Promoting the **QUALITY OF MEDICINES+**

A Proposed Model to Build Capacity for Emergency Use Authorization for Diagnostics

Guidance for National Regulatory Authorities

November 2021

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About PQM+

The Promoting the Quality of Medicines Plus (PQM+) program is a five-year cooperative agreement between USAID and USP to sustainably strengthen medical product quality assurance systems in low- and middle-income countries. The program works to improve medical product quality through cross-sectoral and systems strengthening approaches and the application of international quality assurance standards across the pharmaceutical system. By sharing scientific expertise and providing technical support and leadership, PQM+ helps create resilient and robust local health systems that address diseases such as HIV/AIDS, tuberculosis, malaria, and neglected tropical diseases, as well as improve maternal, newborn, and child health.

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Acronyms

AHWP	Asian Harmonization Working Party
COVID-19	Coronavirus Disease 2019, caused by SARS-CoV-2
EUA	Emergency use authorization
EUAL	Emergency use assessment and listing
EUL	Emergency use listing
FAQ	frequently asked questions
FDA	United States Food and Drug Administration
GMP	good manufacturing practice
HSA	Health Sciences Authority
IMDRF	International Medical Device Regulators Forum
ISO	International Standards Organizations
IVD	in-vitro diagnostics
NRA	National Regulatory Authority
PAHO	Pan American Health Organization
PHE	public health emergency
PQM+	Promoting the Quality of Medicines Plus program
QMS	quality management system
TWG	technical working group
USAID	U.S. Agency for International Development
UW	University of Washington
WHO	World Health Organization
WHO PQ	World Health Organization Prequalification program
ZIKV	Zika virus

Executive Summary

Emergency use authorizations (EUAs) allow for an accelerated, conditional authorization for use of a medical countermeasure or device during a public health emergency (PHE) to help detect and combat a new disease that poses a significant threat. During the Coronavirus Disease 2019 (COVID-19) pandemic, the procedure has been used to accelerate the availability of acceptable vaccines, medicines, and diagnostic devices based on quality, safety, efficacy, and performance data.

The Promoting the Quality of Medicines Plus (PQM+) program, funded by the U.S. Agency for International Development (USAID) and implemented by U.S. Pharmacopeial Convention in collaboration with the University of Washington (UW), the International Diagnostics Centre at the London School of Hygiene and Tropical Medicine, and the Global Health Impact Group, assessed 16 PQM+ countries for EUA readiness for COVID-19 vaccines and diagnostics.

Most countries reported an overall regulatory framework was in place that included political will and legal framework and the use of commercially available and approved COVID-19 tests. The reported accelerated approval processes included waivers, formal listing of test kits, and in-country validations or evaluations. What was not clear was a process to gain full, regular approval and how to expedite necessary in-country validations and avoid unnecessary evaluations.

The findings from the country assessment, including desk reviews and consultations with experts and key stakeholders, has informed the development of this practical guide with an accompanying checklist aimed to facilitate the establishment and operationalization of an EUA regulatory pathway for COVID-19 diagnostics. This assessment intends to provide a practical approach for countries to establish EUA for COVID-19 and other diagnostics and a model pathway for a more mature regulatory review system for national regulatory authorities (NRAs).

1. Introduction

National regulatory approval for drugs and vaccines provides safeguards for the safety and effectiveness of these medical products used in a country. Most countries have established a process for reviewing the evidence from clinical trials to support the introduction of new drugs and vaccines. Over time, this process has improved the quality of these medical products used in countries. Unfortunately, this is not true of medical devices, especially in the developing world. Apart from tests used for blood banking, only about 50 percent of countries regulate medical devices, including in vitro diagnostics (IVD), for infectious diseases.[1] Medical devices are often sold and used in most of the developing world without any formal evaluation of their performance and effectiveness. Access to good-quality medical devices is problematic in these countries, as companies with good-quality products are often unable or reluctant to compete in

a market that is flooded with cheap, poor-quality products.
In countries that do regulate medical devices, the regulatory landscape is highly variable and continually changing, resulting in greater challenges associated with transparency, language barriers, costs, and the need to respond to PHEs. Regulatory reviews consist of technical and administrative components that can vary significantly among countries, even in the same region. Time frames for approval and the complexity of the approval process vary widely. Because of the onerous process and costs, companies tend to target countries with markets that allow for a substantial return for investment. Smaller countries in the developing world are currently paying significantly higher prices for medical devices than countries with sizeable markets, largely because of the many distribution channels that health programs and providers need to go through to access the products that they need. Another important outcome from this scenario is that these complex, lengthy, and variable regulatory approval processes have driven up the cost of goods—making products unaffordable—and become a major disincentive to innovation.

Why is there a need to accelerate access to quality-assured diagnostics?

Epidemics of infectious diseases are increasing in frequency and severity and are a global health security threat. Diagnostics are needed to detect the cause of epidemics, identify cases, and facilitate effective control and prevention. Diagnostic tests typically take 2–5 years to develop and 5–10 years to undergo evaluations, regulatory approval, and policy and guideline development before procurement, training, and deployment can be initiated. These timelines are far too long in the event of an outbreak, epidemic, or pandemic. Early identification of outbreaks leading to appropriate control interventions will also reduce the socioeconomic burden often associated with epidemics.

Innovative solutions to accelerate this pathway are urgently needed as an integral part of epidemic preparedness.

2. Scope of Guidance

PQM+ prepared this guidance to provide practical instruction to NRAs on adopting, implementing, and managing expedited approval pathways for IVDs, with a focus on EUAs for COVID-19 diagnostics. However, the considerations in this report may also be useful for reviewing or strengthening review procedures for other types of diagnostics in response to future PHEs. In this guidance, we use the term EUA to refer to any expedited review pathway to adoption by an NRA to facilitate broad access to a medical product during a PHE and prior to the product meeting all requirements for full registration and market approval.

The primary audiences for this report are NRAs and other stakeholders in countries that have yet to reach Maturity Level 4 based on the World Health Organization (WHO) regulatory authority Global Benchmarking Tool.[2] This guidance may be useful to NRAs without a current EUA pathway and to NRAs looking to strengthen an existing diagnostics EUA framework. The goal of this report is to facilitate greater international collaboration, harmonization, and data sharing among NRAs to reduce duplication and facilitate rapid access to safe, effective, and quality diagnostics in response to PHEs.

This guidance is also intended to help improve communication and transparency to the public to maintain trust in the rigor of the regulatory review process and confidence in the safety and quality of approved diagnostics.

The guidance includes the following three sections: 1) immediate expedited procedures during PHEs, such as COVID-19 pandemic, to accelerate diagnostics; 2) transitioning from EUA to full approval status; 3) a model and checklist to provide countries with practical considerations and a roadmap for establishing an EUA process and mature regulatory framework.

13. Methods

PQM+ prepared this guidance based on the following methods:

First, PQM+ conducted a desk review of EUAs and other expedited approval pathway policies and regulations. This review used varying terminology and consultations with experts. Second, PQM+ used findings from an EUA assessment across 19 PQM+ countries to identify the current state of COVID-19 diagnostics approvals in these countries and any expedited approval pathways.[a] PQM+ reviewed referenced EUA policies and guidance as well as other relevant guidance from WHO and international authorities for expedited and emergency approval pathways. PQM+ held a consultative webinar on October 18, 2021 and shared the draft guidance at that time. PQM+ then prepared and published a final version in December 2021.

4. Immediate Expedited Processes

This section summarizes practical considerations for NRAs when designing and implementing EUA procedures for diagnostics, with a focus on diagnostics for COVID-19. Countries should already have laws and policies requiring diagnostics to be approved prior to market entry.

[a]Bangladesh, Benin, Burkina Faso, Democratic Republic of Congo, Ethiopia, Ghana, Guinea, Kenya, Kazakhstan, Liberia, Mali, Madagascar, Mozambique, Nepal, Nigeria, Pakistan, Rwanda, Senegal, and Uzbekistan.

Many of the considerations in this section may be applicable in non-emergency settings, but the considerations herein are especially relevant for PHEs when diagnostic interventions have not yet obtained full market approval. **Appendix I** provides a high-level checklist for COVID-19 diagnostics EUA guidance.

A. Granting emergency use authorization

Emergency use authorization

EUA is defined as an expedited regulatory mechanism or pathway that allows the use of vaccines and other medical products (drugs, diagnostics, devices, biologics) during a PHE, such as the COVID-19 pandemic.

During a U.S. Food and Drug Administration (FDA) issuance of EUA, the FDA evaluates the totality of available evidence and carefully balances any known or potential risks with any known or potential benefits of the product for use during an emergency.[3] When used to detect COVID-19 cases in the intended target population, the known and potential benefits outweigh the known and potential risks.

Emergency use assessment and listing

The WHO developed the emergency use assessment and listing (EUAL) procedure in response to the 2014 -16[4] Ebola Virus Disease outbreak in west Africa.

"The EUAL is a risk-based procedure for assessing and listing candidate in vitro diagnostics (IVDs), therapeutics and vaccines for use primarily during public health emergencies of international concern (PHEIC) but also in other public health emergencies, if appropriate." [5]

The EUAL procedure for IVDs consists of three key components:

1) Review of the documentation relating to the **manufacture of the product**, including compliance with WHO manufacturing quality norms and standards
2) Review of documentation relating to **safety and efficacy/ performance**, especially with respect to use during the PHE
3) For IVDs, an **independent laboratory evaluation**, coordinated by WHO, of the product's performance and operational characteristics

Emergency use listing

On March 27, 2020, in response to requests from regulators and manufacturers for better guidance on validation data required for EUAL, WHO published the Emergency Use Listing (EUL) procedure to streamline the process by which new or unlicensed products can be used during PHEs.[6] The EUL replaces the EUAL procedure, used during the West Africa Ebola outbreak of 2014–2016.

The EUL is a risk-based procedure for assessing and listing unlicensed vaccines, therapeutics and in vitro diagnostics with the ultimate aim of expediting the availability of these products to people affected by a PHE.

The EUL procedure sets out conditions for companies wishing to submit their products to interested UN procurement agencies and Member States for use during health emergencies. The acceptability of specific products is based on an essential data set of quality, safety, and efficacy and performance of the product.

Emergency declaration

Many EUA pathways require an emergency declaration by a governmental authority to issue an EUA. Consultation with other governmental authorities may be required prior to issuance of the emergency declaration. The law or policy establishing the EUA can also prescribe the standards that must be met in order to declare the emergency, such as the emergence of a disease that is contagious and imminently life-threatening or threatens national security and for which there is no approved, adequate and available product to diagnose, treat, or prevent the disease or condition. The emergency declaration that opens an EUA pathway can be different than emergency declarations issued by other governmental authorities.

EUA issuance criteria

Laws, regulations, and policies for EUAs should clearly establish the criteria for issuing EUAs. Below is a list of illustrative issuance criteria adapted from the U.S. EUA statute[7] that countries can consider adopting to guide EUA decisions. The agent/virus/bacteria (hereinafter referred to as agent) is the subject of an emergency declaration issued pursuant to national law.

- The agent can cause a serious or life-threatening disease or condition;
- Based on the totality of scientific evidence available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing such disease or condition;
- The known and potential benefits of the product, when used to diagnose, prevent, or treat such disease or condition, outweigh the known and potential risks of the product, taking into consideration the threat posed by the disease or condition; and
- That there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating such disease or condition.

Note that this last issuance criteria above requires that there not be an alternative product that is adequate, approved, and available. Therefore, a test may still be eligible for an EUA even after other tests have been approved for the same agent (e.g., COVID-19), if the previously approved tests are not adequate and sufficiently available to meet the PHE.

B. Termination of EUA declaration

The grounds for declaring and rescinding an emergency declaration relating to EUAs can be different than the bases for declaring and rescinding other types of PHE declarations and allows the governmental authority overseeing EUAs more discretion regarding when to declare and end the EUA emergency declaration.[8]

C. Eligibility of candidate products

The EUL concerns three product streams (vaccines, therapeutics and IVDs). For IVDs, the specific requirements for products to be eligible for evaluation under the EUL procedure are:

1) The disease for which the product is intended is serious or immediately life threatening; has the potential of causing an outbreak, epidemic or pandemic; and there are no licensed products for the indication or for a critical subpopulation (e.g., children).
2) The product is manufactured in compliance with current good manufacturing practices (GMPs) under a functional quality management system (QMS).
3) The applicant undertakes to complete the development of the product (validation and verification of the product in the case of IVDs) and apply for WHO prequalification (WHO PQ) once the product is licensed.

Challenges and experience with EUAL for IVDs during the Ebola and Zika virus (ZIKV) outbreaks

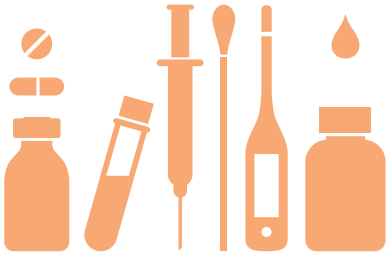
Challenges encountered during the review of IVDs applications included:

1) Poor quality of submissions and assay validation data
2) Lack of international standards to guide the assessment
3) Lack of reference preparations and panels for validating assays (manufacturers and regulators agreed that there was a need for the availability of international reference materials and other validation materials)
4) Missing ethical clearance related to the sourcing of these materials
5) Lack of sustainability mechanism for transitioning from EUL to full regulatory approval

In the last two decades, funding for development and evaluation of diagnostics needed for case management and outbreak control has been available during epidemics but rapidly re-allocated to other priorities once the epidemic is ends, leaving an unfinished agenda and countries with no better diagnostic tools to combat the next epidemic.

When WHO declared ZIKV infection a PHE of international concern and observed microcephaly and other neuro syndromes in children born to pregnant women with ZIKV infection, diagnosis of acute ZIKV infection became problematic. Molecular tests to identify ZIKV were not useful because the period of viremia was transient and tests to detect anti-ZIKV IgM antibodies as a marker of recent infection were cross-reactive with other members of the flavivirus family. Without a more specific anti-ZIKV IgM test, it was difficult to make a definitive clinical diagnosis of ZIKV infection, estimate the risk of having a baby with microcephaly, and assess the true extent of the outbreak, especially in dengue endemic areas.

From February 2016, when the Zika virus emergency was declared, to September 2017, the US FDA granted EUA status to 19 requests for Zika virus diagnostics and WHO granted EUAL to 2 requests. By February 2018, only 5 diagnostics products remain on EUA status. In the end, only one molecular test for use in blood screening subsequently achieved full standard IVD regulatory approval.[9]



5. Transitioning from EUA/EUL to full approval status

Regardless of whether a country has a procedure for transitioning products granted EUA or EUL to full approval status, it is really the companies that decide whether they will invest the time and effort to conduct more costly clinical trials in settings of intended use and to submit to a QMS audit to gain full approval status for their product. That decision is often driven by the market demand and return on investment.

A. Difference between EUA and a full regulatory approval process:

EUAs that have been issued by WHO or FDA for IVDs during a pandemic or a PHE are authorizations but not approvals. These authorizations are only in effect for as long as the public health emergency lasts.

During the period that EUA or EUL is in effect for a product, an NRA should use their **post-marketing monitoring mechanism** to ensure that the product continues to fulfil the safety, quality, and performance criteria upon which the authorization has been granted. If a safety or performance issue comes up, WHO or FDA has the right to request the removal of authorization of such a product.

Table 1. Full regulatory review compared to EUA.

Items	Full regulatory review	EUA
1. Review of data on the **quality of manufacturing**	Conduct audit to document compliance with QMS, e.g., International Organization for Standardization (ISO) 13485 or reliance on the results of the International Medical Devices Regulatory Forum (IMDRF) Single Audit System	A review of the manufacturer's QMS documentation and specific manufacturing documents is the first step in the process. At the conclusion of this step, WHO or an NRA may decide to proceed or to request further documentation or to terminate the application. The decision to proceed with the assessment process will be made if there is sufficient evidence that the applicant is the manufacturer, that there is evidence of an adequate QMS in place, and that the requisite manufacturing capability exists.
2. Review of documentation on **safety and clinical performance studies**	Clinical performance studies in settings of intended use performed by intended users' full review of data with a fixed time frame such as 180 days for some NRAs	Independent laboratory evaluation only; no field or clinical trials required; paper review of data in accelerated time frame
3. **Post-market monitoring**	NRAs use this mechanism to monitor the safety and performance of products on an ongoing basis and investigate if necessary.	NRAs should use this mechanism to monitor the performance of products and remove authorization status if necessary.

Table 2. List of activities for the 3 phases of the EUA based on the WHO EUL 2020.[10]

ACTIVITY	PRE-EMERGENCY PHASE	EMERGENCY PHASE	POST-DEPLOYMENT PHASE
Agreements with NRAs	✔		
Roster of experts	✔		
Eligibility of specific products	✔		
Consensus on requirements	✔		
Assignment of Assessment pathway	✔		
Establishment of ad hoc committees	✔	✔	
Assessment of submission	✔		
Decision on listing		✔	
Adverse event monitoring			✔
Extension of listing			
Post-EUL changes			

WHO EUL is designed to provide a minimum level of assurance of the quality, safety, and performance of unlicensed products for the primary purpose of use in the setting of a current PHE. This focus means that WHO may still undertake some extra assessment activities if deemed necessary or request the dossier that was assessed previously through other emergency mechanisms.

Table 3. Assessment of In vitro diagnostics

IVDs assessment approach	Assessment approach and inspection	
Product assessed through another emergency mechanism of an acceptable standard?	Abridged initial assessment of reports	Desk review of the QMS
Product not assessed through another emergency mechanism of an acceptable standard?	Full initial assessment by WHO of the submitted documentary evidence	Desk review of the QMS and/or inspection if required

6. Model Guidance for establishing EUA a mature regulatory framework

A. Roadmap for establishing EUA

In general, each country should have a single recognized national standards body with procedures in place for the recognition of new standards or adoption of international standards. For medical devices, some countries have several bodies that each claim to the mandate for regulating medical devices, IVDs and/or laboratory testing, including test kits. Hence, **our first**

recommendation is every NRA should have an appropriately skilled and experienced technical working group (TWG) or Committee would be appointed that fully represents the full range of stakeholders to ensure the EUA framework, standards and procedure have widespread acceptance and relevance.

The subsequent steps in the roadmap for establishing an EUA process will depend on the maturity and capacity of the NRA. The different pathways can be:

A. NRA with no legal framework for medical devices:

1. Establish a TWG on IVD EUA framework and process.
2. Convene the TWG to review of either WHO or other EUA process established by stringent NRAs with the following goals:
    a. to grant authorization to IVDs already granted authorization by WHO or stringent NRAs without further action
    b. to review the data from the IVDs granted EUA with a view to conducting small validation studies in-country by the national reference laboratory
3. Develop plans to develop an official EUA mechanism which may require lengthy consultations and stakeholder endorsement.

B. NRAs with a legal framework for regulating medical devices but limited capacity to conduct safety and performance reviews and QMS inspections

1. Establish a TWG on IVD EUA framework and process.
2. TWG should examine the EUA process of either WHO or other stringent NRA and determine how EUA framework and mechanisms can be leveraged by an existing regulatory framework and processes to accelerate the establishment of an EUA mechanism.
3. The TWG may also recommend partnering with other NRAs in the region to harmonize the assessment pathway, share the load of dossier reviews (given the >1,000 IVDs being developed for COVID-19) and benefit from the expertise and experience of more mature NRAs.
4. The new EUA may opt to:
    a. authorise IVDs already granted authorization by WHO or stringent NRAs without further action.
    b. review the data from the IVDs granted EUA with a view to conducting small validation studies in country by the national reference laboratory.

C. NRAs with a mature system for medical device regulation but no EUA:

1. Establish a TWG on IVD EUA framework and process.
2. TWG should examine the EUA process of WHO or other stringent NRAs and determine how it can leverage the existing regulatory process to accelerate the establishment of EUA mechanism for the NRA.
3. Develop plans to develop an official EUA mechanism which may require lengthy

consultations and stakeholder endorsement.

4. In the meantime, the TWD can authorize IVDs already granted EUA by WHO or other stringent NRAs.

B. WHO EUL procedure

As reference, the WHO EUL procedure for IVDs has been included in **Appendix II**. This also includes what the data package should include for approval.

C. The Singapore Health example of an NRA with an expedited approval process for IVDs

IVD product registration in Singapore is overseen by the Health Sciences Authority (HSA), a statutory board of the Singapore Ministry of Health, before devices can be imported and placed on the market.[11]

There are many types of medical devices with varying degree of potential risk to patients and public health. A rule-based system has been developed to determine the extent of the review needed. It is dependent on the intended purpose and indications for use claimed by the product owner. If a medical device may be assigned into two or more classes of medical devices, the highest risk class must be assigned.

Table 4. The HSA guidelines for IVD device classification

Class	Individual Risk	Public Health Risk	Examples
A	low	low	Specimen receptacle
B	moderate	low	Vitamin B12, Pregnancy self testing, Anti-Nuclear Antibody, Urine test strips
C	High	moderate	Blood glucose self-testing, HLA typing, PSA screening, Rubella IgM,
D	high	high	HIV blood donor screening, HIV diagnostic kit

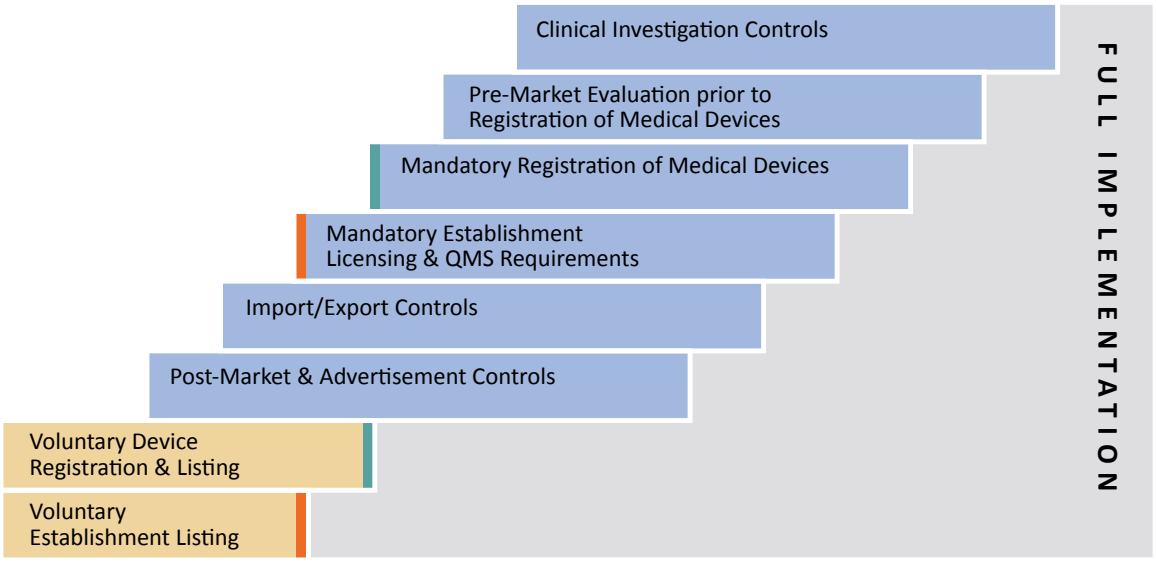
Most diagnostics for infectious diseases fall into either Class B or C, and most blood-borne infections such as HIV are in Class D. Their expedited approval pathway is shown in **Appendix III**.

D. The AHWP Playbook phased approach to the development and implementation for a medical device regulatory framework

As previously mentioned, NRAs have adopted different regulatory systems depending on available resources and many other circumstances. In 2014–2015, as part of an initiative to strengthen regulatory capacity for medical devices, the Asian Harmonization Working Party (AHWP), developed a Playbook for Implementation of Medical Device Frameworks that lays out a phased approach to the development and implementation for a medical device regulatory framework (**Figure 1**).[12]

A group of regulatory affairs professionals in Asia Pacific formed the AHWP in 1996–1997 in response to the growing interest of regulators in working towards greater harmonization of medical device regulations in Asia. In the last 2 decades, AHWP has grown to be a distinctive organization with 31 member economies spread across Asia, the Middle East, and Africa, where regulators and industry work collaboratively to establish harmonized requirements, procedures, and standards. As an important pillar of their strategic framework, AHWP will continue to expand its geographical coverage and work with international organizations such as IMDRF, WHO, Organization for Economic Cooperation and Development, and Asia-Pacific Economic Cooperation to optimize efforts on harmonization.

Figure 1. Phased Implementation Plan for a Medical Device Framework.



[b]Source: Asian Harmonization Working Party. Playbook for Implementation of Medical Device Frameworks. 2016.

In the early process of regulatory implementation, a country may first recognize basic medical device standards, which are the foundation technical guidelines of compliance to the medical device regulatory framework. In 2017, WHO updated its model regulatory framework for medical devices. These two documents[1,12] provide countries with the foundation they can use to gradually build up their regulatory framework for medical devices.

As new international standards are developed, it is important that NRAs have a mechanism to incorporate such standards into their framework and practice. The AHWP Playbook states that coordination between the medical device regulatory authority and national standards authority is important in recognition of standards for regulatory purposes. An example of a basic standard is the widely adopted ISO 13485, a QMS standard covering design and manufacture of medical devices.[13]

The AHWP Playbook provides a model for recognition of new standards by NRA as follows:

In general, each country should have a single recognized national standards body, with procedures in place for the recognition of new standards or adoption of international standards. An appropriately skilled and experienced committee would be appointed that fully represents all affected stakeholders, to ensure the standard retains widespread acceptance and relevance.

Consider the benefits to be achieved and key stakeholders that will benefit from the development of a new standard. Overall, benefits should exceed the costs likely to be imposed on dealers, patients, users, etc. as a result of its development and implementation.

Several options may be available:

1. **If a standard already exists for a certain product or process, the regulatory authority is to consider if it is acceptable.**
2. **If multiple standards exist, the regulatory authority may need to select one that is best suited or combine desired elements of each standard.**
3. **If no suitable or acceptable standards for the purpose exists, the regulatory authority may check if an existing standard can be adapted, by adding or modifying requirements, or whether a complete new needs to be drafted.**

A NRA using the AHWP playbook to build regulatory capacity can use the following strategy to determine how they would adopt or develop an EUA process:

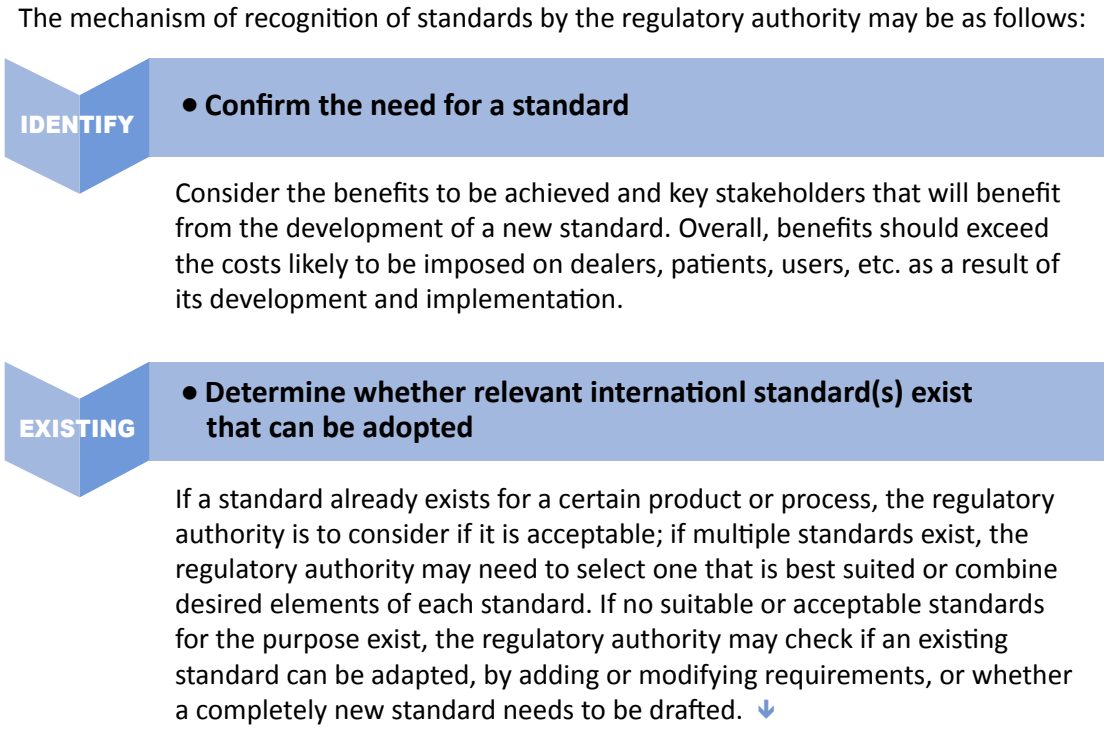
1. Identify gap (i.e. is there a mechanism to expedite IVD regulatory approval for PHEs.
2. Confirm the need for developing a regulatory process.

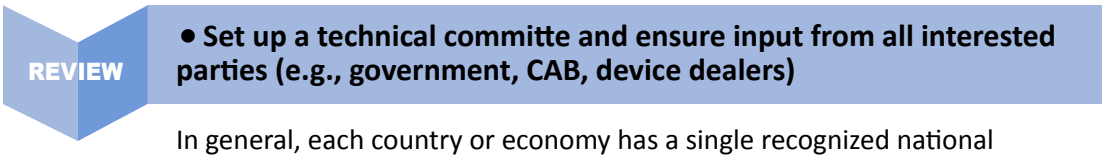
3. Determine which relevant emergency use or expedited process exists that can be adopted.
4. Set up technical committee and ensure input from all interested parties (e.g., government, users, distributors, device manufacturers).

   From this point, a NRA can go down one of several pathways:
   A. Rely on the International standard such as WHO EUAL.
   B. Use the existing standard to develop their own draft standard and procedure; invite public comments of draft standard; assess comments and feedback; and revise draft for adoption.
   C. If the development of a new standard is considered necessary, the AHWP recommends that NRAs do so together with other NRAs, and even more preferably, in close communication with the ISO and IMDRF.

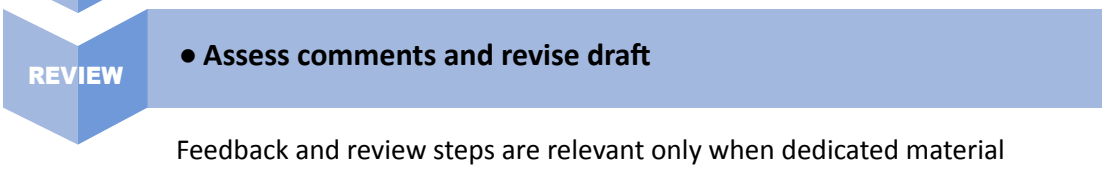
As a follow-up, a mechanism of regular review and realignment of locally recognized standards to the international standards needs to be in place, especially when a recognized standard is updated or an international standard is published or amended. Reasonable transition periods should also be established to allow manufacturers to adapt to the requirements of new standards or revised standards.

Figure 2. A proposed model for the development of an EUA process based on the AHWP model

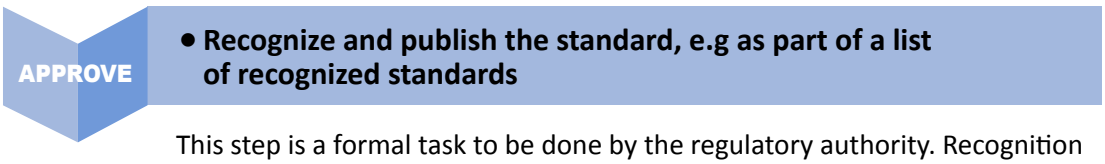




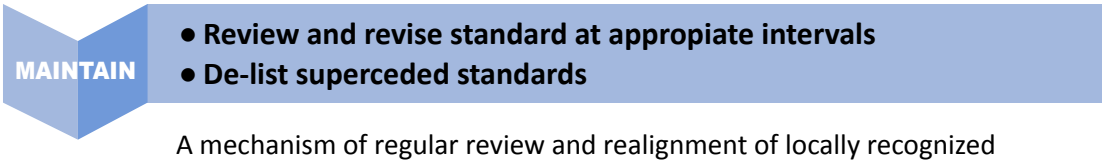
In general, each country or economy has a single recognized national standards body, with procedures in place for the recognition of new standards or adoption of international standards. An appropriately skilled and experienced committee would be appointed that fully represents all affected stakeholders, to ensure the standard retains widespread acceptance and relevance.



Feedback and review steps are relevant only when dedicated material is being developed. If development of a new standard is necessary, it is recommended member economies do so preferably together with other member economies, and even more preferably, in close communication with the international standards organizations ISO or IEC.



This step is a formal task to be done by the regulatory authority. Recognition may occur by publication of lists identifying existing voluntary standards that the regulatory authority has found will meet specific requirements.



A mechanism of regular review and realignment of locally recognized standards to the international standards needs to be in place, especially when a recognized standard is updated or an international standard is published or amended. Reasonable transition periods should also be established to allow manufacturers to adapt to the requirements of new standards or revised standards.

Regulatory reliance

WHO has recently published a document on best practice for regulatory reliance to improve efficiency and build more trust among NRAs. This provides the simplest and fastest option for countries to have an expedited process to approve IVDs by relying on the results of the WHO or FDA EUA process without having to set up its own process, which may take months, even during emergencies. But that will work only if the IVDs on the WHO EUAL or the FDA EUA are available to the country in question. Hence, while NRAs can use reliance in a

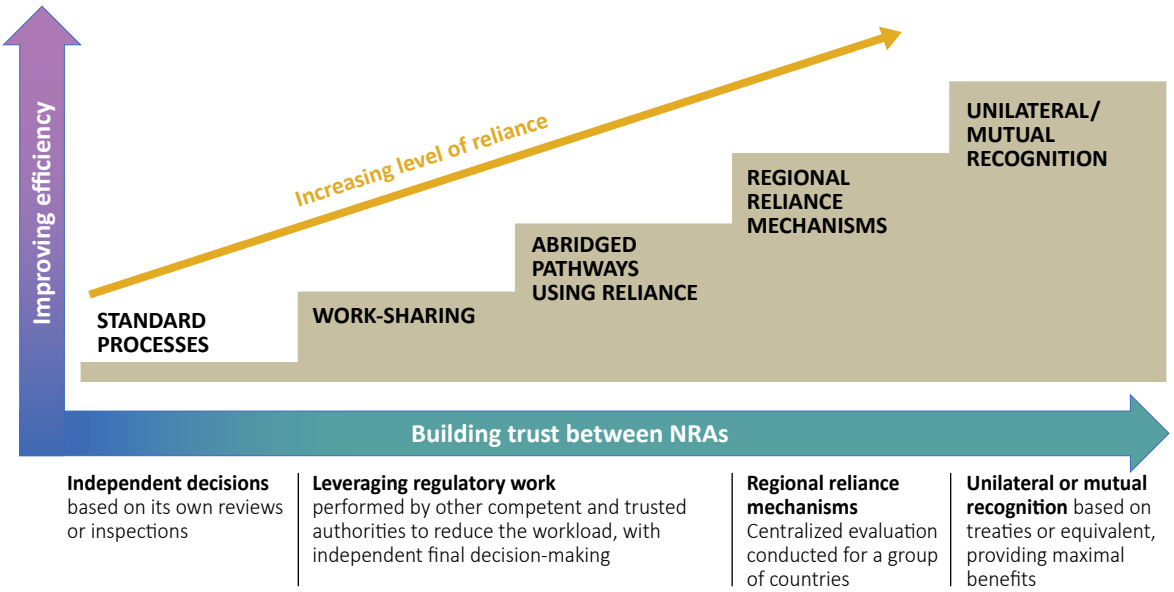
pandemic, in the long term it is advisable for NRAs to learn from WHO and other stringent NRAs on how EUA works and draft its own standard and processes so that the standard and process can be applied to all diseases of public health importance in-country.

In 2020, the Inter-American Coalition for Regulatory Convergence was launched by 17 principal members representing more than 10 countries representing the Americas.[c] The coalition engages all stakeholders and organizes private sector positioning, training, and communication with governments to minimize regulatory barriers between patients and access to lifesaving and life-improving medical technologies.

Central to this work is private and public engagement in the development and use of international standards as a basis for national regulations and conformity assessment measures across the Americas. The coalition also promotes the implementation of foundational, cross-sectoral good regulatory practices that can institutionalize "whole-of-government" regulatory approaches and remove limits to sector-specific regulatory convergence efforts. The coalition has unified the 17 largest industry bodies for the medical technology sector in the region, enabling them to provide hemispheric industry consensus recommendations for regulatory convergence priorities.

Based in 10 countries, these 17 industry bodies serve more than 3,000 member companies that develop, manufacture, distribute, or support the utilization of medical technology. These companies operate across every country in the hemisphere and serve as the overwhelming majority of enterprises operating in the sector.

Figure 3. WHO Good Reliance Practices in Regulatory decision-making



The reliance mechanisms in **Figure 3** shows how NRAs can utilize the reliance mechanism to adopt EUA procedures from WHO or regional bodies such as PAHO or the Inter-American Coalition for Regulatory Convergence.

[c] https://www.interamericancoalition-medtech.org

7. Transparent Communication and Community Engagement to Build Trust in Diagnostics

Open and transparent communication builds public trust in diagnostics and regulatory review processes. Unfortunately, the communication processes and guidance are severely lacking with NRAs. This section provides a model leveraging the Centers for Disease Control and Prevention COVID-19 Testing Communication Toolkit.[14]

The Toolkit provides communication resources about COVID-19 testing, including fact sheets and social media. While this is more on actual testing, it is framed on communication guidelines for outbreak responses and pandemic influenza, which provide helpful principles and approaches for managing communication with communities.

NRAs could use this framework and tools to develop a comprehensive communication strategy that provides information to a wide range of audiences, including key stakeholders. For diagnostics, a number of medical regulatory agencies have developed diagnostic-specific web pages and social media channels to share information broadly on specific diagnostics and improve communications with the public.

NRAs could consider developing a standardized communication plan. These communication plans should consider language and disability access to ensure that materials are accessible to the entire population in the country. Collaboration with regulatory professional associations, such as the Asian Regulatory Professionals Association, increases the trust and acceptability of the new procedures and standards.[d] Some of the components of a standardized communication package could include:

- Decision memorandum/assessment report explaining rationale for the regulatory decision to improve transparency and knowledge
- Letter of authorization to support/promote diagnostics uptake
- Press release from NRAs
- Fact sheet for diagnostics community – laboratory, program, healthcare professional and patient
- Frequently asked questions (FAQ) page/document for broader audience

Appendix IV leverages medical regulatory agencies' diagnostic guidance and contains more detailed guidance on possible communication content.

[d] https://arpaedu.com/ask-arpa/

Appendix I: COVID-19 Diagnostics EUA Guidance Checklist

1. No EUA process described

Below are suggested beginning steps for countries with minimal or no EUA processes. Even countries with established EUA guidance may consider reviewing to strengthen EUA processes and build a more robust regulatory framework.

- Establish a national legal framework for in vitro diagnostics (IVD) regulation
  - See *WHO Global Model Regulatory Framework for Medical Devices including in vitro diagnostic medical devices, Annex 4:* https://www.who.int/medicines/areas/quality_safety/quality_assurance/trs1003_annex4.pdf?ua=1

  This site provides a stepwise approach to regulating medical devices.

- Establish a process for import requirements for IVDs
  - See *FDA Importing Medical Devices:* https://www.fda.gov/medical-devices/importing-and-exporting-medical-devices/importing-medical-devices-and-radiation-emitting-electronic-products-us#process

  The required entry information includes:
    - country of origin
    - importation product code, which is a combination of the FDA panel code and FDA product code
    - importer product description
    - manufacturer
    - shipper
    - applicable affirmations of compliance codes
    - Harmonized Tariff Schedule (HTS) code for the product described in the importing documents.
    - The HTS code is a classification code used to provide the applicable tariff rates and statistical categories for items imported into the U.S. For questions and guidance on tariff rates, please contact your local CBP Port of Entry.

- Create a regulatory agency, working group, or committee for IVDs
  - See *European Commission Medical Device Coordination Group Working Groups:* https://ec.europa.eu/health/md_dialogue/mdcg_working_groups_en

  The Medical Device Coordination Group is broken into 13 subgroups that provide advice and draft guidance on their expertise field. The members of the subgroups are appointed by the Member States for a duration of three years. Stakeholders participate as observers and are appointed following a call for applications procedure also for a duration of three years. They meet regularly with the EU Commission as Chair.

This site provides terms of references for:

- Notified bodies oversight
- Standards
- Clinical investigation and evaluation
- Post-market surveillance and vigilance
- Market Surveillance
- Borderline and classification
- New technologies
- European Database on Medical Devices
- Unique device identification
- International matters
- IVD medical devices
- Nomenclature
- Products

- Decide whether regulatory reliance on already approved IVDs is viable
  - Country policies may mandate level of assurance for IVDs based on existing approvals (e.g., WHO PQ, US FDA approval or CE Mark) as well as additional clinical evidence from a geographically relevant region. The Medical Device Innovation Consortium provides *A Framework for Developing Credible Evidence of Analytical Validity, Clinical Validity, and Clinical Utility for IVDs:* https://mdic.org/wp-content/uploads/2019/08/Clinical-Evidence-IVD-Framework-FINAL.pdf

2. Implementation of a Reliance Mechanism

Regulatory reliance is increasingly being used by NRAs of all maturities to better manage resource capacity issues while strengthening regulatory systems. Regulatory reliance is promoted by WHO, PAHO, the European Medicines Agency (EMA), etc.

- Understand how other countries/international organizations review and approve IVDs
  - Examples: WHO, EU, US FDA, Canada, Australia, Brazil

WHO defines regulatory reliance as "The act whereby the regulatory authority in one jurisdiction may take into account and give significant weight to – i.e., totally or partially rely upon – evaluations performed by another regulatory authority or trusted institution in reaching its own decision. The relying authority remains responsible and accountable for decisions taken, even when it relies on the decisions and information of others." See *International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) Position Paper with Considerations for effective regulatory reliance:* https://www.ifpma.org/wp-content/uploads/2019/06/IFPMA-Position-Paper-Regulatory-Reliance.pdf

This site outlines practical considerations and opportunities for successful implementation of regulatory reliance, which include:

- Public health priorities based on medical needs and regulatory capacity
- Reduce regulatory burden and offer an opportunity for faster and more predictable approvals
- Pilot programs for reliance-based regulatory procedures
- Managing post-approval changes
- Decide which approvals will be accepted, under what circumstances and for how long
    - NRAs should convene their working group or expert committee to decide what approvals will be accepted. Depending on the IVDs in question, prior approvals may already exist globally (e.g. WHO PQ, UNICEF procurement listing) or regionally (e.g., PAHO) or from a country with a stringent regulatory authority as defined by the International Medical Devices Regulatory Forum.
    - Once the decision for regulatory reliance has been made, then the working group should decide on the circumstances of the reliance and for how long should this mechanism be in place (e.g., EUAs have finite periods of validity and would end as soon as the emergency is over).

3. Implementation of an Expedited Review Process

Steps 1 and 2 above are relevant to countries with minimal to no EUA processes; provide them with a checklist to assess their current situation and examples of resources to support an expedited EUA. This step provides a checklist to expedite the review process, part of the EUA framework, to expedite overall EUA. An example of Expedited Review Processes developed by the Singapore HSA can be found in Appendix III.

- Create a process for IVD approval.
- Decide what steps can be expedited or moved to post-approval.
- Decide if additional in-country testing will be needed; if so, identify suitable testing laboratory/laboratories and a testing protocol.

4. Implementation of an EUA Process

- Review EUA frameworks from other countries
    - Examples: WHO, US FDA and other stringent NRAs
- Adapt EUA process to local needs, e.g. some IVD products that are on the WHO EUL or US FDA EUA list may not be available in certain markets. In that case, NRAs would need to adapt the standards used by WHO, US FDA or other stringent authorities to evaluate locally available IVDs before granting EUA.

5. Post-Approval Steps

- Implement a testing readiness and distribution plan.
- Create a post-marketing surveillance system for IVD monitoring.

Over time, regulatory requirements across countries or regions may become more similar or "aligned" as a result of the gradual adoption of internationally recognized technical guidance documents, standards, and scientific principles. For example, in the Americas an Inter-America Coalition for Regulatory Convergence for the Medical Technology Sector has been formed. It brings together industry, government, health care professionals, providers, patients, and standardization bodies in the first public-private partnership that extends across the Western Hemisphere focused on achieving medical device regulatory convergence and implementing foundational good regulatory practices.

The Inter-America Coalition for Regulatory Convergence's Vision is one standard, one test, accepted everywhere for any medical technology scope. This Vision implies that medical technology regulators across the Americas base their national medical device regulations, standards, and conformity assessment criteria on the relevant international standards for medical technology. (https://www.interamericancoalition-medtech.org/)

Appendix II. WHO EUL Procedure for In-vitro Diagnostics

1) Quality Manufacturing Review

A review of the manufacturer's QMS documentation and specific manufacturing documents is the first step in the process. At the conclusion of this step, the recommendation will be to proceed, request further documentation, or terminate the application. The decision to proceed with the assessment process will be made if there is sufficient evidence that the applicant is the legal manufacturer, that there is evidence of an adequate QMS in place, and that the requisite manufacturing capability exists.

- Evidence of implementation of a manufacturing QMS (e.g., ISO 13485 certificate) and most recent regulatory (or certification body) audit report, quality manual, exclusions or non-applications, list of valid quality management documentation, management review report
- Details of the production workflow including quality control points (in process and final release activities)
- Critical supplier list including supplied products (components/raw materials) and services
- Details on the experience with the product (when the product developed and when was it first placed on the market, if applicable);
- Details on the manufacturing capacity (existing inventory, minimum time to provide finished product, maximum batch/lot size).

2) Product dossier review

The second step is the assessment of the documentary evidence of safety and performance. It is acknowledged that many of the required studies to meet full regulatory requirements may not have been performed for IVDs undergoing EUAL assessment. Based on the submitted documentation, a risk-based judgment will be made on whether there is a favorable benefit/risk profile. An initial evidence base that includes studies using banked specimens from previous studies, relevant studies in the literature, and studies using contrived specimens to supplement testing of clinical specimens including representative analytes may be acceptable in the absence of complete analytical and/or clinical performance studies if this evidence base provides a reasonable assurance of safety and performance.

In some jurisdictions, minimizing potential harm of an IVD approved through an emergency authorization mechanism is achieved by active post-market surveillance. However, it cannot always be assumed that, in the PHE settings this EUL process serves, there are sufficient resources and institutions in place for any consistent effective surveillance. It will be critical for the manufacturer to detail what, if any, post-emergency-use-listing safety monitoring activities are planned if the EUL is granted.

The outcome of this step will determine whether the application will proceed to the third step, whether further documentation should be requested, or whether the application should be terminated.

The sections below should be submitted by the applicant following the requirements laid down in documents PQDx_018 Instructions for compilation of a product dossier and PQDx_049 Product dossier checklist:

5. Product Information
5.1. Regulatory versions of this product
5.2. Product description including variants (configurations) and accessories
5.3. Essential Principles Checklist
5.4. Risk analysis and control
6. Design and Manufacturing Information
6.1. Product design
6.1.1. Design overview
6.1.2. Formulation and composition
6.1.3. Biological safety
6.1.4. Documentation of design changes
6.2. Manufacturing processes
6.2.1. Overview of
6.2.2. Sites of manufacture
6.2.3. Key suppliers
7. Product Performance Specification, and Associated Validation and Verification Studies 3
7.1. Analytical studies
7.1.1. Specimen type
7.1.2. Analytical performance characteristics
7.1.2.1. Accuracy of measurement
7.1.2.1.1. Trueness of measurement
7.1.2.1.2. Precision of measurement
7.1.2.1.2.1. Repeatability
7.1.2.1.2.2. Reproducibility
7.1.2.2. Analytical sensitivity
7.1.2.3. Analytical specificity
7.1.2.4. Traceability of calibrators and control material values
7.1.2.5. Measuring range of the assay
7.1.2.6. Validation of assay cut-off
7.1.2.7. Validation of assay procedure – reading time
7.2. Stability (excluding specimen stability)
7.2.1. Claimed shelf life
7.2.2. In-use stability
7.2.3. Shipping stability
7.3. Robustness Studies
7.4. Clinical evidence (clinical or diagnostic sensitivity and specificity)

Appendix III. Singapore HSA expedited approval pathway

Class B IVD devices that have been registered in two reference countries, or one reference country for more than three years without any "safety concerns" qualify for Immediate Registration (IBR).

HSA (application and evaluation) fees $1,440; Processing time is immediate upon submission.

Class B IVD devices that have been registered in one reference country qualify for Abridged Registration.
HSA (application and evaluation) fees $2,365; Processing time is 100 working days.

All other Class B IVD devices undergo a Full Registration process:
HSA (application and evaluation) fees $4,120; Processing time is 160 working days.

Class C IVD devices that have been registered in two reference countries, or one reference country for more than 3 years without any "safety concerns" qualify for Expedited Registration (ECR).

HSA (application and evaluation) fees $3,605; processing time is 120 working days.

Class C IVD devices that have been registered in one reference country qualify for Abridged Registration.
HSA (application and evaluation) fees $4,120; processing time is 160 working days.

All other Class C IVD devices undergo a Full Registration process:
HSA (application and evaluation) fees total $6,385; Processing time is 220 working days.

Class D IVD devices that have been registered in two reference countries without any "safety concerns" qualify for Expedited Registration.

HSA (application and evaluation) fees $6,075; Processing time is 180 working days.

Class D IVD devices that have been registered in one reference country qualify for Abridged Registration.
HSA (application and evaluation) fees $6,385; Processing time is 220 working days.

All other Class D IVD devices undergo a Full Registration process:
HSA (application and evaluation) fees $12,115; Processing time is 310 working days.

Appendix IV. Communication Product Guidance

a) NRA Diagnostics Webpages

An NRA website presents a space for the NRA to share key information about diagnostics and regulatory review with the public. NRAs could publish a specific web page for each diagnostic to help with disseminating and collecting information (e.g., post-market surveillance). The web pages can include a document repository that includes all versions of key documents, including safety updates, news, review reports, documents, and letters. Below is a list of suggested components that NRAs could consider including:

- About the NRA
- Diagnostics and Regulatory Overview Section
- Downloadable Package Insert, per diagnostic
- FAQs
- Fact Sheets for Lab, program and healthcare professionals
- Letters of Authorization (and amendments thereto)
- Review Memorandum/Assessment Reports
- Press Releases

b) Review or Decision Memorandum/Assessment Report

The purpose of a Review Memorandum (also referred to as a Decision Memorandum or Assessment Report) is to collect and synthesize the NRA analysis and rationale underlying the NRA decision. The format of the decision memorandum may vary depending on the level of review (e.g., full review, review of basic documentation, reliance, and recognition).

c) Letters of Authorization

A Letter of Authorization is usually written by the NRA to the applicant documenting the decision of the NRA. These letters can be published on the NRA website to increase awareness and transparency regarding the scope and conditions of the authorization. An EUA Letter of Authorization could include the following sections:

- Criteria for Issuance of Authorization
- Scope of Authorization
- Product Description
- Conditions of Authorization
- Duration of Authorization

d) Press Releases

Publishing press releases can be an important mechanism for communicating with the public and specifically with mass media, such as news websites, TV, and radio. Press releases

are generally summaries of key information and will frequently include quotes from key NRA officials, which can then be used in media reports. The WHO Regional Office for Europe has published guidance on how to prepare a press release that includes guidance on the elements of a press release, strategies for media engagement, and model press releases as examples. This guidance specifically focuses on press releases relating to vaccine and immunization programs but is a helpful resource for strategizing how to structure a press release to optimize uptake and dissemination of diagnostics through a broad range of media.

e) Fact Sheet for Diagnostics Community

Fact Sheets for the diagnostics community (laboratory, program, healthcare professional, patient) could be structured to deliver the most critical information about a diagnostic. The Fact Sheet could provide key instructions, such as information related to storage and handling, instructions for use, etc. The Fact Sheet could also summarize information related to its EUA authorization status. The Fact Sheet could inform decision-making to support uptake and appropriate use (e.g., limitations and benefits) and provide information how to report on post-market surveillance.

f) Frequently Asked Questions (FAQs)

An FAQ page and/or document can be a useful tool for communicating with the public about a diagnostic approved under an EUA. The FAQ format is helpful for delivering information succinctly and can be updated regularly to respond to new concerns or questions. FAQs can also be a helpful tool for responding to concerns or rumors circulating on social media, in part because FAQs can easily be converted into social media messages and shared by the NRA on social media to respond to rumors or misinformation circulating online.

g) Social Media Content

Posting key regulatory documents online is important for building public trust in diagnostics regulatory decisions, but it is also important to ensure that key information is shared with the public using social media and other channels where many people receive their news and information. NRAs should strongly consider mapping the landscape of social media being used by their population and sharing key regulatory information on social media accounts on those platforms. Often this will require converting regulatory decisions into different formats (e.g., shorter statements, infographics, photo boards, videos). These abbreviated communications can then link to full documents to provide the public with easy links to the full documentation prepared and published by the NRA. The time investment to publicize key information, especially FAQs, via social media can be well worth the cost to ensure that the public is adequately educated about the scientific evidence underlying regulatory decisions and the rigor of underlying clinical trials. Community advisory mechanisms, such as community advisory boards, can be helpful for identifying active social media platforms and early identification of rumors that are circulating on social media. Community advisory and engagement boards can also help with designing and providing feedback on social media content that maximizes circulation on social media platforms.

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