DELIVERING QUALITY-ASSURED MEDICAL HEALTH PRODUCTS FOR ALL
2019–2023

WHO’s five-year plan to help build effective and efficient regulatory systems

DRAFT – for comments by 19 April 2019
DELIVERING QUALITY-ASSURED MEDICAL PRODUCTS FOR ALL 2019–2023

WHO’s five-year plan to build effective and efficient regulatory systems
© World Health Organization 2019. All rights reserved.

This is a draft intended for review by all interested parties for the purpose of consultation on the draft text. The content of this document is not final, and the text may be subject to revisions before publication. The document may not be reviewed, abstracted, quoted, reproduced, transmitted, distributed, translated or adapted, in part or in whole, in any form or by any means without the permission of the World Health Organization.
Table of Contents

Foreword ........................................................................................................... v
Acronyms and terms ......................................................................................... vi
Executive Summary .......................................................................................... 1
Introduction ....................................................................................................... 3
Major regulatory challenges and responses ...................................................... 7
Strategic priorities and goals ........................................................................... 14
   An essential support in the drive towards UHC .............................................. 14
   Key principles: reliance and collaboration ................................................... 14
   Strategic Priority 1: Strengthen country and regional regulatory systems in line with the drive toward UHC ................................................................. 15
   Strategic Priority 2: Increase regulatory preparedness for public health emergencies .............................................................. 19
   Strategic Priority 3: Strengthen and expand WHO prequalification and product risk assessment processes ......................................................... 21
   Strategic priority 4: Increase the scope and impact of WHO’s regulatory support activities ............................................................. 22
An ambitious agenda ....................................................................................... 25
Annex A: Strategic priorities and goals ............................................................ 27
Annex B: Prequalification Timeline and Key Performance Indicators (KPIs) .............................................................. 31
Foreword

A good regulatory system for health products is the lynchpin of quality prevention, diagnosis and treatment. Our work in this area strives for universal health coverage built on safe, effective and quality medicines, vaccines, medical devices and vector control products.

True access and the health gains that come with it can only be achieved if globally, regionally and nationally these products can do what they are meant to do – prevent illness and improve people’s health. They can only do that if sound regulatory systems are in place. We know that this is a key and actionable contribution to reaching the 3-billion target set by WHO’s new Global Programme of Work.

Our record in this area speaks for itself. Thanks to WHO’s robust guidance to national regulatory authorities, Tanzania has become the first country in Africa to achieve a well-functioning, regulatory system for medical products.

Our work to assess medical products for supply to countries through the Prequalification scheme has contributed to treating millions of people with quality, cost-effective HIV medicines today, as well as to the vaccination of millions of children through Gavi, the Vaccine Alliance.

Last but not least, our core function of setting standards for medical products continues to ensure that manufacturers and regulators have clear norms to adhere to and a global point of reference. This is particularly important in a globalised world, where the manufacture and trade of medical products are sourced from different countries with sometimes differing regulatory standards and requirements.

Globalisation can sometimes be a barrier to accessing quality products in low-income countries, but WHO is leveraging globalisation in a positive way. With regional and national networks all over the world, we are proposing a collaborative and reliance model for regulatory authorities. Collaboration helps them cut costs and reduce the time it takes to get sorely needed medical products to patients.

Good regulation ensures oversight of medical products throughout their lifecycle – from laboratory to health facilities. This is the ethos and approach of our plan. With its four strategic objectives for regulatory support, it is an ambitious but also feasible plan and, I would argue, essential to achieving the Sustainable Development Goals and Universal Health Coverage.

Dr Mariângela SIMÃO
Assistant Director-General
Access to Medicines, Vaccines and Pharmaceuticals
Geneva, 2019
Abbreviations

ADRs  Adverse Drug Reactions
AEFI  Adverse Events Following Immunization
AEIVD  Adverse Events related to IVDs
AEMD  Adverse Events related to Medical Devices
AMRH  African Medicines Regulatory Harmonization
AVAREF  African Vaccine Regulatory Forum
CIP  Coalition of Interested Parties
CPP  Certification of Pharmaceutical Products
CRP  Collaborative Registration Procedure
EAC  East African Community
EDL  Essential Diagnostics List
EML  Essential Medicines List
EMP  Essential Medicines and Health Products
ERP  Expert Review Panels
EUAL  Emergency Use Assessment and Listing (EUL)
GBT  Global Benchmarking Tool
GPW  General Programme of Work
GSMS  Global Surveillance and Monitoring System
GVSI  Global Vaccine Safety Initiative
HICs  High-income Countries
ICDRA  International Conference of Drug Regulatory Authorities
IDP  Institutional Development Plan
IVDs  in vitro diagnostics
LMICs  Low- and middle-income countries
MSM  Member States Mechanism
NRAs  National Regulatory Authorities
PHEs  Public Health Emergencies
PIDM  Programme for International Drug Monitoring
PQ  Prequalification
SBPs  Similar biotherapeutic products
SF  Substandard and Falsified
SRAs  Stringent Regulatory Authorities
UHC  Universal Health Coverage
VCPs  Vector Control Products
WHOPES  WHO Pesticide Evaluation Scheme
WLAs  WHO Listed Authorities
Executive Summary

Our new Plan for 2019–2023 is designed to help national regulators to deliver regulation that protects the public while enabling timely access to quality products, while encouraging innovation. Closely aligned with WHO 13th General Programme of Work (GPW 13), this Plan prioritises regulatory initiatives to help achieve universal health coverage (UHC), support health emergency responses, and promote healthier populations. Building on its current activities, WHO will focus on four priorities.

**Strategic Priority 1: Strengthen country and regional regulatory systems in line with the drive toward UHC**

In 2018, too many countries had weak regulation of medicines, vaccines, other pharmaceuticals, in vitro diagnostics (IVDs) and medical devices. People in these countries face an unnecessary and additional barrier to access the essential medicines and medical products they need to lead healthy lives. Solutions have to be tailored to the diverse needs of countries – a country that imports all of its essential medicines and diagnostics will have different regulatory needs to a country with significant manufacturing capacity and export potential. Solutions should incorporate the trend for harmonized standards and increased collaboration between regulators as a way to efficiently strengthen regulatory decision-making. Solutions also have to address well-documented regulatory challenges, such as the ubiquity of substandard and falsified (SF) medical products; the underreporting of adverse reactions to medicines and other health technologies; and the limited global capacity to regulate medical devices. WHO has standardized tools to objectively assess regulatory needs and the necessary experience, in collaboration with interested parties, to help countries improve their regulatory systems.

In five years, it is our ambition that 60 countries will have improved their regulatory systems as a result of the help provided by WHO. A total of 24 countries will reach a level of system maturity commensurate with a stable, well-functioning regulatory environment for medicines and vaccines. Of these, seven countries will achieve this by incorporating concepts of reliance on work done by other advanced regulators and by WHO through the collaborative registration procedure. Furthermore, at least 30 LMICs countries will have introduced a risk-based regulatory framework for medical devices, including IVDs, consistent with the WHO global regulatory model.

**Strategic priority 2: Increase regulatory preparedness for public health emergencies**

Responding to a public health emergency – for example an emerging infectious disease – requires decision-making in a context that is different to “business as usual". Being prepared with the necessary plans and tools, and being rehearsed, is just as essential for regulators as for other actors in an emergency situation. WHO has considerable experience in helping regulators improve and test their preparedness so that they are sufficiently robust and responsive in a public health emergency. However too many countries remain inadequately prepared.

In five years, we expect that at least 10 low- and middle-income countries will have adapted their regulatory infrastructure to address the specific challenges of public health emergencies.

**Strategic Priority 3: Strengthen and expand WHO prequalification and product risk assessment processes**

Many populations in the poorest countries now have increased access to life-saving vaccines, quality-assured HIV, TB, malaria, and human reproductive medicines, reliable IVDs for HIV and malaria, and effective vector control products (VCPs). Procurement agencies and governments have come to rely on recommendations made by the WHO prequalification team as ensured quality products. It is therefore critical to ensure that WHO continues to operate an efficient and effective prequalification programme.
In five years, we expect to have expanded the scope of prequalification to cover products important for other priority diseases; while continuing to make prequalification recommendations for active pharmaceutical ingredients, finished pharmaceutical products, IVDs, immunization devices & cold chain equipment, vaccines, vector control products, and medicines quality control laboratories.

At the same time, we plan to develop new routes to prequalification listing as a way to ensure optimal use of the processes, for example expanding reliance on advanced regulators (identified as WHO listed authorities). We also plan to introduce new listings via risk-based approaches to support time-limited procurement. We also intend to expand the types of products that are eligible for prequalification. This will be based on previous experience in increasing the scope of the prequalification work. For example, in June 2018, WHO launched a pilot for the prequalification of selected biotherapeutic products, a step towards making some of the most expensive treatments for cancer more widely available in low and middle-income countries. In five years, we expect an expansion, beyond the 2018 baseline, of products that are eligible for prequalification. These products will be from the Essential Medicines List (EML) (including vaccines) or the Essential Diagnostics List (EDL).

**Strategic Priority 4: Increase the impact of WHO’s Regulatory Support activities**

WHO Headquarters will provide leadership in planning, coordination of delivery, and generating/pooling of resources across WHO regulatory support activities. WHO will develop, implement and publish specific, measurable, achievable, relevant, time-bound (SMART) indicators to permit effective monitoring of progress towards objectives and goals. Priority will be given to collaborative and integrated approaches to work across WHO (Headquarters, Regional Offices and Country Offices) regulatory support activities, coupled with greater alignment with WHO disease programmes. More effective coordination with external partners will also be addressed. Impact measurement will become a core activity. We will apply these metrics across activities and processes and make greater use of mechanisms to enhance accountability to stakeholders. In five years, we expect to have reinforced how we monitor and report on WHO’s impact on regulation and access to medicines and health products.

**An ambitious agenda**

In many cases WHO is already heavily invested and active in the relevant areas and it is important to note that all core activities will be maintained. This is true for example of the Prequalification Programme which is estimated to enable approximately US$ 3.5 billion per year in donor procurement of quality, safe and efficacious products, roughly half of which accounted for by vaccines. The impact of prequalification goes considerably beyond the donor-funded market, as countries also rely on listing of products by the Prequalification Programme to guide national self-procurement decisions.

Though ambitious, the plan is implementable, building on the consolidation and optimization of the regulatory support work at WHO from 2013 to 2018. That Member States recognize the importance of addressing the challenges for regulators is reflected in World Health Assembly Resolution 67.20 which calls for global political support to strengthen regulatory authorities and regulatory processes around the world. The high-level support for regulatory system strengthening represents a major opportunity to advance a well-articulated agenda, and to implement the plans presented in the following pages.
Introduction

The degree to which regulation facilitates the flow of quality goods and services depends on how well it is designed and implemented. Too often regulation is perceived as a barrier to access - and that perception is often justified.

A 2016 study estimated that the overall time to registration for new, innovative medicines and vaccines in low- and middle-income countries (LMICs) is typically four to seven years after submission of a marketing authorization dossier.¹ This compares with one to two years, on average, in high income countries (HICs).²,³,⁴ Reasons for the longer registration times in LMICs include bottlenecks caused by multi-stage approval processes, inadequate funding, and different standards and requirements applied by national regulatory authorities (NRAs), all of which impose additional or duplicative work on manufacturers’ applications.

Medical product regulation is often thought to be solely concerned with the quality, safety and efficacy of those products – the so-called ‘guardian’ role. However, while this role is fundamental, well-functioning regulation also enables quality-assured products to reach the people who need them more quickly.

The study by Ahonkhai et al. cited above, for example, notes that regional collaboration in 2010 among NRAs in Sub-Saharan Africa (with technical support from WHO) permitted rapid approvals of a meningitis vaccine in several countries and “resulted in a huge drop in meningitis cases that has been well documented.”

Of course, product quality is in itself an enabler of access. This, in essence, is the point of the WHO Prequalification Programme, which makes approximately US$3.5 billion worth of urgently needed, safe, and effective quality-assured products accessible to people every year, including roughly US$1.5 billion worth of vaccines for routine immunization programmes.⁵

Prequalification is a trusted symbol for safety, quality and efficacy. It has helped to bring down prices of medicines and vaccines by providing an avenue for LMIC manufacturers to compete in the donor-funded market. Prequalification has enabled donors to trust the products that are procured with their funds and countries to rely on the products coming into their jurisdiction.
Prequalification has also guided innovation and early stage development that is relevant to LMICs – for example it played a key role in bringing paediatric TB products to market in Sub-Saharan Africa, and in promulgating the deployment and use of HIV-1 viral load in vitro diagnostics adapted for use with dried blood spot specimens.

WHO, in coordination with Member States and key stakeholders, works in four main areas to support regulators worldwide:

- establishing and promulgating the norms and standards on which effective product regulation is based
- strengthening the regulatory systems of Member States, including regulatory preparedness for public health emergencies
- implementing and encouraging improved safety monitoring and vigilance
- ensuring, through the Prequalification Programme, that quality-assured products suitable for public health challenges are available for developing markets via both donor-funded and pooled-procurement initiatives.

During the 2013–2018 period, WHO consolidated the four prequalification programmes under one management and optimised the procedures used by each programme. Through these efforts, WHO Prequalification now operates much more consistently, and the “WHO time” required for a prequalification assessment is now comparable to that taken by regulators in high-income countries. WHO has also helped NRAs use the tools and procedures of the Prequalification Programme to inform their own decision-making. This has enabled much more efficient national registration of essential medicines and has provided another avenue for national regulators to build their own national capacities. Based on the successes achieved in both consolidation and optimisation, WHO is poised to look to the future with its stakeholders and build further on the strong foundation achieved to date.

WHO is uniquely placed to help shape responses to emerging regulatory challenges at global, regional and national levels. Prominent among these is the transition away from donor-funded procurement towards more locally managed procurement of medical products. To successfully negotiate this transition, it will be necessary to support country and regional accountability and ownership of regulation. WHO is committed to supporting Member States in a continuation of its evolving regulatory work. This initially focused on standards and products (e.g., activities dealing with norms and standards, and the Prequalification Programme). While continuing and, in some cases, expanding its work in these vitally important product-specific areas, WHO is sharpening its focus on the regulatory systems of Member States, helping to build national and regional capacity while also encouraging greater regulatory collaboration, decreasing regulatory burden through harmonised standards and reliance. WHO is also putting greater emphasis on safety and vigilance. (see Figure 1)

What are medical products?

“Medical products” include medicines, vaccines, in vitro diagnostics, medical devices (including immunization devices), cold chain equipment, vector control products, blood products, sera, anti-venoms, monoclonal and other biotherapeutic products (including similar biotherapeutic products).
To support these efforts, WHO has developed this Plan for the period 2019–2023, designed to generate greater impact at country level. The Plan is closely aligned with WHO 13th General Programme of Work (GPW 13), which sets out the broad strategic goals for the Organization in the coming five years and prioritizes three objectives: increased health coverage; increased health emergency response; and increased population health. Ensuring quality, safety and efficacy is prioritized by WHO as one of two interlinked strategic areas necessary to support access to medical products. The Plan is also aligned with the Essential Medicines and Health Products (EMP) department’s “Towards Access 2030” framework, which makes strengthening regulatory capacity and practices a primary goal.

While ensuring the quality of medical products procured at the international, regional and national levels remains an overarching principle, the 2019–2013 Plan shifts the focus towards supporting countries and regions, and towards promoting regulation informed by the principles of regulatory collaboration and reliance. Although ambitious, the plan is feasible given the appropriate support, and will enable Member States to tackle many of the regulatory challenges they will face in the next five years.

References


Biotechnology Innovation Organization (BIO); 2016.


4 Jawahar. N and Datchayani. B. Comparison of generic drug application

5 WHO “Impact assessment of WHO Prequalification and Systems Supporting Activities” (in preparation for publication)


7 WHO Prequalification programme: Evolution and progress 2013-2018 (accompanying figures – publication in preparation)


11 Regulatory collaboration: collaboration, not competition: developing new reliance models. WHO Drug Information. 2016;Vol. 30, No. 4
Major regulatory challenges and responses

The main regulatory challenges can be broken down into two broad groups. The first are ongoing challenges such as limited resources, and policies and approaches that hamper many NRAs from realising their potential. The second are emerging issues such as more complex medical products (e.g. biotherapeutic products), and increased demand for regulatory responses to conditions arising in health emergencies. Both sets of challenges affect national regulatory systems and processes, including crucial measures that support product safety, vigilance, and supply chain integrity. On a broader scale, they threaten countries’ abilities to achieve the (Sustainable Development Goals (SDGs), and place serious obstacles in the way of the drive to reach universal health coverage (UHC).

Challenge: Limited capacity to carry out all core regulatory functions

Capacity issues facing many NRAs loom large among the on-going regulatory challenges facing Member States. According to WHO surveys based on independent, peer-reviewed audits, in 2018 only 30% of NRAs had the capacity to successfully regulate products on their markets. In general, there was greater capacity to regulate medicines (and vaccines) than to regulate other products.

Capacity limitations affect a range of basic regulatory functions such as assessment of new products and the task of managing variations to already approved products. Lack of capacity to assess new and innovative products slows the journey from laboratory to market of urgently needed products. A 2016 study revealed that overall time to registration for medicines and vaccines in LMICs typically takes four to seven years after completion of Phase 3 trials and assembly of a marketing application dossier, compared to average intervals of one to two years in HICs.

Other important access issues arise as a result of poorly designed or maladapted regulation. For example, multi-stage approval processes can delay products’ achieving widespread availability by several years. Moreover, because regulatory legislation differs from country to country, manufacturers are too often obliged to navigate multiple regulatory systems to register the same product across countries, resulting in increased costs and delays. The challenges presented by regulatory fragmentation are exacerbated by increased globalization of trade. There are increasing numbers of difficult-to-regulate global supply chains, in which multiple companies may be involved in producing products that then move through
several countries and several distributors before finally reaching a patient.

**Response: Build capacity, increase collaboration**

WHO has the knowhow and experience to help countries strengthen their regulatory systems. In 2018, for example, Tanzania, with the support of WHO, became the first documented NRA in Africa to have a stable, well-functioning and integrated regulatory system.16

However, as LMIC countries transition from internationally-funded procurement mechanisms to local procurement of products, pressure will increase to develop the regulatory capacity required to ensure that those products are of assured quality, safety and efficacy. Since the majority of NRAs worldwide lack the resources and capacity to perform all regulatory functions well and increasing number of medical products are manufactured and distributed globally, there is a growing trend for them to work together in regulatory networks. Regulatory collaboration can take a variety of forms, from information and/or work-sharing to mutual or unilateral recognition of assessment and inspection results. Because mutual recognition agreements can take a long time to set up, NRAs are increasingly moving towards various forms of ‘reliance’. In general, reliance implies that one NRA relies on outputs (e.g. scientific assessments, inspections, post-marketing safety data) from an advanced authority while adapting that work to its own circumstances and retaining its own regulatory decision-making responsibilities17.

In the coming years, WHO can play an important role in supporting the transition from donor- to country-based procurement by strengthening regulatory systems for selected countries. This would include focusing on regulators in LMICs in which manufacturing hubs for global medical products have been or will be established. A strong voice from WHO will be needed to reduce the risk that individual countries may implement strategies to promote local production as part of their national development agenda without parallel efforts to ensure quality, safety and efficacy of the products concerned. To achieve this, WHO will require robust policy tools and a coordinated approach to country support, working closely with other UN agencies and partners to ensure adequate supplies of quality-assured medical products that are manufactured within effective regulatory environments. WHO will also continue providing practical hands-on capacity building activities at county and regional levels.

**Challenge: Current scope of the prequalification eligibility list**

Initially created to quality-assure vaccines bought by the United Nations International Children's
Emergency Fund (UNICEF), the prequalification process has since been applied to medicines, IVDs, certain medical devices and immunization-related equipment, and devices for high burden diseases in LMICs. Prequalification programme, as identified in the GPW13, is a tool to facilitate access to quality assured medical products. The Organization will continue to support the availability of quality-assured medical products for procurement by global agencies and countries through the WHO Prequalification Programme, which will evolve to meet the changing health needs of countries.

As of December 2018, WHO has prequalified 1 770 medical products\(^7\), including:

- 663 finished pharmaceutical products (FPPs)
- 140 active pharmaceutical ingredients (APIs)
- 88 in vitro diagnostics (IVDs)
- two male circumcision devices
- 333 vaccines (for 24 priority diseases)
- 413 immunization devices and cold chain equipment
- 80 vector control products (including insecticide treated nets, and indoor sprays)
- 53 medicines quality control laboratories.

In 2018, prequalification of medicines focussed on treatments for HIV/AIDS, malaria, TB, reproductive health, hepatitis, diarrheal diseases, influenza and a selection of neglected tropical diseases. Prequalification of vaccines evaluated all vaccines required for routine immunization against 24 priority diseases, the immunization devices and cold chain equipment needed for an effective national vaccination programme, and also provided risk assessment of vaccines that might be used in a public health emergency. Prequalification of IVDs assessed a wide variety of in vitro diagnostics for both endemic and epidemic diseases in LMICs, with focus on high burden diseases such as HIV/AIDS, malaria and hepatitis C, vector control products (for example, insecticides against malaria, dengue fever, Zika virus diseases, etc.).

Prequalification does not yet cover products such as anti-cancer therapies, anti-diabetics, anti-hypertensives, antimicrobials (beyond those used for cases of HIV and TB), or in vitro diagnostics for meningitis, and non-communicable diseases.

**Response: Expand prequalification list**

Subject to endorsement by a consultative process – both public and specialized WHO advisory groups, eligibility for prequalification assessment will be expanded based on an evaluation of specific needs for products on the Essential Medicines List and the Essential Diagnostics List. This expansion should, on the one hand, address priority unmet needs and, on the other hand, not jeopardize ongoing prequalification work, or undermine the confidence that procurement agencies and Member States have in WHO’s Prequalification Programme. It is also important to ensure that the programme remain nimble and responsive to rapid shifts that may occur in the types and quantities of products needed.
**Challenge: Gaps in capacity to respond to public health emergencies**

A matter requiring particular attention from NRAs in coming years will be to strengthen their contribution to public health emergency responses. Recent crises have exposed major regulatory challenges in global preparedness for such emergencies, notably the 2014 Ebola outbreak. A particular challenge is to quickly evaluate candidate products developed during the emergencies themselves, often based on limited data while the situation is evolving. Poor engagement of some product developers with affected country regulators also has been observed.

In July 2018, using the Global Benchmarking Tool to map emergency provisions for clinical trial oversight in 40 countries, WHO found that approximately 70% of countries lack legal provisions to permit deviation from routine clinical trial procedures or fast-track clinical trial authorizations (WHO, unpublished). The same mapping showed that 50% of countries lacked legal provisions to permit routine product registration procedures to be bypassed in the interest of public health. Many NRAs also reported to WHO that they lacked the capacity or tools to communicate effectively with stakeholders during crises, particularly the media and general public (see Table 1).

**Response: Develop expedited regulatory process**

WHO’s Emergency Use Assessment and Listing (EUAL) procedure was developed in 2015 to expedite the availability of medicines, vaccines and IVDs needed in public health emergencies. An informal WHO consultation regarding regulatory preparedness for health emergencies held at WHO headquarters in May 2017, produced a number of recommendations to guide the development of expedited regulatory procedures for previously unlicensed medical products during public health emergencies. The meeting also recommended renaming the process “EUL”; exploring a preparatory process or “pre-EUL” to improving preparedness, and that the procedure include risk management.

**Table 1. Forty countries benchmarked to map emergency provisions for clinical trial oversight**

<table>
<thead>
<tr>
<th>Afghanistan</th>
<th>Gambia</th>
<th>Georgia</th>
<th>Malaysia</th>
<th>Somalia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangladesh</td>
<td>Guinea-Bissau</td>
<td>Maldives</td>
<td>South Sudan</td>
<td></td>
</tr>
<tr>
<td>Bhutan</td>
<td>India</td>
<td>Mongolia</td>
<td>Sri Lanka</td>
<td></td>
</tr>
<tr>
<td>Burundi</td>
<td>Indonesia</td>
<td>Mozambique</td>
<td>Sudan</td>
<td></td>
</tr>
<tr>
<td>Cambodia</td>
<td>Islamic Republic of Iran</td>
<td>Nepal</td>
<td>Syrian Arab Republic</td>
<td></td>
</tr>
<tr>
<td>Cape Verde</td>
<td>Kazakhstan</td>
<td>Niger</td>
<td>Thailand</td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>Kenya</td>
<td>Pakistan</td>
<td>Timor-Leste</td>
<td></td>
</tr>
<tr>
<td>Egypt</td>
<td>Lao People’s Democratic Republic</td>
<td>Papua New Guinea</td>
<td>Uganda</td>
<td></td>
</tr>
<tr>
<td>Eritrea</td>
<td>Lebanon</td>
<td>Saudi Arabia</td>
<td>United Republic of Tanzania</td>
<td></td>
</tr>
<tr>
<td>Ethiopia</td>
<td>Liberia</td>
<td>Serbia</td>
<td>Viet Nam</td>
<td></td>
</tr>
</tbody>
</table>
surveillance, and communication provisions. A roadmap was subsequently developed to put these recommendations into practice and to develop the regulatory processes in receiving countries to authorize the use of products listed by WHO.

For their part, regulators must ensure that their processes for emergency reviews are robust, effective and responsive.

Regulatory networks are a key element of strengthening regulatory preparedness, as demonstrated by the African Vaccine Regulatory Forum (AVAREF) during the Ebola crisis and reconfirmed in a November 2017 “table top exercise” undertaken with stakeholders.

**Challenge: A flood of substandard and falsified medical products**

Weak regulatory systems create opportunities for the manufacturers and purveyors of substandard and falsified (SF) products. Broadly speaking, substandard products reach patients when tools and technical capacity are inadequate to enforce quality standards in manufacturing and the supply chain. The circulation of falsified products is facilitated by corruption and unethical practices by wholesalers, distributors, retailers and health workers.

According to a 2017 WHO report, one in ten medicines in LMICs is substandard or falsified, while an estimated $30 billion is wasted on such medicines in LMICs every year. All therapeutic classes are concerned, but most SF medical product reports entered into WHO’s Global Surveillance and Monitoring System (GSMS) in 2018 related to anti-malarials (19.5% of total reports) and antibiotics (16.9%). Both generic and innovator products, expensive and inexpensive, are affected, and SF versions are available in both the public and private supply chains. Promotion and distribution of SF products through the internet is a major concern both in HIC and, increasingly, in middle-income countries (MICs). The increasing globalisation of the medical products market is also greatly complicating the task of regulators, not least because of jurisdictional complexities when multiple countries are involved.

**Response: Invest in prevention, detection and response**

Effective responses to SF products are founded on preventing the conditions that permit their manufacture, distribution and consumption. Regulatory system strengthening and oversight has a key part to play in this. It is also critical that Member States develop the capacity to detect SF products quickly and share the information via the GSMS. It is also vital to suspend production and distribution, recall products, and punish offenders. WHO focuses its efforts in prevention detection and response, working within the Member States Mechanism (MSM) which was established at the request of the World Health Assembly in 2012.

**Challenge: Underreporting of adverse reactions to medicines, and poor post-marketing monitoring by authorities**

The under-reporting of adverse drug reactions (ADRs), adverse events following immunization (AEFI) and adverse events related to use of medical devices (AEMD) including IVDs, continues to be a core concern, particularly in LMICs. This is borne out by the roughly 16 million VigiBase reports accumulated over nearly 50 years, only 12.5% of which come from LMICs. The main reason for underreporting is the lack of resources to establish functional
pharmacovigilance\textsuperscript{1} systems. Another ongoing challenge is low priority given to ADR/AEFI/AEMD reporting by policy makers and decision takers, who may not recognize its importance to their population’s health. The introduction of products, including malaria vaccines and tuberculosis treatments which have been launched either exclusively in LMICs or simultaneously in LMICs and HICs, is putting increased pressure on NRAs to meet their obligations and highlights the need for more proactive post-marketing monitoring. Another growing challenge is the spread of false safety concerns regarding vaccines via the internet and social media. These have reduced coverage due to mistrust of vaccines and have led to outbreaks of vaccine-preventable disease such as measles in Europe and the Americas.

\textit{Response: Improve monitoring and reporting on adverse events and safety issues and ensure health authorities make use of results}

Improving the reporting of ADRs, AEFIs and AEMDs requires greater investment in the systems established for this purpose, notably the Programme for International Drug Monitoring (PIDM), the VigiBase electronic database, and the Global Vaccine Safety Initiative (GVSI). Investment is also required to strengthen National Pharmacovigilance Centres. Currently 164 Member States have a recognized National Pharmacovigilance Centre and participate in the WHO PIDM. 130 of these contribute reports, to varying degrees of quality and quantity, to the WHO VigiBase. However, very few of these countries use or act on their national data. It is important that more countries collecting good quality pharmacovigilance data, but equally that these countries receive support in order to use the data that they collect.

While access to essential, priority medicines has improved over the years, pharmacovigilance systems haven’t kept up or improved proportionately. New products such as bedaquiline and dolutegravir, have been introduced into countries with little or no capacity to monitor the safety of these products, underscoring the fact that, a robust and responsive pharmacovigilance system is needed, to safely access and use these products effectively.

Pharmacovigilance has an important role to play, offering unique insights into the real world of interactions between people and the medical products on which they rely. However, it is vital that health authorities make use of the information that is being gathered. Risk-based prioritization of pharmacovigilance efforts that consider smarter and more proactive approaches should therefore be explored. Opportunities to consider smarter and more proactive approaches are therefore being explored, such as Project 3-S. This partnership between WHO and the Bill & Melinda Gates Foundation aims to integrate “Smart Safety Surveillance” for priority medical products in four to six countries at different levels of pharmacovigilance readiness.\textsuperscript{26}

\textbf{References}

\begin{itemize}
  \item \texttt{http://apps.who.int/iris/handle/10665/272972}
  \item Belgharbi L, Khadem Broojerdi A, Rodriguez-Hernandez C and Wood\textsuperscript{13}
\end{itemize}

\textsuperscript{1}\textsuperscript{1} Pharmacovigilance includes vigilance of various medical products as described on page 5
WHO Regulatory 5-year Plan_v20March2019_clean.docx


WHO Global Surveillance and Monitoring System for SF Products” https://www.who.int/medicines/regulation/ssffc/publications/GSMS_Report_layout.pdf?ua=1


Strategic priorities and goals

Based on an analysis of the challenges faced and a careful assessment of where WHO can most add value in supporting regulators, four strategic priorities were identified. Aligned with the GPW and supporting the global drive towards universal health coverage, these strategic priorities were informed by the dual imperatives of assuring the quality of medical products and supporting optimal access. The strategic priorities are:

1. Strengthen country and regional regulatory systems;
2. Improve regulatory preparedness for public health emergencies;
3. Reinforce and expand WHO prequalification and product risk assessment;
4. Increase the impact of WHO regulatory support activities.

Activities to achieve these priorities will be guided by carefully defined goals and objectives, which are detailed in Annex A. This section presents an overview of the main goals and their implications for the work of WHO. In many cases WHO is already working in the relevant areas. In others, achieving the goals and objectives identified will require new activities and adopting different approaches.

An essential support in the drive towards UHC

Effective and efficient regulation of medical products is crucial to both to global health and to achieving sustainable development. In fact, the two are indivisible. Sustainable Development Goal 3.8 specifically refers to “access to safe, effective, quality and affordable essential medicines and vaccines for all” as central to UHC. Similarly, Sustainable Development Goal 3.b underscores the pressing need for new medicines to be developed if persistent treatment gaps are to be solved.

The current context is marked by increasing demand for greater product access, often in the context of health systems striving towards UHC. This demand will bring with its regulatory demands that will be difficult for many resource-constrained countries to meet.

WHO’s prequalification activities are an essential and well-established support in the drive towards both UHC and the SDGs, and provide guidance to countries and procurement agencies on quality assured medical products. Launched in 1987 to quality-assured vaccines bought by UNICEF, since then the prequalification process has been applied to medicines and IVDs for high burden diseases, immunization devices and cold chain equipment and vector control products.

Key principles: reliance and collaboration

The manufacture and distribution of modern medical products is increasingly globalized. For this reason, cooperation between national and regional regulators has become essential, and a variety of types of collaboration are being applied in different parts of the world. A key
approach to collaboration is “reliance”, seen as a means of spreading knowledge and best practices while avoiding duplication of work. As WHO noted in a publication:28

In general, reliance implies that the work done is shared by the advanced authority (e.g. through assessment or inspection reports), while the receiving authority uses this work according to its own scientific knowledge and regulatory procedures and retains its own regulatory responsibilities. For example, when an assessment report for a medicine authorized in the EU is shared with a regulatory authority in Africa, the receiving authority might still need to consider differences in conditions of use, patient population and other parameters. In many cases reliance on the assessment or inspection work carried out by another advanced regulatory authority can be the best way to cooperate effectively. Reliance can be unilateral, bilateral (mutual) or multilateral.

“Reliance” implies that one NRA relies on outputs (e.g. scientific assessments, inspections, post-marketing safety data) from an advanced authority while adapting that work to its own circumstances and retaining its own regulatory decision-making responsibilities.

Strategic Priority 1: Strengthen country and regional regulatory systems in line with the drive toward UHC

Summary: In five years, it is our ambition that 60 countries will have improved their regulatory systems as a result of the technical support provided by WHO. A total of 24 countries will reach a level of system maturity commensurate with a stable, well-functioning regulatory environment for medicines and vaccines. Of these, seven countries will achieve this by incorporating concepts of reliance on work done by other advanced regulators and by WHO through the collaborative registration procedure. Furthermore, at least 30 LMICs countries will have introduced a risk-based regulatory framework for medical devices, including IVDs, consistent with the WHO global regulatory model. All of this supports the over-arching goal of universal health coverage.

Goal 1: Implement regulation in an increasing number of countries through reliance and NRA networks

As noted above, the majority of NRAs worldwide lack the resources and capacity to perform all regulatory functions well. Gaps in regulation and enforcement compromise product safety, quality, and efficacy while also hampering access. As countries move towards more independent approaches to medical product procurement, including through local production, pressure is building to ensure regulatory systems are adequately resourced and effective. To meet these challenges, regulators are increasingly employing smart regulatory approaches based on national policy coherence among ministries, collaboration, networks, harmonisation and reliance. Strong regulatory capacity to oversee local manufacturing is essential before investing in local production of medical products, underscoring the urgency of assisting LMICs as they create plans for local medical product manufacture.

WHO is already active in supporting the efforts of regional and global regulatory networks to improve standards, reduce duplication of effort, and eliminate bottlenecks. A notable initiative is the African Vaccine Regulatory Forum (AVAREF), which was founded by WHO in 2006 to help strengthen regulatory capacity for clinical trials. In 2016, AVAREF adopted a strengthened and expanded structure to support the
African Medicines Regulatory Harmonization (AMRH) initiative. Since 2015, AMRH has carried out a variety of regulatory harmonization interventions, including joint assessment of applications in the five East Africa Community (EAC) countries. This work will continue to expand, including initiatives in other parts of the world such as those under the aegis of SADC/ZAZIBONA, ECOWAS, IGAD (all to be spelled out), the South East Asia Regulatory Network (SEARN) and more.

WHO’s Collaborative Registration Procedure (CRP) has significantly accelerated national registration by improving information-sharing between the Prequalification Programme and NRAs. Whereas NRA approval of a prequalified medicine previously could take as long as two years, in 2017 the average approval period for products that have gone through CRP was 93 days. WHO has also established a Facilitated Registration Procedure to accelerate registration of medical products that are not eligible for prequalification assessment but have been approved by well-established NRAs (formerly known as Stringent Regulatory Authorities). By relying on these improved procedures, NRAs can avoid duplication of work, speed up delivery of quality-assured products and make these more widely available.

In the coming period, WHO will expand the scope of the CRP to additional product streams (vaccines and IVDs) and beyond the 34 countries which used the procedure in 2017. WHO will also develop new guidance on using regulatory reliance and network-based collaboration. To help stakeholders identify “reliable” NRAs, WHO will publish a list of NRAs that meet international performance benchmarks assessed via the Global Benchmarking Tool (GBT). These will be termed WHO Listed Authorities (WLAs). The list will also identify NRAs on whom WHO will rely when it performs an “abridged” prequalification assessment for products that have already received stringent assessment.

In 2018, WHO began working with a group of partners called the Coalition of Interested Parties (CIP) in a pilot approach to strengthening regulatory systems in a number of countries and regions. The pilot is being used to inform and formalize the operation of a coalition-based approach that could be used in other countries. Towards this end, AMRH has established an African chapter of the CIP called the AMRH Partnership Platform.

**Goal 2: Increase regulatory convergence through wider implementation of WHO quality standards**

Robust norms and standards are the foundation of effective regulation of products. Ensuring their definition and implementation will be crucial to strengthening country and regional regulatory capacity. WHO’s work in this area dates back to the Organization’s inception and has significantly reduced the risk of harm and inefficacy in medical products over the past six decades. As part of norms and standards work, WHO also establishes International Nonproprietary Names, chemical reference materials and biological reference materials. This essential work will continue under the current Action Plan. In response to the rapidly changing global medical products landscape, more emphasis will be placed on promoting WHO norms and standards in international regulatory harmonization and on supporting their adoption at national level.

A number of urgent scientific challenges need to be addressed in the coming years. One is related to the introduction of new classes of therapeutic products such as biotherapeutics and similar biotherapeutic products (SBPs). These will require, at the very least, an updating of guidelines or developing questions and answers (Q&A) documents, taking into account technological advances. In some cases (e.g. cell and gene therapies) WHO can provide a platform for experienced regulators to share...
knowledge and insights, especially where agreement exists, but also to note where harmonization has yet to be achieved and to document areas of uncertainty. Another challenge is managing variations to approved/listed products, which is a large part of the work of regulators and of the regulatory affairs divisions at manufacturers. In addition to the guidelines on variation to a prequalified APIs and FPPs, WHO has now established general guidelines on post-approval changes for vaccines and for biotherapeutics. Widespread implementation of these guidelines is anticipated to substantially reduce regulatory burden.

Increasing demand for greater product access, often in the context of health systems striving towards UHC, will also bring with its regulatory demands that will be difficult for many resource-constrained countries to meet. One way to address this issue whilst helping to build reliance and trust between regulators will be to encourage Member States to utilize the standard procedure of the WHO Certification of Pharmaceutical Products (CPP) programme. WHO CPP provides an assurance to regulatory authorities that imported medicines have been evaluated against rigorous and publicly-defined standards of quality, safety, and efficacy. It also provides assurance that they have been approved for marketing. WHO will update the CPP template, including the development of e-certificates (“eCPPs”) to replace the paper CPP, which will ensure secure documentation is shared among relevant stakeholders, improve product approval process and timelines and increase the efficiency in accessing new and innovative medicines in countries.

**Goal 3: Strengthen national regulatory capacity to ensure quality of medical products**

Working in collaboration with country regulators, WHO has developed a Global Benchmarking Tool (GBT). The tool is used to formulate country-specific institutional development plans (IDP), including regulatory workforce development goals. In 2018, the GBT addressed regulation of medicine and vaccines, but in coming years is expected to cover medical devices including diagnostics and blood and blood products including for hemovigilance. The tool also will be adapted to address needs, including human resources and other needs associated with approaches outlined in this plan, such as regulatory collaboration and reliance, emergency preparedness, overseeing local manufacturing, and implementation of collaborative registration procedures.

As of July 2018, the GBT has been used in 55 countries, and over 25 IDPs have been developed. This follows similar efforts with earlier tools in over 125 countries over the last two decades. WHO has facilitated technical collaboration at the regional level, with mature NRAs providing training and technical support to NRAs with limited capacity through twining programmes and other formal collaborative mechanisms. WHO’s experience in NRAs strengthening shows that implementation of IDPs often requires engagement not only from the health sector but also from non-health sectors of government such as trade and industry, science, and education.

WHO also provides direct technical assistance or coordination to build on country IDPs, including technical advice and training. At least 85 regulatory
support training activities in the form of e-learning, face-to-face courses, implementation workshops, and webinars were provided by WHO in 2018. A “landscape analysis” will be used to critically evaluate quality features of WHO regulatory support learning initiatives. On completion, the information will be used to develop a learning strategy for WHO regulatory support activities, providing a global vision for education of regulators.

**Goal 4: Strengthen pharmaceutical sector capacity especially in countries that manufacture products for LMICs and/or local supply**

All countries need access to quality-assured products, but the quality of locally-produced medical and other medical products in many LMICs may not be well assured. Reasons include lack of government commitment, legal and regulatory framework, weak regulatory oversight, and low manufacturing standards. Applying its expertise in benchmarking and building regulatory capacity at country/regional-level, WHO can play an important role in supporting more sustainable access to quality-assured products by focusing on regulators in selected countries, including those in LMICs where manufacturing hubs for medical products have been or will be established.

Another priority is to support NRAs in countries that are transitioning away from internationally-funded procurement to domestically financed procurement. To increase confidence in the quality, efficacy and safety of locally produced medical products, efforts to strengthen regulatory oversight will be complemented with capacity building and technical assistance for the pharmaceutical sector. Robust guidance will be needed from WHO to help reduce the risk of local manufacturing bases developing without parallel strengthening of local or regional medical product regulation. WHO’s past experiences have shown that promoting local production is a complex and cross-sectoral endeavour. To be successful, it requires a holistic, collaborative approach towards setting long-term strategies, policy coherence, capacity building and technical support.

Working with other UN agencies and trusted partners, WHO will:

- develop tailored national/regional strategies and roadmaps to strengthen both local production and quality assurance;
- map capacity building activities and technical support currently provided by WHO technical teams and other stakeholders, with the aim of developing a coherent approach in promoting quality local production;
- coordinate and organize the capacity building and technical support in collaboration with trusted partners;
- establish a virtual training platform for LMICs and transitioning countries, including repositories of reference documents, tools and e-learning modules, such as GMP and other WHO technical quality assurance guidelines.

**Goal 5: Strengthen safety surveillance to support and safeguard the uptake of new locally-manufactured products**

WHO employs a life-cycle approach to regulation of medical products. An essential part of that approach is reviewing the risk-benefit profile of products as new data becomes available. This is accomplished through effective post-marketing surveillance and pharmacovigilance. WHO is already working in this area, focusing on improving the reporting of ADRs, AEFIIs and AEIVDs, and encouraging greater use of those reports by public health authorities.

Increased investment is required to improve the reporting and use of ADRs/AEFIIs/AEIVDs, not only in the systems established for this purpose (PIDM, VigiBase, GVSI), but in the National Pharmacovigilance Centres which are responsible for collecting and transmitting Individual Case Safety
Reports. As noted above, products such as malaria vaccines and innovative tuberculosis treatments are increasingly launched either exclusively in LMICs or simultaneously in LMICs and HICs, putting serious pressure on less resourced NRAs. High-disease-burden countries often have weaker systems for gathering information on the real-life safety, efficacy or performance of products that are new to their markets, and less capacity to assess the information, communicate outcomes and coordinate necessary actions among stakeholders. WHO will use a Smart Safety Surveillance approach to enhance both reactive and proactive surveillance of safety, quality or performance of priority products that are marketed in high disease burden settings. This will include providing support for data analysis to enable public health policy actions to be taken.

**Goal 6: Improve prevention, detection and response to substandard and falsified (SF) medical products**

WHO’s work on SF medical products focuses on prevention, detection, and response. It works within the Member States Mechanism (MSM) which mobilises political support and promotes Member States’ collaboration around SF-related activities. The MSM is also committed to strengthening national and regional capacities and contributes to the work of WHO departments addressing product access. MSM also facilitates cooperation with relevant stakeholders and promotes collaboration on surveillance of SF products.

Launched in 2013, WHO’s Global Surveillance and Monitoring System (GSMS) has worked to improve reporting of SF medical products and provide immediate co-ordination and technical support in emergencies. GSMS also issues rapid alerts and assesses the scope, scale and harm caused by SF medical products.

In 2019–2023, WHO will take a comprehensive approach to the SF products challenge, utilizing the experience gained with medicines to help regulate SF products across all product streams. This will include:

- improving countries’ ability to carry out risk-based post-market surveillance within their territories
- improving reporting and rapid alert systems
- securing supply chains to minimize penetration by SF products
- updating standards for prevention, detection and response to SF products
- supporting NRAs in their local implementation of these measures, in collaboration with key stakeholders.

**Goal 7: Support regulatory convergence through the convening power of WHO**

WHO has transparent, well-defined interactions with key non-State actors, and comprehensive network of WHO Regional and Country Offices. Working in coordination with all UN Member States, WHO is thus uniquely placed to establish, convene and maintain global and regional platforms for discussion and decisions in response to regulatory challenges. Making full use of this capacity and these platforms has significant practical applications. For example, WHO has the convening power to adapt a regional initiative and introduce it in a global context, thus further encouraging harmonization and streamlining of approaches.

In low- and middle-income countries, one in ten medicines is substandard or falsified, and an estimated US$30 billion is wasted on such medicines every year.

**Strategic Priority 2: Increase regulatory preparedness for public health emergencies**

**Summary:** In five years, we expect that with the assistance of WHO, 10 countries will have adapted their
regulatory infrastructure to address the specific challenges of public health emergencies. These 10 countries will have done this also by working together in regional networks. All emergency prone countries familiar with the WHO through the emergency use listing procedure.

**Goal 1: Strengthen national and regional regulatory procedures for risk-based evaluations during public health emergencies (PHE)**

One of the regulatory challenges faced in the response to a PHE or a shortage of essential medical products is expediting evaluations of new or alternative products without jeopardizing the scientific quality of the assessments. Experience has exposed a number of shortcomings of NRAs in this regard, including lack of risk-based procedures to evaluate candidate products developed for or during emergencies. Following the 2014 Ebola outbreaks in West Africa, WHO introduced Emergency Use Assessment Listing (EUAL) procedures for candidate vaccines, diagnostics and therapeutics. Based on experience of assessing products for both the Ebola and Zika public health emergencies, WHO will implement updated procedures for emergency reviews (renamed EUL), including development of "pre-EUL" procedures.

Support will be provided to clarify the roles and responsibilities of NRAs in countries producing products for use in public health emergencies. For products listed by WHO through EUL procedures, support will be provided to receiving countries to expedite local clinical trial authorizations and/or emergency use of such products. New WHO norms and standards will be developed and implemented in parallel, including support for moving from emergency use (the current practice) to in-country approval routinely managed by NRAs.

**Goal 2: Increase WHO’s capacity to support regulatory preparedness for public health emergencies**

WHO is mandated by Member States to play a pivotal role in the response to PHEs. It is thus vital that WHO be given the resources to ensure its own state of readiness. Activities in support of this goal will include defining priorities for WHO's work in PHEs, leveraging WHO risk-based outcomes through regulatory networks, and ensuring WHO has knowledge of and access to surge capacity to respond to PHEs. Lessons learnt from recent emergencies will be used, as necessary, to revise its services and ways of working.

**Goal 3: Increase the number of countries that have adapted their regulatory preparedness for PHEs and are using regional networks for expedited evaluations**

WHO will identify gaps and assist priority countries to adapt their regulatory systems so that they are robust, responsive, and able to address the conditions arising during PHEs. One proven way of doing this is through joint reviews in which a group of countries formally agree to work together to conduct scientific reviews. African regulators and ethicists pioneered this approach using the AVAREF platform. Joint reviews through the AVAREF process were especially useful in assessing clinical trial applications of candidate Ebola vaccines during the 2014–2016 outbreak.

During the period of this Plan, the GBT will address the regulatory workforce levels needed to work in networks during a PHE. WHO will help establish or strengthen existing networks and processes that facilitate joint reviews during PHEs, and also promote other measures to build regulatory preparedness, including through regular "tabletop exercises" (i.e. facilitated discussions of different scenarios) to test procedures. Regulatory pathways also will be tested when countries conduct deployment capacity assessments and
exercises for global and regional stockpiles.

**Strategic Priority 3: Strengthen and expand WHO prequalification and product risk assessment processes**

**Goal 1: Improve efficiency, capacity and awareness of prequalification programme**

In order to ensure that the Prequalification Programme is responsive to rapid shifts in the types and quantities of products needed, the prequalification process will be kept under continuous review and efficiencies introduced to maximize optimal use of resources. Feedback from countries and partners will be used to identify the need for new or updated norms and standards, and to provide real-time information of national regulatory capacities. Improved communications will raise awareness of underappreciated impacts of prequalification, such as the positive spill-over effect of prequalification on manufacturing standards, and guiding innovation and early-stage product development that is relevant to LMICs.

**Goal 2: Strengthen and expand WHO’s prequalification lists**

It is estimated that the Prequalification Programme (currently covering APIs, FPPs, IVDs, immunization devices and cold chain equipment, vaccines, vector control products, and medicines quality control laboratories) enables approximately US$ 3.5 billion per year in procurement, roughly half of which is accounted for by vaccines. It provides a concrete means of access for manufacturers to participate in donor-funded as well as pooled procurement of key medicines, vaccines and IVDs. The Prequalification Programme also provides technical guidance to ensure the LMIC context is a driver of innovation and product development. As a result, many populations in the poorest countries now have access to affordable life-saving quality-assured vaccines, quality-assured HIV, TB, malaria, human reproductive medicines and other medical products. WHO is committed to maintaining and further optimizing the Prequalification Programme for all product streams for the lifetime of the Plan, and beyond. Specific attention will be given to strengthening and expanding the prequalification of IVDs during the 2019–2023 period, as well as to continue to evolve the processes and procedures for prequalification of vector control products.

**Goal 3: Develop new pathways to prequalification listing and new risk-based approaches to support time-limited procurement**

In order to ensure optimal use of the prequalification process, additional pathways to prequalification (especially using the principle of reliance), will be developed and introduced. Among other benefits, these will improve the ability of procurers and countries to identify sources of quality-assured products. Following wide consultation with NRAs and regional regulatory networks, a concept paper will be written on possible new pathways to prequalification for all product streams. Once validated through consultation and due diligence has been completed to ensure sustainability, the new pathways will be implemented.

A similar approach will be taken to develop and implement new risk-based approaches to support time-limited procurement. These will be based on current approaches used by expert review panels (ERP) or the evaluation of snake antivenoms.

**Goal 4: Expand the range of products eligible for pre-qualification**

While supporting access to quality-assured HIV, TB, malaria, human reproductive, and other medical products, the Prequalification Programme does not yet cover products such as anti-cancer therapies, anti-diabetics, anti-hypertensives and antimicrobials, or quality-assured IVDs for syphilis, meningitis and non-communicable diseases. WHO thus
proposes that the scope of prequalification be expanded, just as it has been expanded in the past.

In 2018, WHO launched a prequalification pilot for the biotherapeutic products rituximab and trastuzumab and their corresponding similar biotherapeutic products (SBPs). This is an important step towards making some of the most expensive treatments for cancer more widely accessible in LMICs. Prequalification of vector control products was introduced at the beginning of 2017 to replace and improve upon the assessment previously undertaken by the WHO Pesticide Evaluation Scheme (WHOPES).

In 2019–2023, WHO will expand the types of essential products that are eligible for prequalification beyond the 2018 baseline. The expansion will be based on the Essential Medicines List (EML), including vaccines) and the Essential Diagnostics List (EDL). As mentioned above, WHO will consult widely with relevant stakeholders and develop a concept paper on possible new product streams for prequalification listing. A discussion will be necessary at that time regarding the need for increased capacity within NRAs and WHO to deal with the expanded workload.

In marshalling resources for its strategic priorities, WHO will emphasise transparency and optimal communication with donors and all relevant stakeholders. To support these efforts, and in consultation with stakeholders, WHO will develop a strategic and collectively-agreed resource approach reflecting best practice in resource reporting.

**Goal 2: Improve targeting and alignment of WHO regulatory support activities**

Every disease management strategy requires access to quality medical products for prevention, diagnosis, treatment, palliative care and rehabilitation. For example, the Global Action Plan on Antimicrobial Resistance calls for urgent investment in the development of new antimicrobial medicines, as well as in diagnostic tools and vaccines. These research and development activities will require extensive interactions with regulators so that the main goal of ensuring treatment and prevention of infectious diseases with quality-assured, safe and effective medical products is achievable.

The Plan requires long-term investment, including in building regulatory capacities. WHO regulatory support programmes therefore will interact and collaborate extensively with many WHO programmes to align, strengthen and maximise country impact of the Organization’s regulatory activities.

Alignment is also crucial where there is a need for WHO to implement pharmacovigilance interventions for novel products, such as malaria vaccine, which may require a multi-year lead time to collect data in target countries on background rates of conditions of interest.

During 2019–2023, priority will be given to collaborative work across all WHO regulatory support activities (i.e. at Headquarters, Regional Offices and Country Offices), and greater alignment with WHO disease programmes. Opportunities for closer and more
effective coordination with external partners will also be pursued.

To help meet this goal WHO will compile information on future demand for regulatory support activities. WHO headquarters will lead on the adaptations needed to respond to stakeholders’ changing priorities for technical support, such as a need to do more on the regulation of medical devices or on biotherapeutics. These adaptations may include enhancing the skill sets available at WHO and establishing or supporting skill centres within Regional Offices to help perform selected global activities. One possibility for exploration is that of a decentralized hub concept to work in close proximity to countries that often receive WHO support or are the subject of frequent prequalification interventions, such as inspections of manufacturing sites.

**Goal 3: Enhance monitoring of WHO’s impact on regulation and access to medical products**

In 2019-2023, we will apply metrics across all activities and processes, and enhance accountability to stakeholders. Measures of impact at country level will be developed as a collaborative and iterative process with stakeholders. In addition to WHO outputs, key performance indicators of NRAs will be collected to measure impact and reported regularly.

Rather than inventing new reporting mechanisms for these impact measurements, we will focus on making better use of existing opportunities. For example, the International Conference of Drug Regulatory Authorities (ICDRA) convened by WHO is the largest worldwide meeting for regulators, and an ideal occasion for them to discuss and explore the way forward. Similar platforms are also convened at a regional level by some WHO Regional Offices. The norms and standards developed by WHO Expert Committees are reported to the Executive Board of WHO. In summary, we will work to increase the visibility and use of the existing opportunities Member States have to scrutinize the regulatory support work of WHO and to provide strategic direction.

**Goal 4: Establish and implement Quality Management System**

Quality management system (QMS) plays a key role in setting and maintaining efficient standardized operations. Through QMS, we will harmonize processes to ensure consistency and resources are used in most effective and optimum manner. KPIs will also be developed to measure impact made in countries. Furthermore we will develop risk mitigation plan in coordination with relevant WHO departments to ensure continuing sustainable and effective implementation of regulatory action plan.

**References**


30 Formerly known as Stringent Regulatory Authorities (SRA)

31 Abridged prequalification assessment - Prequalification of In Vitro Diagnostics.
Geneva: World Health Organization; 2017

33 Guidelines on procedures and data requirements for changes to approved vaccines
https://www.who.int/biologicals/vaccines/Annex4_Guidelines_changes_to_approved_vaccines_eng.pdf

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


http://www.who.int/medicines/publications/druginformation/issues/WHO_DI_31-4.pdf?ua=1


38 WHO Assessment and Listing of Snake Antivenoms

An ambitious agenda

While the list of regulatory challenges set out in this document is daunting, it is clear that the responses required to meet them exist. For example, regulatory collaboration—whether in the form of regulatory harmonisation of standards and mutual recognition, or implementation of regulatory reliance—has been shown to mitigate problems arising from disparate NRA standards and requirements. Similarly, the positive impact of the prequalification programme is well documented and universally acknowledged. WHO is committed to continuing its work in these and other areas in response to demands from Member States, and in consultation with various partners and stakeholders.

However, the coming five years will bring several new challenges, notable among them the need to develop the regulatory capacity of LMICs to support the transition towards more government-financed procurement. In order to meet this challenge WHO is shifting its focus towards country and regional support. A second major emerging challenge is to ensure that regulatory systems are prepared to support public health emergency responses. WHO will focus on supporting priority countries as they adapt their regulatory infrastructures, including developing processes for emergency reviews that are robust and responsive.

Implementing the Plan will require action both on the part of WHO and national governments, and will, of course, require significant investment. However, as was noted in the Foreword, bad (or no) regulation ends up costing more than good regulation.

Member States recognize the importance of addressing the challenges set out in this document. This was reflected most recently in World Health Assembly Resolution 67.20, which calls for global political support to strengthen regulatory authorities and regulatory processes around the world. Regulatory system strengthening has also been called for by ICDRA gatherings.
Ultimately, however, there is no greater recognition of the importance of regulation than Sustainable Development Goal 3, which demands “access to safe, effective, quality and affordable essential medicines and vaccines for all.” Experience teaches that this is impossible without functioning regulatory and procurement systems.


Clearly, high level support for regulatory system strengthening exists. There is therefore a major opportunity to advance the regulation agenda by implementing the plans set out in this document.

References
## Annex A: Strategic priorities and goals

### Strategic Priority 1: Strengthen country and regional regulatory systems in line with the drive toward UHC

<table>
<thead>
<tr>
<th>Goals</th>
<th>Objectives</th>
</tr>
</thead>
</table>
| SP1.1 Implement regulation in an increasing number of countries through reliance and NRA networks | SP1.1.1 Establish and apply concept of WHO Listed Authorities (see WHO Technical Report Series, No. 1010, p43-44)  
SP1.1.2 Promote smart regulation  
SP1.1.3 Promote adoption of best regulatory models and practices through harmonized guidelines, standards and processes for smart regulation  
SP1.1.4 Promote reliance for clinical trial authorization and on outputs from regulatory GMP inspections  
SP1.1.5 Promote reliance for registration of quality-assured products  
SP1.1.6 Promote reliance on outputs from National Control Laboratories  
SP1.1.7 Ensure an efficient and effective Collaborative Registration Procedure, inclusive of all product streams, for prequalified products and products registered by WHO Listed Authorities |
| SP1.2 Increase regulatory convergence through wider implementation of WHO quality standards | SP1.2.1 Ensure cost-effectiveness of developing WHO standards and align WHO standards portfolio with evolving global health priorities  
SP1.2.2 Continue to deliver WHO’s norms and standards setting  
SP1.2.3 Raise awareness of the WHO norms and standards and their impact  
SP1.2.4 Increase implementation of WHO norms and standards |
| SP1.3 Strengthen national regulatory capacity to ensure quality of medical products | SP1.3.1 Enhance external support for and internal capacity to carry out capacity building, training and regulatory systems strengthening at the regional and country levels  
SP1.3.2 Prioritize NRAs for assessment and strengthening  
SP1.3.3 Increase national quality control laboratory capacity to monitor medicines and vaccines quality  
SP1.3.4 Optimize and expand regulatory strengthening tools, expertise, and training strategies  
SP1.3.5 Working through collaborative mechanisms in transitional countries and pharmaceutical hubs in LMIC to strengthen regulatory oversight and quality local production |
<p>| SP1.4 Strengthen pharmaceutical sector capacity especially in | SP1.4.1 Define local production and develop a model strategy for quality-assured local production |</p>
<table>
<thead>
<tr>
<th>Strategic Priority</th>
<th>Goals</th>
<th>Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Countries that manufacture products for LMICs and/or local supply</td>
<td>SP1.4.2 Encourage local production to focus on quality-assured products</td>
</tr>
<tr>
<td></td>
<td>SP1.5 Strengthen safety surveillance to support and safeguard the uptake of new locally-manufactured products</td>
<td>SP1.5.1 Ensure surveillance systems in place to manage risks of medicines, in particular for anticipated or unknown risks of new, complex medicines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SP1.5.2 Safety surveillance for new vaccines implemented in countries as a means of enhancing uptake</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SP1.5.3 Ensure global and national systems are in place for post-marketing surveillance of IVDs</td>
</tr>
<tr>
<td></td>
<td>SP1.6 Improve prevention, detection and response to substandard and falsified (SF) medical products</td>
<td>SP1.6.1 Implement prevention, detection and response strategies for SF medical products in vulnerable LMICs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SP1.6.2 Expand, refine and enhance WHO Global Surveillance and Monitoring System for SF medical products</td>
</tr>
<tr>
<td></td>
<td>SP1.7 Support regulatory convergence through the convening power of WHO</td>
<td>SP1.7.1 Global and regional platforms for discussion and decision making on regulatory convergence and issues of common concern are established and maintained by WHO</td>
</tr>
</tbody>
</table>

Strategic Priority 2:
Increase regulatory preparedness for public health emergencies

<table>
<thead>
<tr>
<th>Goals</th>
<th>Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>SP2.1 Strengthen national and regional regulatory procedures for risk-based evaluations during public health emergencies (PHE)</td>
<td>SP2.1.1 Revise regulatory procedures and standards for risk-based evaluations during PHEs</td>
</tr>
<tr>
<td></td>
<td>SP2.1.2 Support networks to facilitate expedited assessment of products in the context of a PHE</td>
</tr>
<tr>
<td>SP2.2 Increase WHO’s capacity to support regulatory preparedness for public health emergencies</td>
<td>SP2.2.1 Strengthen WHO processes to provide support to regulators in PHEs</td>
</tr>
<tr>
<td>SP2.3 Increase the number of countries that have adapted their regulatory preparedness for PHEs and are using regional networks for expedited evaluations</td>
<td>SP2.3.1 Identify and fill gaps at country and regional level in capacity to respond to PHEs</td>
</tr>
<tr>
<td></td>
<td>SP2.3.2 Assist countries to adapt their regulatory requirements to effectively address PHEs</td>
</tr>
<tr>
<td>Strategic Priority 3:</td>
<td>Strengthen and expand WHO prequalification and product risk assessment processes</td>
</tr>
<tr>
<td>----------------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Goals</strong></td>
<td><strong>Objectives</strong></td>
</tr>
<tr>
<td>SP3.1 Improve</td>
<td>SP3.1.1 Continue to improve the efficiency, across all product streams, of prequalification activities</td>
</tr>
<tr>
<td>efficiency, capacity</td>
<td>SP3.1.2 Enhance prequalification capacity</td>
</tr>
<tr>
<td>and awareness of</td>
<td>SP3.1.3 Raise awareness of prequalification programme and impact among stakeholders and encourage applications</td>
</tr>
<tr>
<td>prequalification</td>
<td></td>
</tr>
<tr>
<td>programme</td>
<td></td>
</tr>
<tr>
<td>SP3.2 Strengthen and</td>
<td>SP3.2.1 Continue to deliver prequalification recommendations for APIs, FPPs, IVDs, immunization devices &amp; equipment, Vaccines, Vector Control Products, and medicines quality control laboratories</td>
</tr>
<tr>
<td>expand WHO’s</td>
<td>SP3.2.2 Strengthen the prequalification of in vitro diagnostics (PQ Dx)</td>
</tr>
<tr>
<td>prequalification</td>
<td>SP3.2.3 Continue to evolve the processes and procedures for prequalification of vector control products</td>
</tr>
<tr>
<td>lists</td>
<td></td>
</tr>
<tr>
<td>SP3.3 Develop new</td>
<td>SP3.3.1 Develop additional pathways to prequalification with NRAs of maturity level 3</td>
</tr>
<tr>
<td>pathways to</td>
<td>SP 3.3.2 Expand the scope of risk-based approaches to support time-limited procurement</td>
</tr>
<tr>
<td>prequalification</td>
<td></td>
</tr>
<tr>
<td>listing and new risk-</td>
<td></td>
</tr>
<tr>
<td>based approaches to</td>
<td></td>
</tr>
<tr>
<td>support time-limited</td>
<td></td>
</tr>
<tr>
<td>procurement</td>
<td></td>
</tr>
<tr>
<td>SP3.4 Expand the</td>
<td>SP3.4.1 Provide technical guidance to ensure the LMIC context is a driver of innovation and product development</td>
</tr>
<tr>
<td>range of products</td>
<td>SP3.4.2 Expand the scope of prequalification for all product streams</td>
</tr>
<tr>
<td>eligible for</td>
<td></td>
</tr>
<tr>
<td>pre-qualification</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strategic Priority 4:</th>
<th>Increase the scope and impact of WHO’s regulatory support activities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Goals</strong></td>
<td><strong>Objectives</strong></td>
</tr>
<tr>
<td>SP4.1 Ensure that</td>
<td>SP4.1.1 WHO has sufficient capacity to deliver efficiently and effectively against its strategy</td>
</tr>
<tr>
<td>WHO’s regulatory</td>
<td>SP4.1.2 Develop key performance indicators (KPIs) to improve performance and impact management of WHO’s regulatory support work</td>
</tr>
<tr>
<td>support capacity and</td>
<td>SP4.1.3 Global and regional platforms are used to share the results of WHO and country performance analyses</td>
</tr>
<tr>
<td>resources are</td>
<td></td>
</tr>
<tr>
<td>sufficient to</td>
<td></td>
</tr>
<tr>
<td>implement the Plan</td>
<td></td>
</tr>
<tr>
<td>SP4.2 Improve</td>
<td>SP4.2.1 Develop and implement a strategic, collectively agreed resource approach between donors and WHO</td>
</tr>
<tr>
<td>targeting and</td>
<td>SP4.2.2 Internal alignment and coordination is strengthened for regulatory support activities (between Headquarters, Regional Offices and Country Offices; and with WHO disease programmes)</td>
</tr>
<tr>
<td>alignment of WHO</td>
<td>SP 4.2.3 Explore a WHO regulatory ‘hub’ in close proximity with priority countries/regions to provide more responsive, effective and faster collaboration.</td>
</tr>
<tr>
<td>regulatory support</td>
<td></td>
</tr>
<tr>
<td>activities</td>
<td></td>
</tr>
<tr>
<td>SP4.2.5 An approach to prioritize WHO's regulatory support activities to add value is implemented</td>
<td></td>
</tr>
<tr>
<td>SP4.3 Enhance monitoring of WHO's impact on regulation and access to medical products</td>
<td></td>
</tr>
<tr>
<td>SP4.3.1 A validated evidence-base to assess the impact of WHO's work to support improved regulatory capacity</td>
<td></td>
</tr>
<tr>
<td>SP4.4 Establish and implement Quality Management System</td>
<td></td>
</tr>
<tr>
<td>SP4.4.1 Develop KPIs to measure performance improvement made by countries as a result of WHO's work, including risk identification and mitigation plan</td>
<td></td>
</tr>
<tr>
<td>SP4.4.2 Develop risk mitigation plan in coordination with cluster and other relevant clusters and departments</td>
<td></td>
</tr>
</tbody>
</table>
Annex B: Prequalification Timeline and Key Performance Indicators (KPIs)

This summary of the Prequalification Timeline and KPIs contains details of indicators and targets.

<table>
<thead>
<tr>
<th>#</th>
<th>Indicator</th>
<th>% Target</th>
<th>Target time</th>
</tr>
</thead>
<tbody>
<tr>
<td>340</td>
<td>Number of products prequalified</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>341</td>
<td>Median number of dossier review cycles</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>342</td>
<td>% of products prequalified for which the number of dossier review cycles is at or below target</td>
<td>70%</td>
<td>Target number of dossier review cycles: 3</td>
</tr>
</tbody>
</table>

**Change assessment cohort (post-PQ change applications accepted for change assessment in a calendar year)**

Post-PQ change applications accepted for change assessment (i.e. the change assessment cohort)

| 400 | Number of post-PQ change applications accepted for post-PQ change assessment | -        | -                                               |

**Time to post-PQ change first action**

| 410 | Number of post-PQ change first actions                                   | -        | -                                               |
| KPI 4 | % of post-PQ change first actions taken at or below target time | 80%      | APIMF | major amendment: 90 days                      |
|      |                                                                     |          | APIMF | minor amendment: 60 days                      |
|      |                                                                     |          | APIMF | immediate notification: 45 days              |
|      |                                                                     |          | FPP  | major variation: 90 days                     |
|      |                                                                     |          | FPP  | minor variation: 60 days                     |
|      |                                                                     |          | FPP  | immediate notification: 45 days              |
|      |                                                                     |          | IVD  | reportable change: 90 days                   |
|      |                                                                     |          | Vx   | major variation, type A: 90 days             |

**PQ list cohort (all prequalified products on the PQ lists at the beginning of a calendar year)**

Prequalified products on the PQ lists (i.e. PQ list cohort)

| 500 | Number of products on the PQ list                                      | -        | -                                               |
| 501 | Number of products withdrawn after prequalification                   | -        | -                                               |
| KPI 2 | % of screening first actions taken at or below target time            | 80%      | 30 calendar days                               |

**Assessment cohort (PQ applications accepted for PQ assessment in a calendar year)**

PQ applications accepted for PQ assessment (i.e. the assessment cohort)

| 300 | Number of PQ applications accepted for PQ assessment                  | -        | -                                               |

Time to dossier first action

| 310 | Number of dossier first actions                                       | -        | -                                               |
| KPI 3.1 | % of dossier first actions taken at or below target time              | 80%      | 90 calendar days, 120 calendar days for FPPs & APIs (due to fixed assessment sessions) |

Time to inspection first action

| 320 | Number of inspection first actions                                    | -        | -                                               |
| KPI 3.2 | % of inspection first actions taken at or below target time         | 80%      | 210 days                                       |

Time to laboratory first action

| 330 | Number of laboratory first actions                                    | -        | -                                               |
| KPI 3.3 | % of laboratory first actions taken at or below target time        | 80%      | 180 days                                       |

Targets have been set for 2018 and may be revised one year after implementation, to include new targets from 2019 onwards, once preliminary results have been collected and reviewed. This should be read in conjunction with the full background information relating to prequalification timeline indicators.
WORLD HEALTH ORGANIZATION
Regulation of Medicines and other Health Technologies
Access to Medicines, Vaccines and Pharmaceuticals

20 avenue Appia
CH-1211 Geneva 27