to improve the life span of new antibiotics and ensure their responsible use, thus to conserve the new products. This differentiates the Partnership from other R&D initiatives.

Under the GAP-AMR, WHO is tasked with developing options for a global framework on development of new antibiotics and for promoting responsible use stewardship. Such a global framework developed under the leadership of WHO could provide for the necessary mechanisms to ensure responsible use of new antibiotics at country level. This will be much easier for antibiotics that are owned by not-for-profit institutions such as the Partnership.

The fact that the traditional market incentives will not guide the development strategies of the Partnership will allow a public health needs focus and taking conservation into account in the design of the R&D pipeline, so that more responsible use will be built in products. When bringing products to the market, the Partnership, with its industry partners, will develop innovative approaches in packaging and labelling that support such responsible use.

The Partnership will develop an access-driven IP policy that can, in certain cases, support responsible use of newly developed tools, and support controlled distribution and appropriate use of new antibiotics.
IV. **DELIVERABLES, TIMELINES, AND APPROXIMATE INITIAL BUDGET**

**Years 1-2**
- Identify the appropriate legal form and governance of the initiative.
- Publication of priority TPPs.
- Identification of short-term, medium and long-term research projects ready to be initiated during this period as well as collaboration partners.
- Secure additional funding partners and funders to support long-term activities of the initiative.
- Set up a working group and steering committee, comprised of public and private partners engaged with the initiative.
- Develop a sustainable funding model.
- Generate a full business plan and budget of the initiative for a minimum 5-year period, to be used to approach countries, foundations, and the private sector to obtain funding.
- Planned HR expansion to further strengthen the team.

Establish an independent legal entity.
Develop a monitoring and evaluation (M&E) framework.

**Years 3-5**
- Continue to develop projects initiated and implement new projects identified through the preparatory work.
- Implement the business plan, including funding of innovative R&D proposals, and of pilot conservation projects.
- Secure additional funding to support the business plan activities.
- Establish a Board of Directors and a Scientific Advisory Committee.

**BUDGET**
Seed funding of 3 million USD is required for the start-up phase (two years) based on the assumption that four to six full time members are needed to build the core team. This budget covers salaries of the start-up team that will be hired within the DNDi infrastructure, some overheads (mainly IT/Telecommunication, travel, consultancies, meetings), and the initial activities for selected short-term projects. It will also cover the resources required to raise further funding for new projects and the subsequent phases of the Partnership. In WHO, one P staff, some secretarial support and activity money is needed to ensure the liaison and contribute to the work of the initial start-up team.

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