



World Health Organization



DELIVERING QUALITY-ASSURED MEDICAL PRODUCTS FOR ALL

2019-2023



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





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Foreword

People who work in health care expect the products they use to work as described on the box – in fact, to actually be what is described on the box. The fundamental issue is trust: just as patients need to be able to trust in our expertise, health workers need to be able to trust that products they prescribe actually do what they are meant to do: prevent illness and improve people's health.

That, in essence, is what we aim for in this five-year plan, in a context of increasing globalization, technological advance, changing disease patterns and demographics, and the disturbing prevalence of substandard and falsified products.

Good regulatory systems, providing oversight of health products throughout their lifecycle from the laboratory to the health facility, are the linchpin of quality prevention, diagnosis and treatment. They are an essential part of WHO's drive towards universal health coverage (UHC) and a key contribution to reaching the "triple billion" target (1 billion more people benefitting from universal health coverage, 1 billion more people better protected from health emergencies, and 1 billion more people enjoying better health and well-being) set by WHO's 13th General Programme of Work.

Our record in this area speaks for itself. There are many achievements to point to, but the one that stands out for me is a national success story. With WHO's robust guidance based on assessment made by our Global Benchmarking Tool, the United Republic of Tanzania has become the first country in Africa to achieve a well-functioning regulatory system for medical products. I congratulate Tanzania and our Tanzanian colleagues, and look forward to many more countries' commitment to achieving this status over the next five years.

Another source of pride is the quiet but steady work of the WHO Prequalification Programme. Over the years, it has contributed to treating millions of people with quality, cost-effective medicines, including HIV treatments, as well as to protecting millions of children worldwide from vaccines-preventable diseases through safe, effective and quality vaccines. The same goes for our core function of setting standards for medical products, which continues to ensure that manufacturers and regulators have clear norms to adhere to and a global point of reference. This is particularly important in an increasingly globalised world, where medical products are sourced from different countries with sometimes

differing regulatory standards and requirements.

Rather than simply wringing our hands about this challenge, WHO is leveraging globalization in a positive way. Partnering with regional and national networks all over the world, we promote a collaborative reliance model for regulatory authorities. Collaboration helps such authorities to cut costs and reduce the time it takes to get sorely needed medical products to patients; reliance allows the expertise and experience of trusted national regulators to be shared and their benefits amplified.

This is the ethos and approach of our five-year plan. With its four strategic priorities for regulatory support, it is ambitious but feasible.

I have great confidence in the enthusiasm and abilities of my colleagues at WHO, the energy and receptiveness of the national regulatory authorities we work with, and the diverse ways in which our international partners support us. With their cooperation and a clear plan to work from, I look forward to the next five years.



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



Abbreviations

ADRs	Adverse Drug Reactions	IDP	Institutional Development Plan
AEFI	Adverse Events Following Immunization	IGAD	Intergovernmental Authority on Development
AEIVD	Adverse Events related to IVDs	IMDRF	International Medical Device Regulators Forum
AEMD	Adverse Events related to Medical Devices	IPRP	International Pharmaceutical Regulators Programme
AMRH	African Medicines Regulatory Harmonization	IVDs	In vitro diagnostics
APEC	Asia-Pacific Economic Cooperation	KPI	Key Performance Indicator
API	Active Pharmaceutical Ingredient	LMICs	Low- and Middle-Income Countries
ASEAN	Association of Southeast Asian Nations	ML3	Maturity Level 3
AVAREF	African Vaccine Regulatory Forum	MSM	Member State Mechanism
CARICOM	Caribbean Community	NRA s	National Regulatory Authorities
CIP	Coalition of Interested Partners	PHE s	Public Health Emergencies
CPP	Certification of Pharmaceutical Products	PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
CRP	Collaborative Registration Procedure	PIDM	Programme for International Drug Monitoring
EAC	East African Community	PPCs	Preferred Product Characteristics
ECOWAS	Economic Community of West African States	PQ	Prequalification
EDL	Essential Diagnostics List	PSPQ	Programmatic Suitability for Prequalification
EML	Essential Medicines List	SADC	Southern African Development Community
ERP	Expert Review Panel	SBPs	Similar Biotherapeutic Products
EUAL	Emergency Use Assessment and Listing (replaced by EUL)	SEARN	South East Asia Regulatory Network
EUL	Emergency Use Listing	SF	Substandard and Falsified
FPP	Finished Pharmaceutical Product	SMART	Specific, Measurable, Achievable, Relevant, Time-Bound
GBT	Global Benchmarking Tool	TPPs	Target Product Profiles
GMP	Good Manufacturing Practices	SRA s	Stringent Regulatory Authorities
GPW13	WHO 13th General Programme of Work	UHC	Universal Health Coverage
GSMS	Global Surveillance and Monitoring System	UNICEF	United Nations Children's Fund
GVSI	Global Vaccine Safety Initiative	VCP s	Vector Control Products
HIC s	High-income Countries	WHOPES	WHO Pesticide Evaluation Scheme
ICDRA	International Conference of Drug Regulatory Authorities	WLA s	WHO Listed Authorities
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use		
ICMRA	International Coalition of Medicines Regulatory Authorities		



Executive Summary



WHO/Shutterstock

WHO's 2019–2023 Plan to help build effective and efficient regulatory systems is designed to help national regulators to deliver regulation that protects the public while enabling timely access to quality products and encouraging innovation. Closely aligned with WHO's 13th General Programme of Work (GPW13), this Plan prioritizes regulatory initiatives to help our Member States increase access to universal health coverage (UHC), support health emergency responses, and promote healthier populations. Building on its current activities, annual work plans with specific deliverables and key performance indicators (KPIs) will be prepared based on four strategic priorities.

Executive Summary

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

Many countries lack adequate investment of resources (financial and expertise) in regulatory systems, resulting in weak regulation of medicines, vaccines, biotherapeutics, blood and blood products, in vitro diagnostics (IVDs) and medical devices. People in these countries thus face an unnecessary barrier to accessing the essential medicines and medical products they need to lead healthy lives. Solutions to this barrier 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 than a country with significant manufacturing capacity and export potential.

Solutions should also incorporate internationally-recognized, science-based and harmonized standards, along with increased collaboration among regulators to strengthen regulatory decision-making. As well, solutions have to address well-documented regulatory challenges such as the ubiquity of substandard and falsified (SF) medical products, underreporting of adverse reactions to medicines and other health technologies, and the limited global capacity to regulate medical devices. WHO uses standardized tools to objectively assess regulatory needs, and has the necessary experience to help countries improve their regulatory systems, working in collaboration with a variety of partners. Based on defined criteria in the Global Benchmarking Tool (GBT), this Plan aims for 50 countries to have improved their regulatory systems by 2023 as a result of technical assistance provided by WHO. Current data estimates that a total of 24 additional countries will reach a level of system

maturity commensurate with a stable, well-functioning regulatory environment for medicines, medical products and vaccines. Of these, seven countries will achieve this by incorporating the concept of “reliance” on work done by other advanced regulators and through WHO’s collaborative registration procedure (CRP). Reliance will be applied over the entire product life-cycle, including testing, vigilance and post-market surveillance. Furthermore, at least 30 additional countries will have introduced a risk-based approach for regulating medical devices, including IVDs, as reflected in the WHO Global Model Regulatory Framework for medical devices.

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 than “business as usual.” Being prepared with the necessary plans and tools, and being rehearsed, is just as essential for regulators as for other stakeholders in an emergency situation. WHO has considerable experience in helping regulators improve and test their systems’ preparedness so that they are sufficiently robust and responsive in a public health emergency. However too many countries remain inadequately prepared.

In five years, WHO expects that at least 10 additional LMICs will have improved their regulatory infrastructure to address the specific challenges of public health emergencies, adopting

features such as regulatory provisions for reliance, a fast-tracking registration process, and an effective and adapted pharmacovigilance system.

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 medicines for HIV, TB, malaria and women’s health, reliable IVDs for HIV and malaria, and effective vector control products (VCPs). Procurement agencies and governments have come to rely on recommendations included in WHO Prequalification Lists regarding ensured quality products. It is therefore critical to ensure that WHO continues to operate an efficient and effective Prequalification Programme.

In five years, WHO will have expanded the scope of prequalification to cover products important for additional priority diseases. At the same time, new routes to prequalification listing will be developed to ensure optimal use of the processes, e.g. expanding reliance on advanced regulators identified as WHO-Listed Authorities (WLAs). New listings will be introduced using risk-based approaches such as Expert Review Panels (ERPs) and Model Quality Assurance Systems, in order to support time-limited procurement and existing risk-based approaches. Training on regulation through reliance will also be enhanced. As it did in June 2018 with the launch of a pilot for prequalification of selected biotherapeutic products – a



An ambitious agenda

step towards making some of the most expensive cancer treatments more widely available in low and middle-income countries – WHO will expand the types of products that are eligible for prequalification. Products in the WHO’s Essential Medicines List (EML, including vaccines) or the Essential Diagnostics List (EDL) will be taken into consideration.

Strategic Priority 4: Increase the scope and impact of WHO’s regulatory support activities

WHO headquarters will provide leadership in planning, coordination of delivery, and generating/pooling of resources across the Organization’s regulatory support activities. WHO will develop annual action plans, and will implement and publish specific, measurable, achievable, relevant, time-bound (SMART) indicators to permit monitoring of progress towards objectives and goals. Relevant key performance indicators will be defined to measure the impact of the action plan. Priority will also be given to collaborative and integrated approaches in regulatory support activities across WHO (Headquarters, Regional Offices and Country Offices), coupled with greater alignment with WHO disease programmes. There will also be more effective coordination with external partners. Impact measurement will become a core activity, with metrics applied across activities and processes and greater use of mechanisms to enhance accountability to stakeholders. In five years, WHO will have reinforced how it monitors and reports on its impact on regulation and access to medicines and health products.

WHO is already heavily invested and active in many of the relevant areas, and it is important to note that all core activities will be maintained. For example, the Prequalification Programme enables 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 Programme to guide national self-procurement decisions.

Though ambitious, the 2019-2023 Plan is feasible, consolidating and optimizing the WHO’s regulatory support work 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. Such high-level support for strengthening regulatory systems represents a major opportunity to advance a clear agenda, and to implement the plans presented in the following pages.



IMPROVING ACCESS TO IMPORTANT MEDICAL PRODUCTS

In 2017, The Lancet's Commission on Essential Medicines reported on global progress towards improving access to the most important medical products.

The report stated,

“The Commission believes that achieving sustainable development requires concerted efforts to improve the quality and safety of essential medicines, though building appropriate regulatory system a part of health systems.”

Wirtz et al, Essential Medicines for Universal Health coverage. Lancet. 2016;388

It went on to list five crucial areas of opportunity for improving the quality and safety of essential medicines:

- 1 Expand international regulatory convergence and harmonisation
- 2 Broaden the WHO/UN Prequalification Programme
- 3 Establish good procurement practices at all levels
- 4 Promote surveillance of product quality and safety
- 5 Leverage political attention and commitment to advance accountability.



Introduction





Regulation is sometimes perceived as a barrier to access. However, the degree to which regulation facilitates the flow of quality goods and services depends on how well it is designed and implemented.

A 2016 study estimated that the overall time required for registration of new, innovative medicines and vaccines in low- and middle-income countries is typically four to seven years after a marketing authorization dossier has been submitted.¹ This compares with one to two years, on average, in high income countries (HICs).^{2,3,4,5} 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. Furthermore, although they are not well understood by policy-makers, health-care workers and even by regulators, national requirements for repeated official batch release testing often are a major obstacle to market access.

Medical product regulation is often thought to be solely concerned with the quality, safety and efficacy of 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 2016 study 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.^{6,7,8,9} Initially created to quality-assure vaccines bought by the United Nations Children's 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.

Although WHO is not a regulatory authority, its Prequalification Programme has been recognized as 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 has permitted countries to rely on the products coming into their jurisdiction.

Prequalification has also guided innovation and early-stage development of products that are especially relevant to LMICs. For example, it played a key role in bringing paediatric TB products to market in Sub-Saharan Africa and in the deployment of HIV-1 viral load IVDs adapted for use with dried blood spot specimens.¹⁰ 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 existing prequalification programmes under one management and optimised the procedures used by each programme.¹¹ 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 such successes, WHO is working with its stakeholders to 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 challenges is the transition away from donor-funded procurement towards more locally funded supply of medical products. To successfully negotiate this transition, it will be necessary to support country and regional accountability and ownership of regulation.

WHO's regulatory work initially focused on activities dealing with norms and standards and on 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 and to increase regulatory effectiveness and efficiency. This will be done by encouraging greater regulatory collaboration, increasing regulatory efficiency through reliance mechanisms, and applying harmonised standards that are internationally-recognized and science-based. WHO is also putting greater emphasis on safety and vigilance and on combatting the threat of substandard and falsified (SF) 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 the WHO 13th General Programme of Work (GPW13), 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.¹²

Ensuring quality, safety and efficacy is prioritized by WHO as one of two interlinked strategic areas necessary to support access to medical products (the other is innovation).

The Plan is also aligned with WHO's "Towards Access 2030" framework, which makes strengthening regulatory capacity and practices a primary goal and the recently concluded access roadmap.¹⁵

While ensuring the quality of medical products procured at the international, regional and national levels remains an overarching principle, the 2019–2023 Plan shifts the focus towards supporting countries and regions, and towards promoting regulation informed by the principles of regulatory collaboration and reliance.¹⁶ 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.



What are medical products?
Medical products include medicines, vaccines, in vitro diagnostics, medical devices (including immunization devices), cold-chain equipment, vector control products, blood and blood products, antivenoms, monoclonals and other biotherapeutic products.

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Major regulatory challenges and responses



Major regulatory challenges and responses

The main regulatory challenges can be broken down into three broad groups. The first is ongoing challenges such as limited resources, and policies and approaches that hamper many NRAs from working optimally. The second is emerging issues linked to increasingly complex medical products (e.g. biotherapeutic products), and rising demand for regulatory responses to conditions arising in health emergencies. The third group of challenges is related to the speed and span of advancement in technologies and innovation. All groups of challenges affect national regulatory systems and processes, including crucial measures that support product safety, vigilance (for all medical products, including pharmacovigilance), 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.

Challenge: Limited capacity to carry out all core regulatory functions

Capacity issues facing many NRAs loom large among the ongoing 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 effectively and efficiently regulate products on their markets.¹⁷

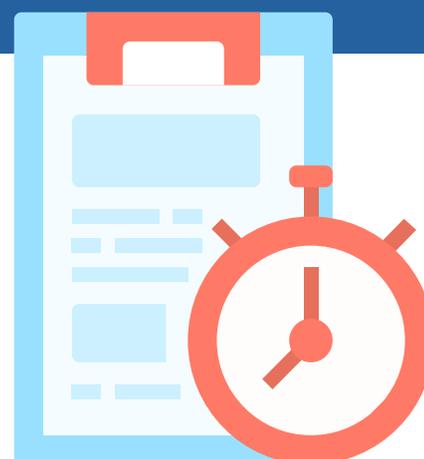
In general, there was greater capacity to regulate medicines and vaccines than to regulate other products.¹⁸

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 authorization dossier, compared to an average of one to two years in HICs.²⁰

Other important barriers to access arise as a result of poorly designed or maladapted regulation. For example, multi-stage approval processes can delay products from achieving widespread availability by several years.²¹ 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.²² The challenges presented by the increasing complexity and globalization of trade are exacerbated by lack of coordinated regulation, even in the same region. 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.

WHAT IS PHARMACOVIGILANCE?

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. Its aims are to enhance patient care and patient safety in relation to the use of medicines and to support public health programmes by providing reliable, balanced information for the effective assessment of the risk-benefit profile of medicines.¹⁹





Response: Build capacity, increase collaboration and reliance

WHO has the knowhow and experience to help countries strengthen their regulatory systems. In 2018, for example, the United Republic of Tanzania's regulatory authority became the first documented NRA in Africa to achieve maturity level 3 (ML3), assessed as having a stable, well-functioning and integrated regulatory system according to the indicators of the WHO Global Benchmarking Tool (GBT). This successful result stemmed from the country's prioritized institutional development plan, which was itself guided by the GBT.²³

However, as LMICs transition from internationally funded procurement mechanisms to local procurement of products, there will be increased pressure to develop the regulatory capacity required to ensure that 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. As stated in the 2018 International Conference of Drug Regulatory Authorities (ICDRA) recommendations,²⁴ the concept of reliance and increasing regulatory collaboration requires both trust and the capacity to share and rely on regulatory work performed by trusted NRAs. Regulatory collaboration can take a variety of forms, from information or work-sharing to mutual or unilateral recognition of assessment and inspection results.

Recognition, which is also a form of reliance, is defined as "the routine acceptance of the regulatory decision of another regulator or other trusted institution. Recognition indicates that evidence of conformity with the regulatory requirements of country A is sufficient to meet the regulatory requirements of country B."²⁵

However, experience shows that mutual recognition agreements may take considerable time to set up, and so NRAs are increasingly moving towards other forms of reliance. In general, reliance implies that one NRA relies

on outputs (e.g. scientific assessments, inspections, batch release testing, post-marketing safety data) from an advanced authority while adapting that work to its own circumstances and retaining its own regulatory decision-making responsibilities.²⁶

In the coming years, WHO will play an important role in supporting the transition from donor- to country-based procurement by strengthening regulatory systems for selected LMICs. A strong voice from WHO will be needed to reduce the risk that individual countries may promote local production as part of their national development agenda without parallel efforts to strengthen regulatory systems – the only way to ensure that products meet international standards of quality, safety and efficacy. 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 that medical products are manufactured within effective regulatory environments. WHO will also continue providing practical hands-on capacity-building activities at county and regional levels.



The United Republic of Tanzania's Food and Drug Authority, with the support of WHO, has become the first documented NRA in Africa to have achieved a stable, well-functioning and integrated regulatory system (ML3).

Dr Tigest Ketsela Mengestu, WHO Representative in the United Republic of Tanzania, congratulates Ms Ummy Mwalimu, the country's Minister of Health, Community Development, Gender, Elderly and Children.





A PROGRAMME WITH TEETH

'The WHO Prequalification Programme is strict and does not hesitate to delist products when the applicant's dossiers are not up to standard. This happened in 2011 for vaccines, when WHO delisted a pentavalent vaccine, and in 2004 for medicines, when the WHO delisted generic ARVs because of irregularities at the clinical study sites where bioequivalence was established, signalling to the industry the Prequalification Programme had teeth.'



Challenge: Current scope of the prequalification eligibility list

The WHO Prequalification Programme is constantly evolving in order to meet the changing health needs of Member States. As of December 2018, WHO has prequalified over 1 770 medical products, including:

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

In 2018, *prequalification of medicines* focused on treatments for HIV/AIDS, malaria, TB, reproductive health, hepatitis, diarrheal diseases, influenza and a selection of neglected tropical diseases. *Prequalification of vaccines* ensured evaluation of vaccines that are required for routine immunization against 24 priority diseases, and of the immunization devices and cold-chain equipment needed for an effective national vaccination programme, and also performed risk assessment of certain 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 a focus on high burden diseases such as HIV/AIDS, malaria and hepatitis C. *Prequalification of vector control products* converted past WHO product evaluations to prequalification and assessed new public health pesticides in a wide variety of formulations, all of which are intended to reduce the burden of vector borne diseases (e.g. malaria, dengue fever, Zika virus diseases, etc.) by controlling the organisms that transmit the diseases to humans.

Prequalification does not yet cover products such as anti-cancer therapies, anti-diabetics, anti-hypertensives, the majority of antimicrobials (beyond those used for HIV and tuberculosis), or IVDs for meningitis and non-communicable diseases.

Response: Expand prequalification list

Subject to endorsement by a consultative process by both public and specialized WHO advisory groups, eligibility for prequalification assessment will be expanded based on an evaluation of specific needs for products (generic or established) and also innovative products on the Essential Medicines List and the Essential Diagnostics List. This expansion should, on the one hand, address priority unmet needs²⁸ and, on the other hand, not jeopardize ongoing prequalification work or undermine the confidence that procurement agencies and Member States have in the 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.



WHO/Emro-Aden

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 and current Ebola outbreaks. 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, WHO used the GBT to map emergency provisions for clinical trial oversight in 40 countries (see Figure 1), finding that approximately 70% of countries lack legal provisions to permit fast-track clinical trial authorizations. The same mapping showed that 50% of countries lacked legal provisions to permit emergency-prone product registration procedures, which may be required 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.

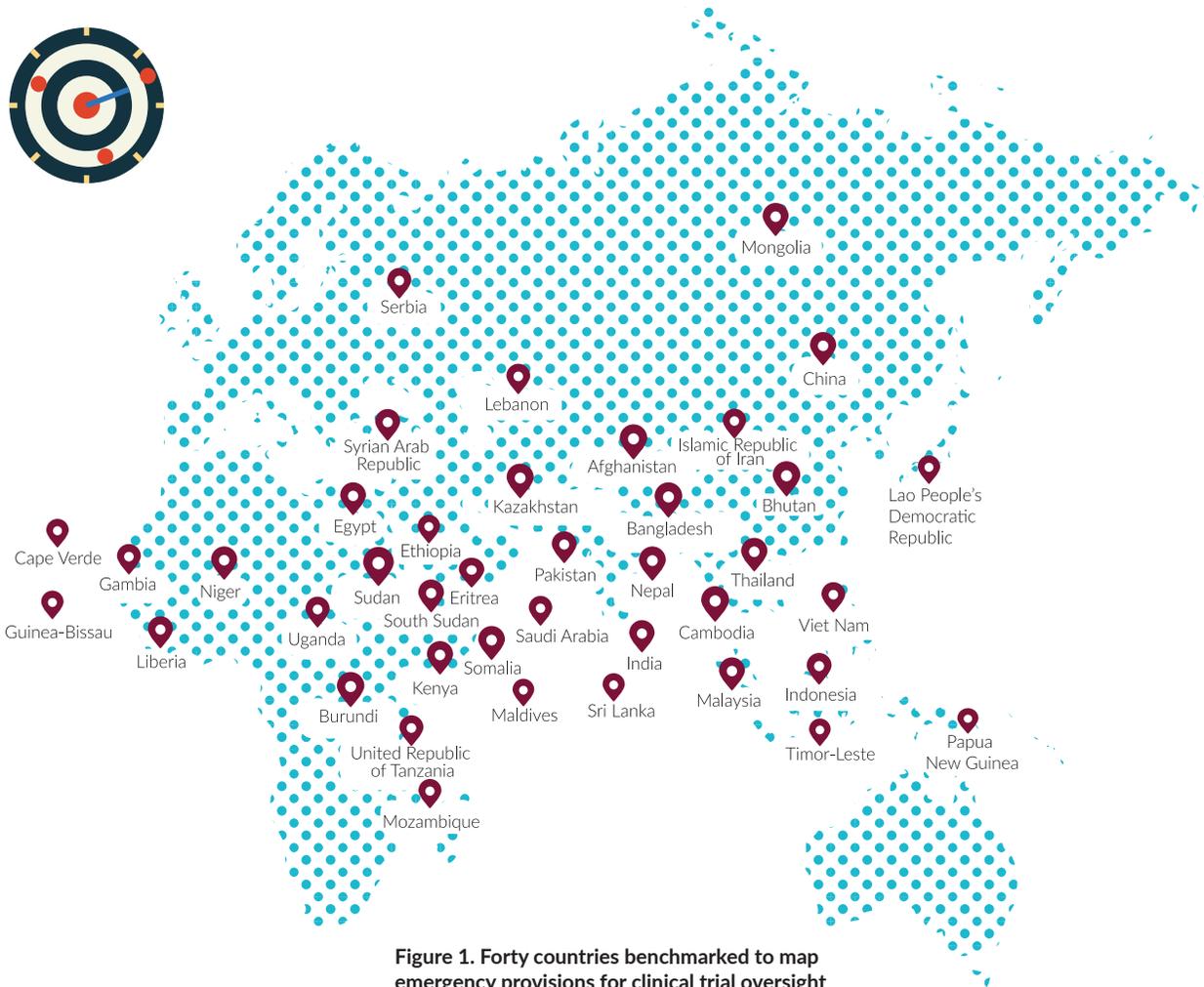


Figure 1. Forty countries benchmarked to map emergency provisions for clinical trial oversight



Response: Develop expedited regulatory processes

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 that the process be renamed Emergency Use Listing (EUL), that the procedure include risk management, surveillance, and communication provisions, and that a preparatory process ('pre-EUL') be explored to improve preparedness. A roadmap was subsequently developed to put these recommendations into practice and to develop processes in receiving countries to authorize the use of products listed by WHO.^{29, 30}

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

Regulatory networks are a key element of strengthening regulatory preparedness. This was demonstrated by the performance of the African Vaccine Regulatory Forum (AVAREF) during the 2014 Ebola crisis³¹ and reconfirmed in a November 2017 'table top exercise' undertaken with stakeholders. WHO has subsequently published a roadmap to coordinate actions and contributions to the licensing and roll out of Ebola vaccine in African countries.³⁰

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 a criminal activity facilitated by corruption and unethical practices involving 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.³² 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 antimalarials (19.5% of total reports) and antibiotics (16.9%).³³

Both generic and innovator products, expensive and inexpensive, are affected, and SF versions are found in both public and private supply chains.³⁴

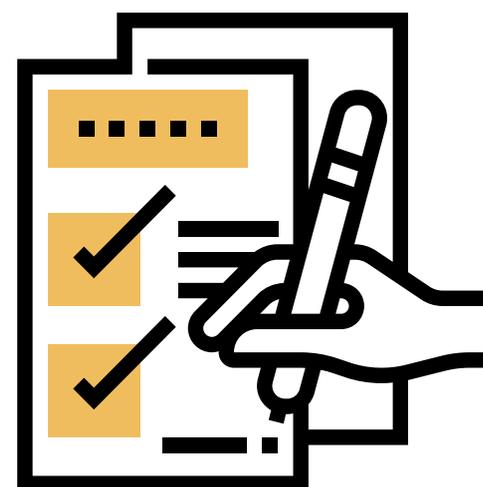
Promotion and distribution of SF products through the Internet is a major concern both in high-income countries and, increasingly, in middle-income countries. The increasing globalisation of the medical products market is also greatly complicating the task of regulators, not least because of jurisdictional 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 halt 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 2012.³⁵

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

The underreporting 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.³⁶





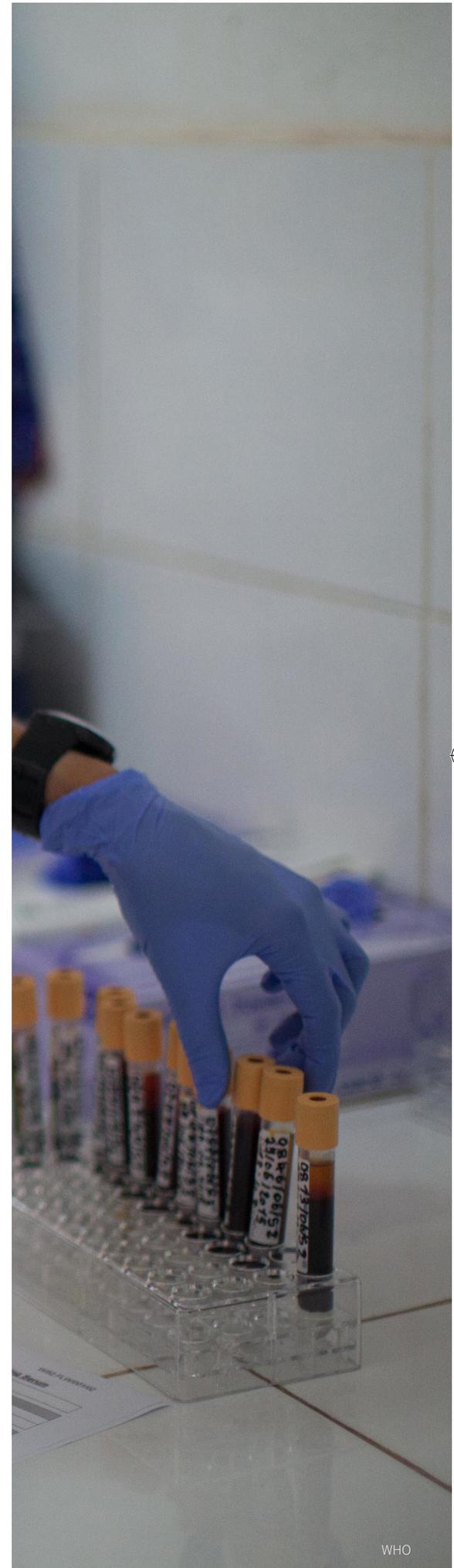
The main reason for underreporting is the lack of resources to establish functional pharmacovigilance systems. Another ongoing challenge is the low priority given to ADR/AEFI/AEMD reporting by policy makers and decision takers, who may not recognize its importance to their population's health. The introduction of products, including malaria vaccines and tuberculosis treatments, launched either exclusively in LMICs or simultaneously in low and high-income countries, 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.³⁷

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 (GVSII). 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. Of these countries, 130 contribute reports, of 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 collect 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 (to treat multi-drug-resistant tuberculosis) and dolutegravir (a new-generation HIV medication), have been introduced into countries with little or no capacity to monitor their safety, underscoring the fact that a robust pharmacovigilance system is needed to safely access and use such 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 be explored. Opportunities to consider such approaches are therefore being pursued. One example is, Project 3-S, a partnership between WHO and the Bill & Melinda Gates Foundation that aims to integrate 'Smart Safety Surveillance' for priority medical products in four to six countries at different levels of pharmacovigilance readiness.³⁸



WHO



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Strategic priorities and goals



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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 have been identified for the current Plan. Aligned with GPW13 and supporting the global drive towards universal health coverage, these strategic priorities are informed by the dual imperatives of assuring the quality of medical products and supporting optimal access. The strategic priorities are as follows:

- 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 (Annex A). Specific activities will be further detailed in annual activity plans and Key Performance Indicators (KPIs) will be developed to monitor progress. This chapter 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 both to global health and to achieving sustainable development. In fact, the two are indivisible. Sustainable Development Goal 3.8 specifically describes “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 it a range of regulatory pressures that will be difficult for many resource-constrained countries to meet.

Key principles: collaboration and reliance

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, a means of sharing knowledge and best practices while avoiding duplication of work.

The concept of reliance is described as follows:³⁹

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.

It is important to note that trust-building between Member States, both at the level of the regulatory authorities but equally at the political and societal level, is important in building reliance among various stakeholders, including patient groups, regulatory initiatives, industry, and more. WHO is currently developing guidance on good reliance practices.





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

Summary: It is intended that in five years, 50 additional countries will have improved their regulatory systems as a result of the technical support provided by WHO, using a prioritization tool and criteria for country selection currently under development. 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 reliance on work done by other advanced regulators and by WHO through a 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.⁴⁰

GOAL 1

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

(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.⁴² Since 2015, AMRH has carried out a variety of regulatory harmonization interventions, including joint assessment of applications in the five East African Community (EAC) countries. This work will continue to expand, including initiatives in other parts of the world, such as those under the aegis of the Southern African Development Community (SADC)'s Zazibona project,⁴³ the Economic Community of West African States (ECOWAS), the Intergovernmental Authority on Development (IGAD), the South East Asia Regulatory Network (SEARN) and more.

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 approved products more widely available.

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, and networks, and on 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 industrial development in this field.⁴¹

In the coming five years, WHO will expand the scope of the CRP to additional product streams (vaccines and IVDs), and beyond the 34 countries and Caribbean Community (CARICOM) which had signed up to the procedure in October 2018. WHO will also develop new guidance on using regulatory reliance and network-based

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

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 2018 the median approval period for products that have gone through CRP was 85 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





collaboration. To help stakeholders identify reliable NRAs, WHO will publish a list of NRAs that meet international performance benchmarks, as assessed by the GBT. These reliable NRAs will be termed WHO Listed Authorities (WLAs).⁴⁴ 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.⁴⁵

In addition, collaboration with a new WHO Department of Digital Health has been initiated to develop and implement guiding principles on use of big data, digitalization of regulatory data and confidentiality.

In 2018, WHO began working with a group of partners called the Coalition of Interested Partners (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. 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 increased safety and efficacy of medical products over the past six decades. As part of norms and standards work in 1953, WHO also established International Nonproprietary Names, chemical reference materials, and biological

reference materials. This essential work will continue under the 2019-2023 Plan.

In response to the rapidly changing global medical products landscape, more emphasis will be placed on promoting WHO norms and standards and supporting their adoption at national level, on international regulatory harmonization as appropriate, and on utilizing or leveraging other international standards such as those of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), and the Pharmaceutical Inspection Co-operation Scheme (PIC/S).

Sustainable development goal 3 demands “access to safe, effective, quality and affordable essential medicines and vaccines for all.” Experience teaches that this is impossible without robust, well-designed regulatory and procurement systems.

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. These will require development of additional guidelines or explanatory documents that take technological advances into account.

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 of manufacturers. In addition to the guidelines on varying prequalified Active Pharmaceutical Ingredients (APIs) and Finished Pharmaceutical Products (FPPs), WHO has now established general guidelines on post-approval changes for vaccines and for biotherapeutics.^{46,47}

Widespread implementation of these guidelines, supported by WHO implementation workshops, is anticipated to substantially facilitate NRAs’ ability to make informed regulatory decisions on variations in a timely manner.

Increasing demand for greater product access, often in the context of health systems striving towards UHC, will also bring regulatory demands that many resource-constrained countries will find difficult 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.⁴⁸ 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 electronic certificates (‘eCPPs’) to replace the paper CPP. This will ensure secure documentation is shared among relevant stakeholders, improve product approval processes and timelines, and increase countries’ efficiency in accessing new and innovative medicines. Moving forward with eCPPs will provide significant advantages for both NRAs and concerned pharmaceutical companies.



GOAL 3 Strengthen national regulatory capacity to ensure quality of medical products

The Global Benchmarking Tool (GBT) is used to formulate country-specific institutional development plans (IDP), including regulatory workforce development goals.

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 past two decades. WHO has facilitated technical collaboration at the regional level, with mature NRAs providing training and technical support to those with limited capacity, through twinning programmes and other formal collaborative mechanisms. WHO's experience in strengthening NRAs shows that implementation of IDPs often requires engagement from non-health sectors of government, such as trade and industry, science and education. Working with the recently-announced WHO Academy,⁴⁹ further shaping of academic curricula and regulatory training programmes covering the entire product life-cycle will be strengthened.

WHO also provides direct technical assistance or coordination to build on countries' IDPs, including technical advice and training. Some 85 regulatory support training activities in the form of e-learning, face-to-face courses, implementation workshops and webinars were provided in 2018. A 'landscape analysis' will be used to critically evaluate quality features of WHO regulatory support learning initiatives. On completion, the analysis 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 and sustainability of locally produced medical products in many LMICs is often problematic. 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 or regional levels, WHO can play an important role in supporting more sustainable access to quality-assured products focusing on regulators in selected countries, including 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 products, efforts to strengthen regulatory oversight will be complemented by 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. Past experience teaches that promoting local production is a complex and cross-sectoral endeavour. To be successful, it requires a holistic, collaborative approach in long-term strategic planning, coherent policy formulation, capacity building, and technical support.

Working with other UN agencies and trusted partners,⁵⁰ WHO will:

- develop tailored national and 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 local production
- coordinate and organize 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, including good manufacturing practices (GMP) and other WHO technical quality assurance guidelines, as well as other well-established international standards.

GOAL 5 Strengthen safety surveillance to support and safeguard the uptake of new or innovative products by LMICs

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, AEFIs and AEIVDs, and strengthening capacity for data analysis to support data-driven regulatory and public health decisions.

Increased investment is required to improve the reporting, analysis and use of ADRs, AEFIs, and AEMDs, not



only in the systems established for this purpose (PIDM, VigiBase, GVS), but in 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 many NRAs. Countries with high disease burdens often not only have weak systems for gathering information on the safety, efficacy or performance of products that are new to their markets, but also have low capacity to assess the information, communicate outcomes, and coordinate necessary actions among stakeholders. WHO will use a Smart Safety Surveillance approach to enhance both active and passive surveillance of safety, quality or performance of priority products that are marketed in high disease burden settings.⁵¹ 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 mobilizes political support and promotes Member State collaboration around SF-related activities. The MSM is also committed to strengthening national and regional capacities and contributes to the work of WHO departments that are addressing product access. It 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 coordination 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 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 a comprehensive network of WHO Regional and Country Offices. Furthermore, WHO, as observer, works in collaboration with global and regional regulatory coordination initiatives, such as ICH, the International Coalition of Medicines Regulatory Authorities (ICMRA) the International Medical Device Regulators Forum (IMDRF), the International Pharmaceutical Regulators Forum (IPRP), Asia-Pacific Economic Cooperation (APEC), and Association of Southeast Asian Nations (ASEAN) Pharmaceutical Product Working Group, to leverage efforts in promoting harmonization capacity-building and reliance. 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, it is expected that with the assistance of WHO, ten additional countries will have adapted their regulatory infrastructure to address the specific challenges of public health emergencies. WHO will aim for these ten countries to working together in regional networks and ensure that all emergency-prone countries to be familiar with the WHO's EUL procedure.

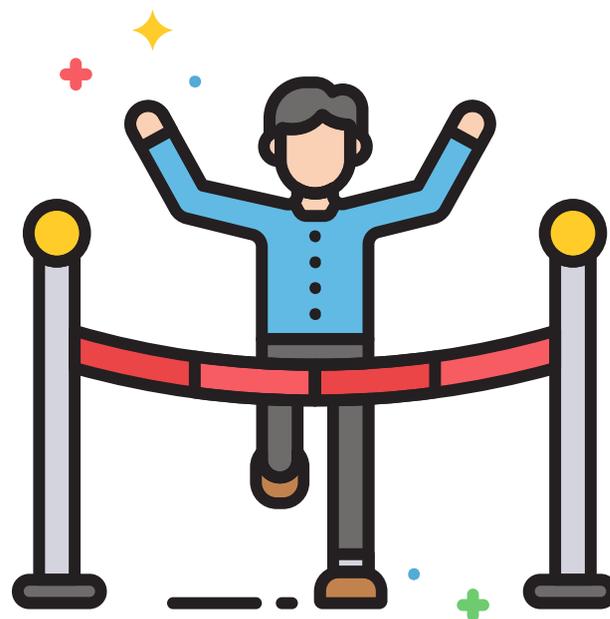
GOAL 1 Strengthen national and regional regulatory procedures for risk-based evaluations during public health emergencies (PHEs)

One of the regulatory challenges faced in the response to a public health emergencies 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 review of products likely to be used in emergency situations (renamed Emergency Use Listing, or EUL), including development of "pre-EUL" procedures.⁵²

Support will be provided to clarify the roles and responsibilities of NRAs in countries producing products for use in such emergencies. Support will also be provided to receiving countries to expedite local clinical trial authorizations and/or emergency use of such products. Pending specificity of needed products and product profiles identified by the WHO R&D Blueprint,⁵³ product lists may also include delivery devices, such as immunization devices or specialized cold-chain equipment, and delivery platforms or platform technologies. 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 approvals 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 public health emergencies. 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, leveraging WHO risk-based outcomes through regulatory networks, and ensuring WHO has knowledge of and access to surge capacity. 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 public health emergencies 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 emergency conditions. One proven way of doing this is through joint reviews in which groups of countries formally agree to conduct scientific reviews together.

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 public health emergencies. Although maturity level 3 (ML3) is the target for a well-functioning NRA, those with lower levels of maturity will be encouraged to integrate the principle of reliance through working with ML3 or ML4 NRAs. Furthermore, WHO will help establish or strengthen existing networks, expand AVAREF-like platforms in other regions, develop processes that facilitate joint reviews during emergencies, and promote other measures to build regulatory preparedness such as 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 national, regional and global stockpiles.



WHO/Eduardo Soteras Jalil





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

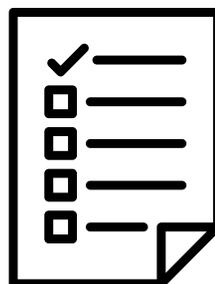
GOAL 1 Improve efficiency, capacity and awareness of the Prequalification Programme

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 about national regulatory authorities. Improved communications will raise awareness of underappreciated impacts of prequalification, such as the positive spill-over effect of prequalification on manufacturing standards, innovation and early-stage product development relevant to LMICs. In addition to existing product information profiles, such as Preferred Product Characteristics (PPCs) and Target Product Profiles (TPPs), or Programmatic Suitability for

Prequalification (PSPQ), which determines the suitability of vaccines for the immunization services where they are planned to be used,⁵⁴ more focus will be placed on informing decisions about products eligible for prequalification.

GOAL 2 Strengthen and expand WHO's prequalification lists

As a result of the Prequalification Programme, 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 continued evolution of 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. These include abridged procedures using an expanded list of WLAs; use of assessments by regional networks that have been quality assured by PQ or other WLAs; and use of WLAs reports to facilitate full prequalification and the CRP (including the recently announced CRP-Lite).⁵⁵ 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, WHO will produce a concept paper on possible new pathways to prequalification for all product streams. Once validation 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, PSPQ, and in the evaluation of snake antivenoms.⁵⁶





GOAL
4 Expand the range of products eligible for prequalification

The Prequalification Programme does not yet cover products such as anti-cancer therapies, anti-diabetics, anti-hypertensives and many of antimicrobials, or quality-assured IVDs for 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 biotherapeutics 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 potentially 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).

Following the 2019 launch of WHO's strategy for prevention and control of snakebite envenoming,⁵⁷ evaluation of snake antivenoms will be explored to ensure safe and effective treatments will be available to all the people who need them.

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.



Strategic Priority 4: Increase the scope and impact of WHO's regulatory support activities

GOAL 1 Ensure that WHO's regulatory support capacity and resources are sufficient to implement the Plan

To make sure that WHO has sufficient capacity to execute this Plan, WHO headquarters will conduct a gap analysis of regulatory support resources (human and financial) across WHO. SMART indicators will be developed for all processes to permit monitoring of progress towards objectives and goals.

In marshalling resources for its strategic priorities, WHO will emphasise transparency and optimal communication with donors and 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.⁵⁸ These research and development activities will require extensive interactions with regulators.

The Plan requires long-term investment, including in building regulatory capacities. WHO regulatory support

programmes therefore will interact and collaborate extensively with many other programmes to align, strengthen and maximise the impact of the Organization's regulatory activities within Member States.

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

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 to 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. The possibility of off-shoring some activities to a lower cost location will be explored.

GOAL 3 Enhance monitoring of WHO's impact on regulation and access to medical products

In 2019–2023, WHO 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, KPIs for NRAs will be collected to measure impact, and will be reported regularly.

Rather than inventing new reporting mechanisms for these impact measurements, WHO 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, there will be an increase in the visibility and use of the existing opportunities for Member States to scrutinize WHO's regulatory support work, and to provide strategic direction.

GOAL 4 Establish and implement Quality Management

Quality management systems (QMS) play a key role in setting and maintaining efficient standardized operations. Using QMS, WHO will ensure that resources are used in most effective and consistent manner. Key Performance Indicators (KPIs) will also be developed to measure impact made in countries. Furthermore a risk mitigation plan will be developed in coordination with relevant WHO departments to ensure continuing sustainable implementation of the 2019–2023 Plan.



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An ambitious agenda



While the list of challenges set out in this document is daunting, it is clear that the responses required to meet them exist. For example, there is evidence that regulatory collaboration – whether in the form of regulatory harmonisation of standards and mutual recognition, or implementation of regulatory reliance – can mitigate problems arising from disparate NRA standards and requirements.⁵⁹ Similarly, the positive impact of the Prequalification Programme is well documented and widely 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, notably the need to increase LMICs' regulatory capacity 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 robust and responsive processes for review of applications in emergency situations.

Implementing the Plan will require action both on the part of WHO and national governments and, of course, significant investment. However, Member States recognize the importance of addressing the challenges set out in this document. This was reflected in the World Health Assembly Resolution 67.20, which calls for global political support to strengthen NRAs and regulatory processes around the world.⁶⁰ Regulatory system strengthening has also been called for by ICDRA gatherings.^{61,62,63}

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 effective 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 measures set out in this Plan.



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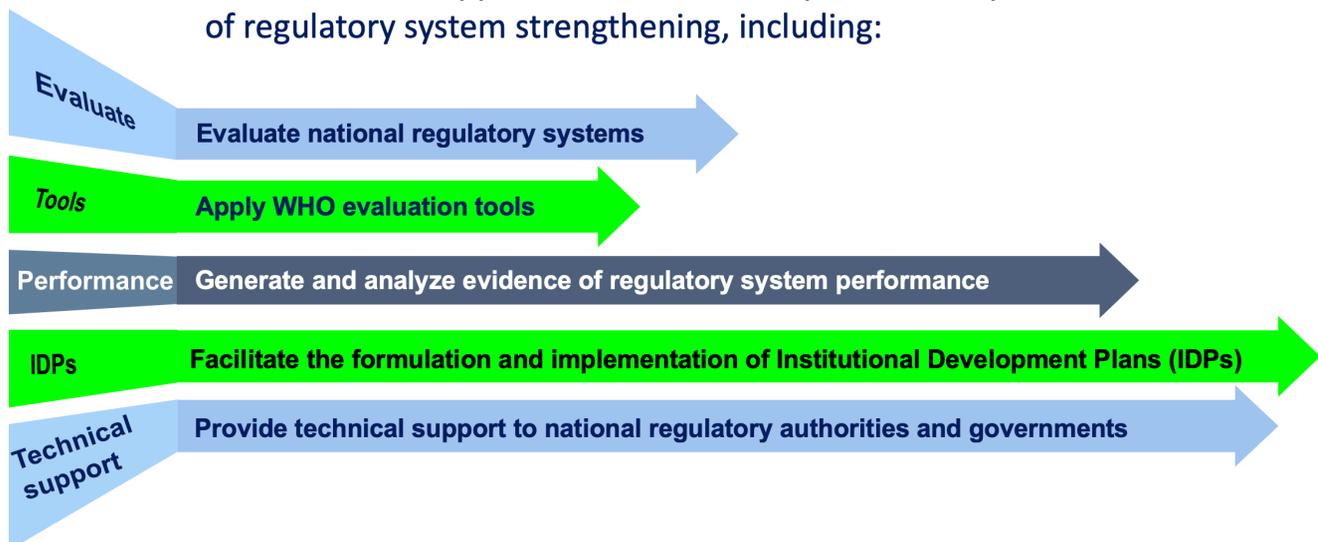


WHA Resolution 67.20

What WHO should do



To continue to support Member States upon their request in the area of regulatory system strengthening, including:



Annex A: Strategic priorities and goals

Strategic Priority 1:	
Strengthen country and regional regulatory systems in line with the drive toward UHC	
Goals	Objectives
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, pp 43-44)
	SP1.1.2 Promote efficient and effective regulation
	SP1.1.3 Promote adoption of good regulatory practices through internationally-recognized, science-based 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, their update or implementation at country level 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
SP1.4 Strengthen pharmaceutical sector capacity especially in countries that manufacture products for LMICs and/or local supply	SP1.4.1 Define local production and develop a model strategy for quality-assured local production
	SP1.4.2 Encourage local production to focus on quality-assured products
SP1.5 Strengthen safety surveillance to support and safeguard the uptake of new or innovative products by LMICs	SP1.5.1 Ensure surveillance systems in place to manage risks of medicines, in particular for anticipated or unknown risks of new, complex medicines
	SP1.5.2 Strengthen safety surveillance for new vaccines implemented in countries as a means of enhancing uptake
	SP1.5.3 Ensure that global and national systems are in place for post-marketing surveillance of IVDs
SP1.6 Improve prevention detection of response to substandard and falsified (SF) medical products	SP1.6.1 Implement prevention, detection and response strategies for SF medical products in vulnerable LMICs
	SP1.6.2 Expand, refine and enhance WHO Global Surveillance and Monitoring System for SF medical products
SP1.7 Support regulatory convergence through the convening power of WHO	SP1.7.1 Elaborate global and regional platforms for discussion and decision-making on regulatory convergence and issues of common concern are established and maintained by WHO

Strategic Priority 2: Increase regulatory preparedness for public health emergencies	
Goals	Objectives
SP2.1 Strengthen national and regional regulatory procedures for risk-based evaluations during public health emergencies (PHEs)	SP2.1.1 Revise regulatory procedures and standards for risk-based evaluations during PHEs
	SP2.1.2 Support networks to facilitate expedited assessment of products in the context of a PHE
SP2.2 Increase WHO's capacity to support regulatory preparedness for public health emergencies	SP2.2.1 Strengthen WHO processes to provide support to regulators in PHEs
SP2.3 Increase the number of countries that have adapted their regulatory preparedness for PHEs and are using regional networks for expedited evaluations	SP2.3.1 Identify and fill gaps at country and regional level in capacity to respond to PHEs
	SP2.3.2 Assist countries to adapt their regulatory requirements to effectively address PHEs

Strategic Priority 3: Strengthen and expand WHO prequalification and product risk assessment processes	
Goals	Objectives
SP3.1 Improve efficiency, capacity and awareness of the Prequalification Programme	SP3.1.1 Continue to improve the efficiency, across all product streams, of prequalification activities
	SP3.1.2 Enhance prequalification capacity
	SP3.1.3 Raise awareness of Prequalification Programme and its impact among stakeholders and encourage applications
SP3.2 Strengthen and expand WHO's prequalification lists	SP3.2.1 Continue to deliver prequalification recommendations for APIs, FPPs, IVDs, immunization devices and equipment, vaccines, vector control products, and medicines quality control laboratories
	SP3.2.2 Strengthen the prequalification of in vitro diagnostics
	SP3.2.3 Continue to evolve the processes and procedures for prequalification of vector control products
SP3.3 Develop new pathways to prequalification listing and new risk-based approaches to support time-limited procurement	SP3.3.1 Develop additional pathways to prequalification with NRAs of maturity level 3
	SP 3.3.2 Expand the scope of risk-based approaches to support time-limited procurement
SP3.4 Expand the range of products eligible for prequalification	SP3.4.1 Provide technical guidance to ensure the LMIC context is a driver of innovation and product development
	SP3.4.2 Expand the scope of prequalification for all product streams

Strategic Priority 4:

Increase the scope and impact of WHO's regulatory support activities

Goals	Objectives
SP4.1 Ensure that WHO's regulatory support capacity and resources are sufficient to implement the Plan	SP4.1.1 WHO has sufficient capacity to deliver efficiently and effectively against its strategy
	SP4.1.2 Develop key performance indicators (KPIs) to improve performance and impact management of WHO's regulatory support work
	SP4.1.3 Use global and regional platforms to share the results of WHO and country performance analyses
SP4.2 Improve targeting and alignment of WHO regulatory support activities	SP4.2.1 Develop and implement a strategic, collectively agreed resource approach between donors and WHO
	SP4.2.2 Strengthen internal alignment and coordination is strengthened for regulatory support activities (between Headquarters, Regional Offices and Country Offices; and with WHO disease programmes)
	SP 4.2.3 Explore a WHO regulatory 'hub' in close proximity with priority countries/ regions to provide more responsive, effective and faster collaboration.
	SP4.2.4 Facilitate improved coordination of external partners
	SP4.2.5 Implement an approach to prioritize WHO's regulatory support activities to add value is implemented
SP4.3 Enhance monitoring of WHO's impact on regulation and access to medical products	SP4.3.1 A validated evidence-base to assess the impact of WHO's work to support improved regulatory capacity
SP4.4 Establish and implement quality management system	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
	SP4.4.2 Develop risk mitigation plan in coordination within division as well as other relevant divisions and departments



Annex B: Prequalification timeline and Key Performance Indicators (KPIs)

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

PQ TIMELINE KPIs			
APPLICATION-BASED PERFORMANCE INDICATORS			
#	Indicator	% Target	Target time

Annual PQ cohort (products *prequalified* in a calendar year)

Products prequalified for applications accepted after 1 January 2015, 2016 for APIs (i.e. the annual PQ cohort)

100	Number of products prequalified	-	-
101	Median number of dossier review cycles	-	-
102	% of products prequalified for which the number of dossier review cycles is at or below target	70%	<u>Target number of dossier review cycles: 3</u>

Time to prequalification (from acceptance for assessment to prequalification) for applications accepted after 1 January 2015, 2016 for APIs

110	Median WHO PQ time	-	N/A
111	Median manufacturer PQ time	-	N/A
112	Median total PQ time	-	N/A
KPI 1	% of products prequalified at or below target WHO PQ time	70% (30% for APIs)	Full assessment: 270 calendar days, 350 calendar days for IVDs prequalified without the alternative laboratory mechanism Abridged assessment: 100 calendar days, 180 calendar days for IVDs prequalified without the alternative laboratory mechanism

Submission cohort (PQ applications *submitted* for PQ assessment in a calendar year)

PQ applications submitted for PQ assessment (i.e. the submission cohort)

200	Number of PQ applications submitted for PQ assessment	-	-
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Time to screening first action

210	Number of screening first actions	-	-
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	-	-
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Time to dossier first action

310	Number of dossier first actions	-	-
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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)
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Time to inspection first action

320	Number of <i>inspection first actions</i>	-	-
KPI 3.2	% of inspection first actions taken at or below target time	80%	210 days

Time to laboratory first action

330	Number of <i>laboratory first actions</i>	-	-
KPI 3.3	% of laboratory first actions taken at or below target time	80%	180 days

Products prequalified

340	Number of products prequalified	-	-
341	Median number of dossier review cycles	-	-
342	% of products prequalified for which the number of dossier review cycles is at or below target	70%	Target number of dossier review cycles: 3

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	-	-
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Time to post-PQ change first action

410	Number of <i>post-PQ change first actions</i>	-	-
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	-	-





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Access to Medicines, Vaccines and Pharmaceuticals

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