Bringing innovation to the frontline for impact:
Long-acting technologies to prevent and treat major infectious diseases

Report on the global technical consultation meeting: 1-2 November 2018

The meeting "Bringing innovation to the frontline for impact: Long-acting technologies to prevent and treat major infectious diseases" took place at the Global Health Campus in Geneva, Switzerland, on 1-2 November 2018. The consultation was the culmination of a Unitaid project in 2018 that explored the science and market landscape of long-acting technologies for use in low-and-middle-income countries (LMICs) to prevent and treat HIV, TB, malaria, and HCV, as well as multi-purpose technologies and opioid substitution therapy. Prior to the consultation meeting, over 50 key informant interviews were conducted and a 172-slide navigable online compendium was created to describe, for the first time, the technology and market landscape for long-acting technologies across diseases, including:

- Current public health challenges across the disease areas within Unitaid's mandate and how they could be addressed through long-acting technologies;
- The global architecture in the long-acting space reflecting current work by stakeholders;
- The science and clinical pipeline of long-acting products, including formulation processes, drugs (both existing products and new chemical entities) and innovative drug delivery devices;
- The market considerations and prior experience;
- Most relevant scientific literature in each case is hyperlinked for ease of consultation, and important background documents developed for this effort are uploaded as hyperlinks too, including a separate intellectual property landscape produced in collaboration with the Medicines Patent Pool (MPP).

The project was guided by an external reference group with representation from the World Health Organization (WHO), the NIH Long-Acting/Extended Release Antiviral Resource Program (LEAP), the Government of the Republic of Kenya, UNAIDS, the Bill and Melinda Gates Foundation Prevention Market Manager (AVAC), and the International Treatment Preparedness Coalition (ITPC).

The consultation was the first global meeting to explore long-acting technologies across the disease areas. It served as an important opportunity for stakeholders to review the Unitaid compendium, test preliminary findings, present and discuss the latest innovations in long-acting technologies - **including disease-agnostic innovations and their application in disease-specific approaches** - and explore challenges and opportunities for addressing supply and demand factors, regulatory issues and approaches to country adoption.

In addition, on the second day, participants met in smaller break-out groups to develop recommendations on priority areas that Unitaid and/or others involved in advancing long-acting

technologies should consider to accelerate product development, implementation and impact for low- and middle-income countries.

The meeting was chaired by Professor Charles Flexner of Johns Hopkins University and LEAP. Sixty people participated in the meeting, representing the following stakeholders:

- Originator and generic pharmaceutical industry and technology developers;
- Researchers from academia, governmental and non-governmental organizations;
- Intergovernmental organizations and technical agencies;
- International research and implementation support organizations;
- Regulatory authorities;
- National policy makers;
- Civil society organizations and community advocates; and
- Research and Scale-up funders.

Unitaid Executive Director Lelio Marmora and WHO Director of Essential Medicines and Health Products Suzanne Hill opened the meeting, noting the exciting opportunities that innovations in long-acting technologies provide for realizing ambitious prevention and treatment targets across disease areas in LMICs.

Consensus was reached on the potential paradigm change that long-acting formulations might bring forward in prevention and treatment of main diseases affecting LMICs. A dynamic pipeline, especially for HIV, but also in other diseases at earlier stages of research, is emerging. Beyond long-acting contraception, effectiveness in "real world" clinical settings of long-acting tools in LMICs has not has yet been demonstrated and a healthy market has yet to be created.

Participants highlighted the need for all stakeholders to engage now to ensure that long-acting innovations meet the needs of populations at risk in LMICs and are accessible in a timely manner to achieve the greatest impact. They emphasized the critical importance of focusing on the entire innovation pathway from early drug discovery and technology design, to preclinical and clinical research, regulatory approval and quality control, market introduction, intellectual property licensing, generic manufacturing, procurement and supply chain systems, user preferences, choice and population segmentation, service delivery approaches, and domestic and international funding for scale-up.

Presentations about the science highlighted the following key themes:

- A number of approaches can be used to develop **long-acting formulations** of new chemical entities and to repurpose oral formulations of approved drugs as long-acting;
- Diverse nanotechnology processes and other technology processes for depot have emerged and are utilized for a variety of products to be formulated as long-acting injectables or other delivery systems;

- Indeed, a variety of drug delivery devices are in development, including gastric residence systems as oral capsules, different types of implants, rings and patches;
- Some of these emerging technologies and delivery systems could lead to **ultra-long acting products** that could represent a paradigm change in managing diseases in coming years;
- To date, several blockbusters have already revolutionized the management of several diseases in high-income countries (e.g. schizophrenia and osteoporosis) and several products are being investigated as long-acting for the potential use in other conditions (e.g. diabetes, Alzheimer's, cancer, pain, and obesity)
- Target product profiles for disease-specific long-acting products have been developed by WHO, LEAP, Medicines for Malaria Initiative and others which include critical elements for their adequate adoption and scale (tolerability and safety risks; resistance profile; route of administration, ease of use; requirements for delivery and removal possibility; duration, cost of goods; storage);
- Although the clinical pipeline is most robust in HIV, research is occurring or about to begin in malaria, TB, HCV and for Multi-Purpose Prevention tools such as those combining HIV prevention and contraception;
- Three buprenorphine-based products (two injectables and one implant) have recently entered the market for Opioid Substitution Therapy;
- Two products are likely to enter the market within the next year to eighteen months (dapivirine vaginal ring for HIV prevention and dual-injectables of cabotegravir and rilpivirine for HIV treatment);
- One product (injectable cabotegravir) for HIV prevention and one broadly neutralizing antibody (VRC-01) for HIV prevention are currently in Phase 3 trials in LMICs;
- A number of currently available oral formulations of drugs are highly suitable for repurposing as long-acting injectables, including for malaria chemoprophylaxis and endectocides, latent TB infection and TB maintenance therapy, and HCV treatment/cure.

Presentations and panel discussions about the market highlighted the following key themes:

- Intellectual property for long-acting technologies can be complex, with patents on the drugs themselves, the long-acting formulation processes and the delivery devices;
- Because demand is unclear, in particular for HIV prevention products, supply forecasting is challenging;
- Generic manufacturing will likely involve significant upfront investments and may require complex technology transfer;
- Regulatory pathways may be accelerated for oral formulations of currently available drugs repurposed as long-acting and those products using systems already applied in other approved drugs;
- WHO Prequalification, in the case of long-acting contraception, has already prequalified several products including implants and injectables;
- WHO and national regulatory authorities are likely to require additional capacity to prequalify and/or approve as well as for post-marketing surveillance of long-acting products;

- A number of user preference studies have been completed, but much more information is needed to appropriately segment populations for specific long-acting products;
- Service delivery approaches will need to be adapted for introduction and scale up of long-acting products; and
- Funding for scale-up is not secured. Long-acting products will need to be cost-equivalent to daily oral medicines to facilitate domestic and international financing.

Recommendations were proposed by the break-out groups focused on 1) accelerating clinical development,2) country introduction of long-acting products, and 3) creating a healthy market. Key ideas generated by the groups included:

Accelerating clinical development

- Target Product Profiles could be further refined, with coordination provided by WHO and further engagement of policy makers in LMICs, and could include greater focus on public health impact, formulation processes and delivery devices and cost;
- There is a need for parallel research in populations such as children, adolescents, and pregnant and breastfeeding women (as relevant) if uptake is to happen without time delay in LMICs.
- A number of "quick wins" could be advanced in the area of repurposing currently available oral formulations as long-acting injectables, specifically for malaria prophylaxis (with atovaquone), treatment of LTBI and perhaps maintenance of drug-susceptible TB, and HCV cure.

Enabling country introduction of long-acting products

- The first long-acting injectable combination that will become available for HIV treatment is likely to be unsuitable for use in LMICs due to the need for a cold chain, lack of activity against HBV in cases of co-infection, and drug interactions with TB medications;
- A small number of products in the areas of opioid substitution therapy and HIV prevention that have already entered or will soon enter the market provide opportunities for a game-changing approach for certain populations if early adoption were to be supported;
- Policy makers and country implementation support entities need to begin considering the adoption challenges for long-acting products, including procurement and supply chain management, health service delivery approaches, community engagement for an increasing number of prevention and treatment choices;
- User-preferences and acceptability will need to be considered, and demand-creation activities would need to be supported.

Creating a healthy market for long-acting products

- Efforts to engage originator and generic manufacturers should be expanded, including for:
    - licensing of drugs, processes and device technologies and to provide greater access by researchers and developers to formulation technologies and delivery devices in development or already on the market;

- creating innovative financing mechanisms to develop generic production that would not happen otherwise or only with a high time-lag, and mitigate and offset the risk of upfront investments for products with uncertain market share;
- assessment of needed market concentration per product (minimum desirable number of producers) and potential total estimated market;
- support strategic planning of production and market visibility on a given final product and other products to be produced leveraging the same technology and hence initial investments.

- Partnerships are crucial to avoid duplication and exploit synergies;
- Both public and private health systems need to be engaged;
- Continued investment in WHO Prequalification and the strengthening of national regulatory authorities' capacities is required;
- Guidelines, implementation tools and monitoring and evaluation systems, at international and national levels, need to be developed and, wherever possible, simplified;
- Optimization of price per unit and cost of production would be a key element to enable scaled and sustained use;
- Identifying most efficient in-country delivery mechanisms would also be needed in order to render the use of these products cost-effective, compared with standard-of-care;
- The business case would need to be developed in each case comparing cost of use at individual and programmatic level, as well as impact.

The meeting generated considerable excitement about the prospects for long-acting technologies to support global public health goals. Participants welcomed the opportunity to engage with their peers across disease areas and disciplines. Recognizing the urgent need to plan now to ensure rapid access to products in LMICs, the participants committed to creating and building upon current collaborations and partnerships to advance scientific and market innovations in this rapidly evolving field.

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