Asian Harmonization Working Party
WORKING TOWARDS MEDICAL DEVICE HARMONIZATION IN ASIA

PROPOSED DOCUMENT

Title:	Regulatory mechanism for Medical Devices including In Vitro Diagnostic Medical Devices and Software as Medical Devices during a public health emergency
Authoring Group:	Work Group 1, Pre-Market Submission and CSDT Work Group 2, Pre-market: IVDD Work Group 3, Pre-market: Software as a Medical Device
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Dr. Seil Park
Chair, Work Group 1

Dr. Wen-Wei Tsai
Chair, Work Group 2

Mr. Abdullatif Al Watban
Chair, Work Group 3

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Preface

The Global Harmonization Working Party established this document based on Emergency use and specific COVID 19 guidelines worldwide. The document is intended to provide non-binding guidance for use in the regulatory system of medical devices, including in vitro diagnostic (IVD) medical devices and software as a medical device (SaMD), and has been subject to consultation throughout its development.

Table of Contents

1.0 Introduction

The objective of the Global Harmonization Working Party (GHWP) is to encourage convergence at the worldwide level in the evolution of regulatory systems of medical devices, including in vitro diagnostic (IVD) medical devices and software as a medical device (SaMD), in order to protect the public health by those regulatory means considered the most suitable.

It is widely recognized that public health emergencies (i.e. COVID-19, SARS, Ebola, MERS, Zika, etc.), whether they rise to the level of global pandemics or not, could have immense impact on all aspects of people's lives and wellbeing, and on economic development and social prosperity. They often strain the entire healthcare system, including regulatory authorities, which play an instrumental role in tackling the public health emergency by enabling timely and adequate access to essential medical products.

GHWP acknowledges the existence and/or recognition of some jurisdictions' (national or regional) guidance's on emergency regulatory mechanisms. However no global guidance on emergency regulatory mechanisms yet exists. Such a guidance could be referenced and adopted by regulatory authorities worldwide without regard to their size or resources, and would be a critical component of national emergency preparedness.

This guidance serves as GHWP's general recommendations and procedures applicable to an **emergency regulatory mechanism for certain Medical Devices including in vitro diagnostic (IVD) medical devices and software as a medical device (SaMD).**

This guidance document has been developed to ensure that **essential medical devices** for diagnosis, treatment, mitigation and/or prevention of a public health emergency, could be adequately accessed in a fast and sustainable manner. This guidance was developed with a risk-based and agile mindset, taking into consideration the evolving medical knowledge around the possibly new pathogen and its mutations, the frequently iterative innovation of products, as well as the unique supply and logistics challenges during public health emergencies.

GHWP believes this guidance will sustain and strengthen national preparedness for public health emergency situations.

Work Group 2 of the GHWP has prepared this guidance document. Comments or questions should be directed to the Chair of GHWP Work Group 2 whose contact details may be found on the GHWP web page (http://www.ahwp.info/).

2.0 Rationale, Purpose and Scope

2.1 Rationale

Regulatory authorities around the world have to respond rapidly in a public health crisis. Governments typically are under extraordinary time pressure to swiftly develop policy responses to address such public health emergencies to contain the severity and spread.

As Medical Devices including in vitro diagnostic (IVD) medical devices and software as a medical device (SaMD) play an instrumental role in managing a public health emergency, guidelines and policies to facilitate accelerated availability of Medical Devices are much needed.

GHWP has developed this guidance to assist interested Member Economies in setting up or modifying the regulatory emergency mechanism to better meet the urgent demands of essential medical devices including in vitro diagnostic (IVD) medical devices and software as a medical device (SaMD) in the context of a public health emergency.

2.2 Purpose

The purpose of this document is to define general regulatory principles as well as specific procedures and minimum requirements in granting adequate access and ensuring the safety and performance and/or effectiveness of Medical Devices, IVD Medical Devices and SaMD during public health emergencies.

2.3 Scope

This guideline addresses the emergency regulatory mechanism for **Medical Devices** including in vitro diagnostic (IVD) medical devices and software as a medical device (SaMD), as defined in the AHWP/WG2-WG1/F001:2016 *Definition of the Terms 'Medical Device' and 'In Vitro Diagnostic (IVD) Medical Device'* guideline and the AHWP/WG3/F001:2015 *Guidance Document on Medical Device Software - Qualification and Classification respectively.*

3.0 References

AHWP/WG2-WG1/F001:2016 - *Definition of the Terms 'Medical Device' and 'In Vitro Diagnostic (IVD) Medical Device'*

AHWP/WG1a/F002:2013 (now restructured to WG2) - *Essential Principles of Safety and Performance/effective of IVD Medical Devices*

AHWP/WG3/F001:2016 - *Guidance document on Risk Categorisation of Software as a Medical Device*

AHWP/WG3/F001:2015 - *Guidance Document on Medical Device Software - Qualification and Classification*

AHWP/WG5/F003:2015 - *Clinical Evidence for IVD Medical Device - Key Definitions and Concepts*

AHWP/WG5/F004:2015 - *Clinical Evidence for IVD - Scientific Validity Determination and*

Performance Evaluation

AHWP "*Guidance on Clinical Evidence for IVD Medical Devices - Clinical Performance Studies for In Vitro Diagnostic Medical Devices*"

AHWP/WG1-WG2/F001:2017 - *Regulation and treatment of e-IFU and e-Label of Medical Devices-Review of International Practice*

AHWP/WG1-WG2-WG3/F002:2019 - *Principles of Regulatory Requirements for Electronic Instructions for Use (eIFU)*

AHWP/WG2/F001:2018 - *Labelling for In Vitro Diagnostic Medical Devices*

AHWP/WG2-WG1-WG3/F001:2019- *Categorisation of Changes to a registered Medical Device*

AHWP/WG1/F002:2016 - *Guidance for Minor Change Reporting*

AHWP/WG4/F001:2015 - *Adverse Event Reporting Guidance for the Medical Device Manufacturer or its Authorized Representative*

AHWP/WG4/F001:2014 - *Adverse Event Reporting Timelines Guidance for Medical Device Manufacturer and its Authorised Representative*

US - Emergency Use Authorization of Medical Products and Related Authorities

US - Immediately in Effect Guidance on policy for diagnostics testing in laboratories certified to perform high complexity testing under CLIA prior to Emergency Use Authorization for Coronavirus Disease-2019 during the public health emergency

US - Guidance for Industry and Food and Drug Administration Staff "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices"

US - Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)

US - Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories Distribution of In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only

Canada - Interim order respecting the importation and sale of medical devices for use in relation to COVID-19

Kingdom of Saudi Arabia - Corona Virus (Covid-19) IVD Tests - Emergency Use Authorization (EUA)

Singapore - Guidance on expedited approval of COVID-19 Diagnostic Tests - Provisional Authorisation

China - Emergency Approval Procedures

Australia - Therapeutic Goods (Medical Devices - Face Masks and Other Articles) (COVID-19 Emergency) Exemption 2020

Korea - Guideline on the review and approval of In vitro Diagnostics Device for COVID-19 (for Industry)

Taiwan - Special Approvals: Nucleic Acid Tests for SARS-CoV-2

Taiwan - Special Approvals: Rapid Screening Antibody Tests for SARS-CoV-2

Taiwan - Special Approvals: Rapid Screening Antigen Tests for SARS-CoV-2

Taiwan - Special Approvals: Ventilator for Patients with Respiratory Failure or Respiratory Insufficiency

WHO - Emergency Use Listing Procedure

WHO - Instructions and requirements for Emergency Use Listing (EUL) Submission: In vitro diagnostics detecting SARS-CoV-2 nucleic acid or antigen

WHO - Instructions and requirements for Emergency Use Listing (EUL) Submission: In vitro diagnostics detecting antibodies to SARS-CoV- 2 virus

WHO - Good reliance practices in regulatory decision-making: high-level principles and recommendations

ISO 13485 Medical devices - Quality management systems— Requirements for regulatory purposes

ISO 14971 Medical devices - Application of risk management to medical devices

ISO 20916:2019 In vitro diagnostic medical devices - Clinical performance studies using specimens from human subjects - Good study practice

ISO 14155:2011 Clinical investigation of medical devices for human subjects - Good clinical practice

4.0 Terminology and Definitions

Emergency Use Authorization (EUA) - Mechanism established by Regulatory Authority to facilitate the availability and use of medical devices during public health emergencies, such as the current COVID-19 pandemic.
Note-Under an EUA, the Regulatory Authority may allow the use of otherwise unapproved products, or unapproved uses of approved products in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions when certain criteria have been met, including that there are no adequate, approved, and available alternatives.

Medical Device - The term is as defined in AHWP/WG2-WG1/F001:2016 - Definition of the Terms ‘Medical Device’ and ‘In Vitro Diagnostic (IVD) Medical Device’

IVD Medical Device - The term is as defined in AHWP/WG2-WG1/F001:2016 - Definition of the Terms ‘Medical Device’ and ‘In Vitro Diagnostic (IVD) Medical Device’

Software as a Medical Device (SaMD) – The term is as defined in IMDRF/SaMD WG/N10FINAL:2013 - Software as a Medical Device (SaMD): Key Definitions

Manufacturer - For the purpose of this document, the term "manufacturer" includes the manufacturer, its authorized representative or any other person who is responsible for placing the device on the market.

Regulatory Authority- It is a government agency or other entity that exercises a legal right to control the use or sale of medical devices within its jurisdiction, and may take enforcement action to ensure that medical products marketed within its jurisdiction comply with legal requirements. (AHWP/WG1a-WG7/PD007)

Risk Management – It is a systematic application of management policies, procedures and practices to the tasks of analyzing, evaluating, controlling and monitoring risk (e.g., ISO 14971:2007 Medical devices - Application of risk management to medical devices)

Recognition - The acceptance of the regulatory decision of another regulator or other trusted institution. Recognition should be based on evidence of conformity that the regulatory requirements of the reference health authority is sufficient to meet the regulatory requirements of the relying authority. Recognition may be unilateral or mutual and may, in the latter case, be the subject of a mutual recognition agreement. (WHO definition - Good reliance practices in regulatory decision-making: high-level principles and recommendations)

Reference health authority - National or regional authority being relied upon by another health authority. (WHO definition - Good reliance practices in regulatory decision-making: high-level principles and recommendations)

Reliance - The act whereby the NRA in one jurisdiction may take into account and give significant weight to assessments performed by another NRA or trusted institution, or to any other authoritative information in reaching its own decision. The relying authority remains independent, responsible and accountable regarding the decisions taken, even when it relies on the decisions and information of others. (WHO definition - Good reliance practices in regulatory decision-making: high-level principles and recommendations)

Clinical Data -Safety, clinical performance and/or effectiveness information that is generated from the clinical use of a medical device (IMDRF MDCE WG/N56FINAL:2019 - Clinical Evaluation)

Clinical Evaluation - A set of ongoing activities that use scientifically sound methods for the assessment and analysis of clinical data to verify the safety, clinical performance and/or effectiveness of the device when used as intended by the manufacturer (IMDRF MDCE WG/N56FINAL:2019 - Clinical Evaluation)

Clinical Evidence -The clinical data and its evaluation pertaining to a medical device (IMDRF MDCE WG/N56FINAL:2019 - Clinical Evaluation)

Real World Evidence (RWE) – It is defined by US FDA as "clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD"RWE can be generated by different study designs or analyses, including but not limited to, randomized trials, including large simple trials, pragmatic trials, and observational studies (prospective and/or retrospective). (US - Guidance for Industry and Food and Drug Administration Staff: Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices)

Real-World Data (RWD) – It is defined by US FDA as are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. Examples of RWD include data derived from electronic health records (EHRs), claims and billing data, data from product and disease registries, patient-generated data including in home-use settings, and data gathered from other sources that can inform on health status, such as mobile devices (US -

Guidance for Industry and Food and Drug Administration Staff: Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Laboratory Developed Test (LDT) - Diagnostic tests developed by a single clinical laboratory for use only in that laboratory *(US Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories* Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)

Research Use Only (RUO) - Products that are in the laboratory research phase of development, that is, either basic research or the initial search for potential clinical utility, and not represented as an effective in vitro diagnostic product. During this phase, the focus of manufacturer-initiated studies is typically to evaluate limited-scale performance and potential clinical or informational usefulness of the test *US Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories* Distribution of In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only

Instructions for Use - Refers to general and technical information provided by the manufacturer to inform the device user of the medical device or IVD medical device's intended purpose and proper use and of any contraindications, warnings, or precautions to be taken. It is provided by the manufacturer to support and assist the device users in its safe and appropriate use. (AHWP/WG2/F001:2018 Labelling for In Vitro Diagnostic Medical Devices)

Note 1: Instructions for use (IFU) can also be referred to as "package insert" or "directions for use" and may also include "User Manual" or "Technical Manual."

Self-testing IVD Medical Device - An IVD medical device intended for use by a lay user who is responsible for collecting the data or specimen, by themselves and on themselves, relying solely on the instructions provided by the manufacturer. This use can also include performing the test and interpreting the results by themselves and on themselves. (Modified from IMDRF/GRRP WG/N47FINAL:2018)

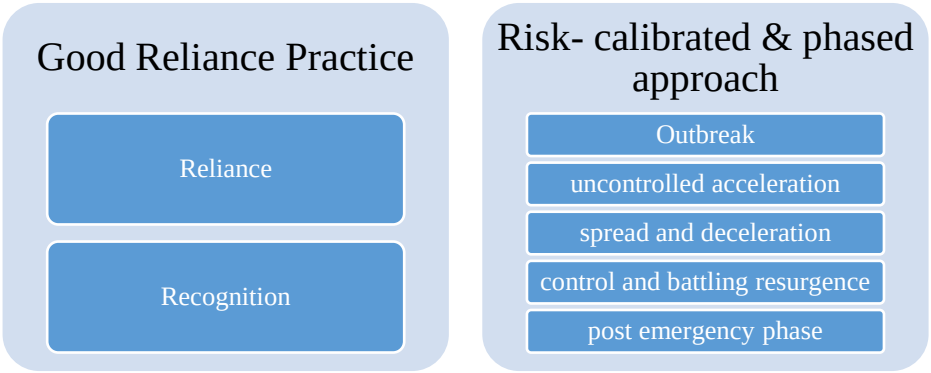
Near-Patient Testing -Testing that is performed near a patient and outside of centralized laboratory testing facilities.
NOTE 1: Users of near-patient testing can include lay or professional users.
NOTE 2: This is not intended to refer to sample collection procedures. NOTE 3: In certain regulatory jurisdictions, this is also referred to as Point of Care Testing.
(IMDRF/GRRP WG/N47 FINAL:2018 Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices)

Lay person - Individual that does not have formal training in a relevant field or discipline.
[SOURCE: ISO 18113-1:2009]

Note: Includes the directions supplied by the manufacturer for the use, maintenance, troubleshooting and disposal of an IVD medical device, as well as warnings and precautions

5.0 General Principles

Respective authorities are recommended to consider the following general principles for the set-up or modification of emergency regulatory mechanism.



5.1 Good Reliance Practice

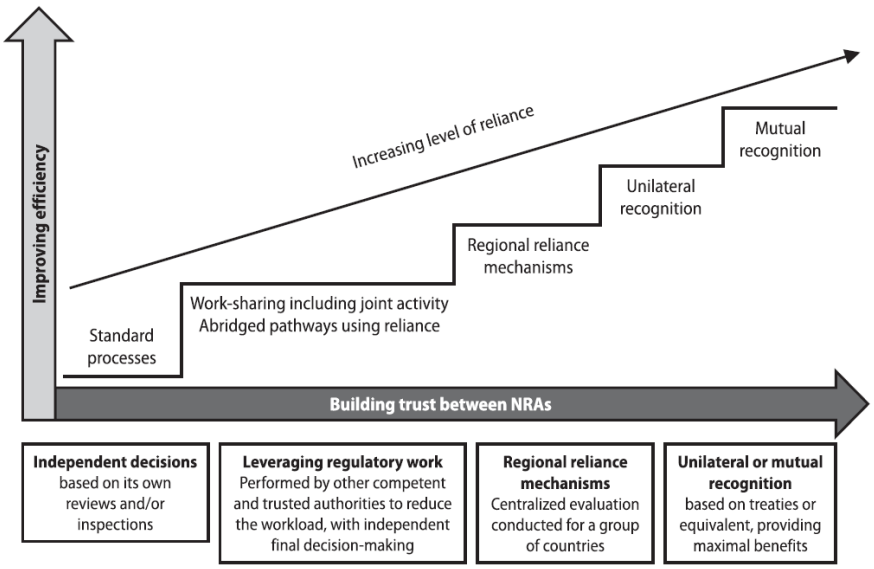
Regulatory authorities should leverage regulatory reliance models, particularly during a public health emergency.

The World Health Organization recently published *Good reliance practices in the regulation of medical products: high level principles and considerations*. This document illustrates (as shown in Fig. 1 below) the key concepts of reliance, with a broad spectrum of models, ranging from work-sharing to mutual recognition.

As described by WHO, good reliance practices are beneficial for regulatory authorities, not only during public health emergencies, but at all times. They enable regulatory authorities to make the best use of available resources and expertise, while facilitating timely access to safe, effective, quality-assured medical products.

Notably it has been highlighted in the WHO guidance that good reliance practices can also **"support regulatory preparedness and response, particularly during public health emergencies."**

Figure 1 Key Concepts of Reliance (reference: WHO guidance)



5.1.1 Recognition

To enable Regulatory Authorities to manage a pandemic as well as performing their core functionality, leveraging recognition of reference health authorities authorizations (**including the WHO Emergency Use Listing**) is highly recommended.

The manufacturer shall provide proof of the authorization granted by a Reference Health Authority or the WHO EUL program for the same product. This evidence should include a copy of the formal approval letter issued by the authority, as well as any review summaries authored by the authority. For absolute certainty, if a Regulatory Authority deems that the evidence of approval by a Reference Health Authority is insufficient, the Regulatory Authority may request additional information.

Note - If a Reference Health Authority chooses to exempt a device, without evaluating in whole or in part, that recognition is not appropriate. Additionally if a foreign jurisdiction waives all (not just partial) pre-market submission and evaluation requirements, this would not be considered a reference authorization for the purposes of granting the emergency use authorization through the recognition pathway.

5.1.2 Reliance

For regulators whose legislative or regulatory frameworks do not allow complete recognition of a Reference Health Authority's authorizations, other reliance models would be recommended to be taken into consideration in managing a public health emergency. Reliance strategies should be tailored to the framework and needs of the national health and regulatory systems.
WHO defines *reliance as the act whereby the Health authority in one jurisdiction take into account and give significant weight to assessments performed by another Health authority or trusted institution, or to any other authoritative information in reaching its own decision. The relying authority remains independent, responsible and accountable regarding the decisions taken, even when it relies on the decisions and information of others.*

GHWP recommends the following principles, which were highlighted by the WHO guidance for implementing regulatory reliance frameworks or strategies:

- **Universality -** Levels of maturity or resources are not drivers of reliance
- **Sovereignty of decision-making -** Reliance implementation requires the existence of competencies for critical decision-making
- **Transparency** is key to new, more efficient ways of conducting regulatory operations, both locally and internationally
- **Respect of national and regional legal basis -** Reliance should be rooted in the national legal framework in alignment with national and regional legal basis
- **Consistency -** Reliance should focus on specific and well-defined categories of products and processes
- **Competence -** The decision to practice reliance, and how best to implement reliance, rests with the country and does not imply dependence, loss of sovereignty and accountability

Additionally, reliance pathways should be considered for all relevant regulatory functions across the medical device product life cycle, as appropriate, such as pre-market evaluation, QMS including audits, post market control, etc.

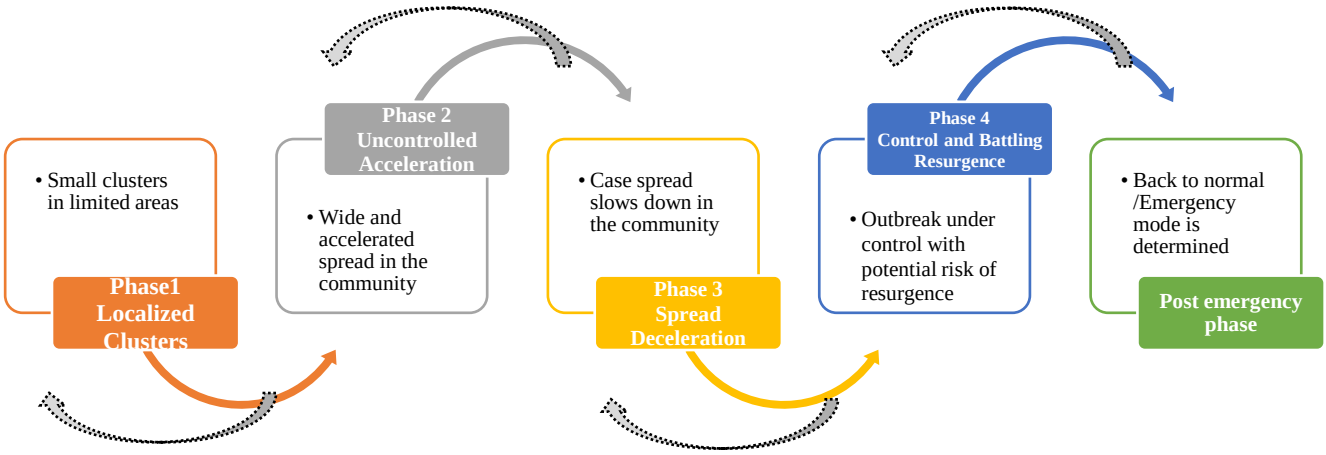
5.2 Risk-calibrated & phased approach

As a public health emergency could evolve along different phases of pandemic/endemic progression (as illustrated in Figure 2), it is critical for regulatory authorities to adopt a risk-calibrated and agile approach to cater for different needs along the disease progression.

It is notable that during the same global pandemic or endemic, the outbreak could progress in a manner to go back and forth between phases as knowledge evolves and mutations occur and could last for a relatively long time period.

Due to the different needs during the different outbreak phases, some special and fit-for-purpose considerations could be put in place by the respective authority as appropriate.

Figure 2: Five different phases in a pandemic/endemic progression (Reference: Mckinsey model/APACMed paper)



Phase 1: In the case of outbreak due to a new pathogen, close collaboration and communication between Regulatory Authorities, developers, health care systems, manufacturers and citizens is encouraged to get medical devices available in the market. Regulatory Authorities might accept unapproved medical devices or unapproved uses of approved products (including research use only products (RUOs) and laboratory-developed tests (LDTs)) if no appropriate medical device is available in the market.

In this phase, Regulatory Authorities are also encouraged to consider products recommended by WHO (e.g. use the WHO recommended reagents and testing protocols).

Phase 2: In the phase of uncontrolled acceleration, Regulatory Authorities should prioritize access to essential medical products that are critical for managing the outbreak. Regulatory Authorities might still accept unapproved medical devices or unapproved uses of approved products. Depending on the supply of the products the Regulatory Authorities might consider to tighten the requirements.

It is highly recommended to recognize the WHO Emergency Use Listing (EUL), and emergency authorizations by other regulatory authorities.

Phase 3: In the phase of deceleration, Regulatory Authorities are encouraged to leverage other reliance models or its own emergency pathways with clear procedural and risk-calibrated requirements and to ask minimum requirements based on the marketed product. Regulatory

Authorities are also encouraged to leverage various regulatory collaboration platforms (such as WHO, IMDRF, AMDC, GHWP, APEC- RHSC, etc.) to share scientific knowledge and best practices for a synchronized and efficient decision-making process.

Phase 4: In the phase of control and battling resurgence, Regulatory Authorities are recommended to still prioritize resources and open fast track for the essential products, taking into consideration of risks of resurgence RA might consider transiting out of EUA and requiring products to be registered under the normal pathway (considering fast track). It is also recommended to apply the fast track for not just pre-market authorization, but also to the post market submission (rolling submission) as well as change submission.

In the **post emergency phase**, it is recommended that emergency regulatory authorizations are allowed to be supplemented with additional evidence (real world evidence should be leveraged) and to be converted into normal license via an efficient route.
If the regulatory system of the country allows a completely new submission for the same product via the normal route, the conversion should not be requested.

6. Emergency Regulatory Mechanism

The purpose of setting up emergency regulatory mechanism is to allow the use of unapproved medical devices, or unapproved uses of approved medical devices in a public health emergency crisis, where some minimal criteria have to be met.

The key concept for emergency regulatory mechanism is making risk-calibrated regulatory decision, weighting the potential benefits against the potential risks caused by the public health emergency, based on the limited evidence at certain time point, supplementing with post authorization monitoring and continued performance evidence to adjust the regulatory decisions as necessary.

The following mechanisms is a full-fledged regulatory set up. Depending on the local adoption of reliance and recognition model across the life cycle of a product, some of the following steps can be omitted.

6.1 Eligibility

Health authorities should set up certain eligibility criteria for assessment of which products will qualify for the emergency regulatory pathway. The following criteria is proposed as reference:

- The disease for which the product is intended for is serious or life threatening, or has severe impact on public health.
- There are urgent clinical needs due to lack of licensed products available in the market for the intended purpose, or the marketed products could not meet the requirements is terms of quality, performance, or scale-up capacity, etc.
- The known & potential benefits outweigh the known & potential risks based on the best available knowledge.

- The product is manufactured under a functional Quality Management System (QMS).
- The applicant undertakes to complete the development of the product (validation and verification of the product).

In certain circumstances, respective authorities could consider special cases where the applicants may not meet the above requirements but due to the heightened risks or other reasons, these may still be considered and supported with justifications.

6.2 Procedures

As shown in **Figure 3,** the Emergency Regulatory Mechanism is activated post the Declaration of Emergency by the respective authority.

502 **Figure 3:** Process Map for Emergency Regulatory Mechanism
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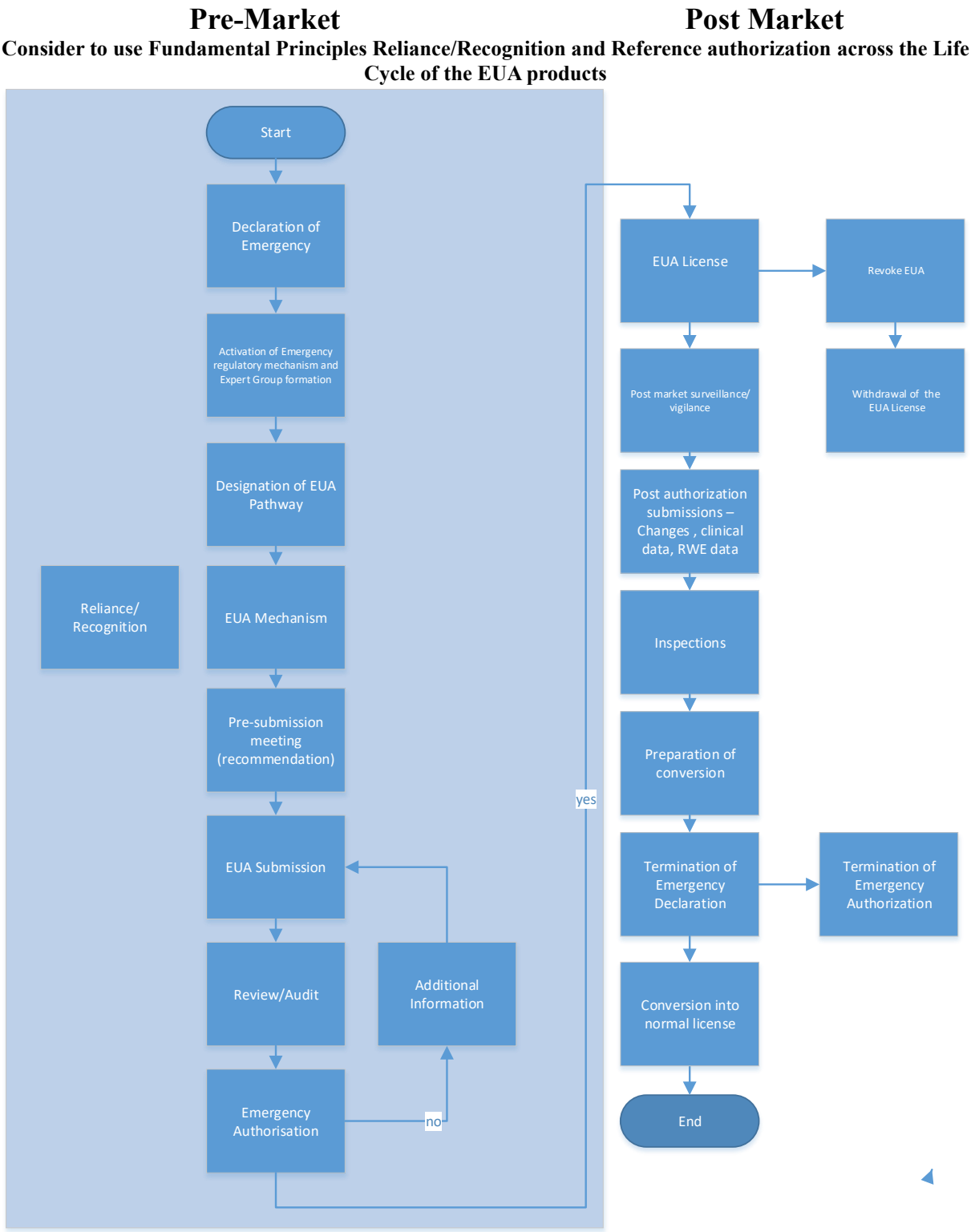

504

6.2.1 Expert group

Expert groups will be formed to consult on the evaluation of a specific product or group of products for the specific disease. It is recommended to have a multi-disciplinary expert group, including medical and clinical experts, R&D specialists, public health professionals, and others.

6.2.2 Pre-EUA submission meeting

It is recommended to set up pre-submission meeting mechanism to enable early conversations during the product development phase. These meetings may be voluntary, but can be helpful in guiding manufacturers to provide the relevant evidence needed for an emergency use authorization.

6.2.3 EUA Submission

It is recommended to allow special submission routes with more flexibility, including fast-route, electronic submission, acceptance of electronic signature, acceptance of non-notarized or non-legalized copy while requesting for later supplements when the notarization/legalization is logistically possible. Regulatory authorities should also accommodate rolling submissions, in which manufacturers submit evidence and Regulatory Authorities review it as completed.

The Annex of this guideline provides the essential requirements for emergency regulatory authorization and documents (section A and B) provided for the EUA submission.

1. **Section A, B and C** of this guideline provide a Table of Contents for the Submission Dossier of a General Medical Device, Software as a Medical Device and IVD Medical Devices.
2. **Section D** of this guideline provides the Quality Management System requirements
3. **Section E and F** of this guideline provide basic Clinical Evidence requirements of a General Medical Device, Software as a Medical Device and IVD Medical Devices.
4. **Section G** of this guideline outlines Labelling requirements

6.2.4 Review/Audit/Inspection

Review and Audit could be optional if the reliance/recognition/reference authorization will be leveraged. In general, remote audit should be allowed.

It is recommended to temporarily postpone all domestic and foreign inspections, while only conducting critical inspections when possible.

Remote inspections require a reliable Wi-Fi network, a stable internet connection, up-to-date remote video communication system, a mobile device enabled with video streaming function and connectivity to the internet (for virtual live tour), document scanner and document exchange platform, where possible. Platforms need to be cyber secure.

6.2.5 Emergency Authorization

The assessment timelines of an emergency authorization should be adapted to an emergency context. It also should be communicated with the public via appropriate channels.

6.2.6 Post authorization monitoring

Once a product is granted emergency authorization, authorities should consider implementing post authorization control measures to mitigate risk and address any product problems quickly, as below:

- Request for reports on safety surveillance or additional information as specified in the emergency approval license;
- Efficacy/effectiveness/performance monitoring/safety;
- Quality complaints and other relevant data that may impact the validity of the listing status.

Regulatory Authorities should periodically review the appropriateness of an EUA. Once the product is on the market, the review should include regular assessment based on additional information provided by the manufacturer as specified in the emergency authorisation decision

If any quality/safety issues are identified post authorization and cannot be resolved to regulatory authority's satisfaction, the regulatory authority may revoke or modify the emergency authorization of the product.

Postmarket surveillance activities should where possible, comply with AHWP/WG4/F001:2015 - *Adverse Event Reporting Guidance for the Medical Device Manufacturer or its Authorized Representative* and AHWP/WG4/F001:2014 - *Adverse Event Reporting Timelines Guidance for Medical Device Manufacturer and its Authorised Representative* (AHWP/WG4/F001:2014)

6.2.7 Changes

It is the applicant's responsibility to promptly inform authorities of all changes regarding intended use formulation, manufacturing process, testing methods, specifications, facilities and any other aspects that might result in a change of the safety and/or efficacy and/or performance of the product.

It is recommended to handle the changes in a prioritized and fast manner as these changes may happen due to the evolving knowledge about the disease, or the evolvement of pathogen itself. It is also recommended to leverage the reliance/recognition model for handling of changes, if it is the same product and same change.

For SaMD it is recommended to use predetermined change control plans to address anticipated future changes.

The manufacturer should where possible, comply with the GHWP guidances AHWP/WG2-WG1-WG3/F001:2019 *Categorisation of Changes to a registered Medical Device and* AHWP/WG1/F002:2016 *Guidance for Minor Change Reporting.*

6.2.8 Duration

In general, the emergency regulatory mechanism will remain in effect for the duration of the Emergency Declaration issued by the Regulatory Authority. It is recommended to refer to the global competent authority (i.e. WHO) decision in the case of global pandemic, due to the potential risks of resurgence and pathogen mutation, etc.

6.2.9 Conversion

Once a medical device has been authorized under the Emergency Use Authorization mechanism, the manufacturer of the device is expected to pursue regular marketing authorization. The EUA ends upon the termination of the emergency situation and, unless regular marketing authorization has been or is likely to be granted, the manufacturer should withdraw the device from the market and recommend to discontinue use of the device. A transition period may be granted.

The Regulatory Authority should consider the post authorization data, including the Real World Data (RWD) and associated Real World Evidence (RWE) as clinical evidence to assess if the requirements of a normal license could be fulfilled. If it can be fulfilled, it is recommended to convert the emergency authorization into full license in a simplified and prioritized manner.

The conversion can happen before or when the emergency declaration is terminated. Regulatory Authorities may consider reasonable transition periods to enable review of products seeking normal licenses, and withdrawal of those for which manufacturers choose not to seek licenses. It is notable that even after the emergency status is over, some of these products may still be critical components for disease monitoring and diagnosis under the normal mode.

Annex: Essential requirements for emergency regulatory authorization of Medical Devices

A. Table of Content for Dossier for Medical Devices

An applicant for the authorization of importation or sale of an emergency use medical device or software as medical device must contain sufficient information and material to enable the Regulatory Authority to determine whether to issue the emergency use authorization.

GHWP recommends that the following information be submitted in any request for an emergency regulatory authorization:

1. the risk class of the device;
2. the identifier of the device, including the identifier of any medical device that is part of a system
3. the name and address of the manufacturer as it appears on the device label;
4. the address where the device is manufactured, if different from the one referred to in paragraph (d);
5. description of the product's approval status (e.g. whether the product is approved in a foreign country for either the proposed use or another use; information on the use of the medical product by either a foreign country or an international organization (e.g., World Health Organization (WHO));
6. description of the product and its intended use
7. discussion of risks and benefits of the Medical Device
8. the known information in relation to the quality, safety and effectiveness of the device;
9. the Instructions for use for the device to be used safely and effectively;
10. an attestation by the applicant that documented procedures are in place in respect of distribution records, complaint handling, incident reporting and recalls; and
11. copy of the label of the device;
12. copy of the manufacturer’s Quality Manufacturing System Certificate, evidence of Good Manufacturing Practices, or others.

B. Table of Content for Dossier for IVD Medical Devices

An applicant for the authorization of importation or sale of an emergency use IVD medical device must contain sufficient information and material to enable the Regulatory Authority to determine whether to issue the emergency use authorization.

GHWP recommends that the following information be submitted in any request for an emergency regulatory authorization:

1. the risk class of the device;
2. the identifier of the device, including the identifier of any medical device that is part of a system, test kit, medical device group, medical device family or medical device group family;
3. the name and address of the manufacturer as it appears on the device label;
4. the address where the device is manufactured, if different from the one referred to in paragraph (d);
5. description of the product's approval status (e.g. whether the product is approved in a foreign country for either the proposed use or another use; information on the use of the medical product by either a foreign country or an international organization (e.g., World Health Organization (WHO));
6. description of the product and its intended use (e.g., identification of the serious or life-threatening disease or condition for which the product may be effective; where, when, and how the product is anticipated to be used; and/or the population(s) for which the product may be used);
7. discussion of risks and benefits of the IVD Medical Device
8. the known information in relation to the quality, safety and effectiveness of the device;
9. the Instructions for use for the device to be used safely and effectively;
10. an attestation by the applicant that documented procedures are in place in respect of distribution records, complaint handling, incident reporting and recalls; and
11. copy of the label of the device;
12. copy of the manufacturer’s Quality Manufacturing System Certificate, evidence of Good Manufacturing Practices, or others.

C. Table of Content for Dossier for Software as Medical Device

An applicant for the authorization of importation or sale of an emergency use medical device or software as medical device must contain sufficient information and material to enable the Regulatory Authority to determine whether to issue the emergency use authorization.

GHWP recommends that the following information be submitted in any request for an emergency regulatory authorization:

1. the risk class of the device, and / or Level of Concern if known;
2. the identifier of the device, including the identifier that may work alone or together with any medical device as part of a system, test kit, medical device group, medical device family or medical device group family, where applicable;
3. the name and address of the manufacturer as it appears on the device label or software interface;
4. the address where the device is manufactured, if different from the one referred to in paragraph (3);
5. description of the product's approval status, including EUA approval status in other jurisdiction (e.g. whether the product is approved anywhere for either the proposed use or another use; information on the use of the medical product by either a foreign country or an international organization (e.g., World Health Organization (WHO));
6. description of the product and its intended use;
7. discussion of risks and benefits of the SaMD;
8. list of unresolved anomalies (for Moderate and Major Level of Concern SaMD, if available);
9. the known information in relation to the quality, safety and effectiveness of the device;
10. the Instructions for use (or operator manual) for the device to be used safely and effectively;
11. an attestation by the applicant that documented procedures are in place in respect of distribution records, complaint handling, incident reporting and recalls; and
12. copy of the label of the device (applicable only if physical optical disc is used for distribution);
13. copy of the manufacturer’s Quality Manufacturing System Certificate, evidence of Good Manufacturing Practices, or others where applicable.

D. Quality Management System Documents

A review of the manufacturer's quality management system (QMS) documentation and specific manufacturing documents is the first step in the process.

The quality management standard *ISO 13485 Medical devices — Quality management systems— Requirements for regulatory purposes* should be considered a benchmark in quality management for manufacturers of Medical Devices by regulatory authorities throughout the world.

Manufacturers will be required to share information to demonstrate that the general MD/IVD medical device/SaMD for emergency use are of consistent quality and effectiveness. This can be demonstrated by either providing a copy of the manufacturer's Quality Management System certificate to ISO 13485:2016, or by submitting evidence of Good Manufacturing Practices and its proper implementation.

In the absence of a valid ISO 13485:2016 certificate, information supporting the following criteria, as a minimum, should be included in an application for a general MD/IVD medical device/SaMD:

Design - A documented process for controlling design and development.

Planning - Evidence of adequate quality planning, such as final approved specification for the product and all components, including labelling, Instructions for Use (IFU), packaging

Purchasing controls - Evidence of adequate purchasing controls

Manufacturing/production - Documented procedures and work instructions

Corrective actions and post-market activities - Documented procedures and work instructions (as appropriate)

E. Clinical Evidence Requirements –Medical Devices and Software as Medical Devices

While the ultimate objective is to fully verify the clinical safety and efficacy of the Medical Device, the pandemic crisis, the urgent need for patient treatment, and the possible lack of supplies might make it difficult to fully evaluate the clinical safety and efficacy that are normally required to gain the product approval under non-emergency circumstances in most jurisdictions.

A limited preliminary clinical evidence may be acceptable. The manufacturer should follow a risk based approach and determine the depth of verification needed. Various scientific evidence can be considered to make an overall risk-benefit determination and such evidence may include but not limited to:

- Results of domestic and foreign clinical trials
- *in vivo* safety and efficacy data from animal models
- *in vitro* efficacy data

The Regulatory Authorities should consider that not all studies are completed when submitting in an EUA submission. When studies are still in progress or plans to commence such studies are in place, the manufacturer should provide the study protocol and an update of progress or the study protocol and plan along with anticipated dates of completion. If more clinical data become available at a later time, the manufacturer should submit these data to the Regulatory Authority. Additionally the Regulatory Authorities might consider establishing some technology-specific guidance documents to support applicants regarding clinical evidence requirements.

F. Clinical Evidence Requirements – IVD Medical Devices

While the ultimate objective is to fully verify the method performance of the IVD Medical Device, the pandemic crisis, the urgent need for patient testing, and the possible lack of reagents and supplies might make it difficult to fully evaluate the performance as outlined in

AHWP/WG5/F003:2015 - *Clinical Evidence for IVD Medical Device - Key Definitions and Concepts,*

AHWP/WG5/F004:2015 - *Clinical Evidence for IVD - Scientific Validity Determination and Performance Evaluation*

AHWP - *Guidance on Clinical Evidence for IVD Medical Devices - Clinical Performance Studies for In Vitro Diagnostic Medical Devices*

A limited preliminary clinical evidence may be acceptable. The manufacturer should follow a risk based approach and determine the depth of verification needed based on the available scientific knowledge at the time of EUA.

Analytical performance studies might include but not limited to:

- Stability of specimen(s)
- Validation of specimens – matrix equivalence studies “Validation of specimens - evaluation of different matrices" Reason is Matrices may not be equivalent due to biological factors, and a matrix with inferior performance may still be useful in situations of scarcity.
- Precision (repeatability and reproducibility)
- Analytical sensitivity
- Analytical specificity (interfering substances and cross reactivity)
- Cut-off value
- Validation of assay procedure:
- Stability studies

Clinical performance studies might include but not limited to:

- Clinical / diagnostic sensitivity
- Clinical/ diagnostic specificity
- Recommended comparator method/ assigning clinical truth to specimens

The Regulatory Authorities should consider that not all studies are completed when submitting in an EUA submission. When studies are still in progress or plans to commence such studies are in place, the manufacturer should provide the study protocol and an update of progress or the study protocol and plan along with anticipated dates of completion. If more clinical data become available at a later time, the manufacturer should submit these data to the Regulatory Authority.

The Regulatory Authorities should consider to accept contrived specimens given that clinical specimens will not always be available in the volumes required, especially when countries are experiencing fluctuating numbers of cases.

The Regulatory Authorities should consider to accept and leverage the clinical evidence (from other countries or regions) rather than asking for local clinical studies. Local studies should only be required if there is a lack of sufficient scientific evidence.
Additionally the Regulatory Authorities might consider establishing some technology-specific guidance documents to support applicants regarding clinical evidence requirements.

G. Labelling

The labelling should clearly display information regarding its status for emergency use only (EUA).

The information contained within the IFU may be electronically provided as an acceptable alternative to be compliant with regulatory requirements. eIFU should, where possible, comply with the GHWP guidance *" Principles of Regulatory Requirements for Electronic Instructions for Use (eIFU), AHWP/WG1-WG2-WG3/F002:2019 "and or local regulations.*