Promoting the
QUALITY OF MEDICINES Plus

Model Dossier: Facilitated Regulatory Pathways for Medicinal Products for Public Health Emergencies and Unmet Medical Needs

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About PQM+

The Promoting the Quality of Medicines Plus (PQM+) Program is a six-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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Executive Summary

Facilitated regulatory pathways (FRPs) are used during public health emergencies or for unmet medical needs and help to decrease the development and regulatory review time for lifesaving medicinal products. FRPs are commonly used by stringent regulatory authorities (SRAs), but the specific pathways used still require complete review of the data submitted. Use of reliance FRPs is crucial for national medicines regulatory authorities (NMRAs) in low- and middle-income countries (LMICs) because they generally do not have the resources needed to conduct a complete review with potentially limited data in an expedited timeframe.

Although using reliance pathways is an efficient way for NMRAs in LMICs to maximize their available resources, it can still be critical to perform minimal review and oversight of the applications to ensure sameness in the medicine product and evaluate issues that are specific to LMICs. It is also important for NMRAs to work toward reducing differences in dossier format and requirements, for example, through harmonization and reliance initiatives that have begun in various regions.

The guidance outlines various FRP pathways used by SRAs and the differences in requirements or review processes, specifically as it relates to risk–benefit considerations, post-approval requirements, and modified post-market or pharmacovigilance surveillance commitments. The model then provides descriptions of reliance FRPs that NMRAs in LMICs can adapt, including specifications for using the pathway and requirements for dossier submission. As additional support, guidance is provided for standardized dossier submission formats, legal and regulatory considerations, priority review areas for LMICs, selection of an approval pathway, and how to overcome variable requirements in structured product labeling and summary of product characteristics package inserts.

The following lists intended uses and audiences of the model dossier:

- As a model dossier applicable to various approval pathways that NMRAs can adapt for use and implementation during a health emergency or for an unmet medical need.
- As guidance for manufacturers to navigate different approval pathways to facilitate dossier compilation and submission.
- To provide an adaptive common technical document (CTD) format that would be acceptable in a health emergency or for an unmet need for a majority of NMRAs in LMICs.
- To provide alternatives to redundant and noncritical review requirements when using reliance pathways that hinge on reviews conducted by SRAs.

The following tools and resources were developed to facilitate adoption of FRPs using the model dossier:

Annex 1: Model Dossier Requirements by Reliance Pathway

Annex 2: Decision Tree for Approval Pathways

Annex 3: Description of ICH CTD organization

Annex 4: Description of ACTD [Association of Southeast Asian Nations] Organization

Annex 5: Proposed Module 1 (ICH CTD) or Part 1 (ACTD)

Annex 6: Comparison between ICH CTD and ACTD

Annex 7: EUA Timelines and Mechanisms for Transition to Full Approval

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Acronyms

ACTD	ASEAN common technical document
ASEAN	Association of Southeast Asian Nations
API	active pharmaceutical ingredient
BTD	breakthrough therapy designation
CTD	common technical document
CRP	collaborative registration procedures
EMA	European Medicines Agency
EUA	emergency use authorization
EUL	emergency use listing
FPP	finished pharmaceutical product
FRP	facilitated regulatory pathway
GMP	good manufacturing practice
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
LMIC	low- and middle-income country
MHRA	Medicines and Health Care Products Regulatory Agency
NMPA	National Medical Products Administration
NMRA	national medicines regulatory authority
PAHO	Pan American Health Organization
PMDA	Pharmaceuticals and Medical Devices Agency
PQM+	Promoting the Quality of Medicines Plus
SmPC	summary of product characteristics
SPL	structured product labeling
SRA	stringent regulatory authority
TGA	Therapeutic Goods Administration
USAID	U.S. Agency for International Development
U.S. FDA	US Food and Drug Administration
USP	U.S. Pharmacopeial Convention
WHO	World Health Organization

Glossary of Facilitated Review Pathways

Abridged emergency use authorization (EUA): Used when a stringent regulatory authority (SRA) evaluated and authorized a product under a full EUA, and a national medicines regulatory authority (NMRA) has the capacity to evaluate specific aspects of the dossier.

Abridged review: Used when at least one reference or competent benchmark authority has registered a medicinal product, and resources are conserved by not reassessing the full scientific supporting data.

Accelerated approval: Allows for approval of drugs for serious conditions that fill an unmet medical need based on surrogate endpoints[1].

Breakthrough therapy designation: Expedites the drug development and review process through early engagement starting as early as phase I trials, eligibility for fast track pathways features, and higher-level agency support. Designation is granted based on preliminary clinical evidence showing improvement on a clinically significant endpoint.

Collaborative procedures for accelerated registration: Used when an SRA has approved a medicinal product, or the product is World Health Organization (WHO) prequalified. Ensures registration within a predefined timeline.

Fast track: Accelerated development processes and review through more frequent agency engagement, rolling review, and eligibility for accelerated approval and priority review.

Full EUA: Used as the first line of authorization, in which a thorough review of all available data is conducted.

Priority review: Decreases the approval timeline through application of an expedited review clock.

Recognition: An agency automatically accepts a regulatory decision made by another NMRA, SRA, or WHO (e.g., WHO prequalification or emergency use listing decision) without needing additional technical evaluation by the recognizing entity.

Regional regulatory harmonization: Initiatives center on creating standard technical requirements within a region or group of countries. Harmonization efforts support use of reliance by establishing common standards and collaborative networks among NMRAs.

Reliance: Used when an SRA or another competent NMRA evaluated and authorized a product, or the product is WHO prequalified, and the regulatory reports are made available to the concerned NMRA.

Reliance EUA: Used when a product was evaluated and authorized under a full EUA by an SRA, and the regulatory reports are made available to the concerned NMRA.

[1] A surrogate or intermediate clinical endpoint is a laboratory measurement, radiographic picture, physical sign, or other measure that has been established as reasonably likely to predict clinical benefit but is not itself a measure of clinical benefit.

Introduction

It is crucial for national medicines regulatory authorities (NMRAs) to facilitate medicinal product approvals in a timely manner during public health emergencies or for unmet medical needs to ensure availability of and access to essential, lifesaving medicinal products. However, standard regulatory review and approval processes can require extensive time (e.g., 18 to 24 months in some regulatory agencies) to assess applications against the scientific data and regulatory requirements to determine the safety, quality, and efficacy of medicinal products. Instead, NMRAs must ensure that efficient, transparent, and responsive review pathways are developed and implemented effectively before and during a public health emergency or for an unmet medical need.

Expedited review and approval pathways, broadly termed facilitated regulatory pathways (FRPs), used in response to health emergencies and unmet medical needs typically require making benefit–risk determinations using limited scientific data on product safety, efficacy, and quality, potentially requiring follow-up studies, and iterating the authorization conditions as more data become available. Even though NMRAs in low- and middle-income countries (LMICs) are not encouraged to perform a full expedited review, they should be aware of the FRPs used by stringent regulatory authorities (SRAs) and the differences in requirements or review processes, specifically related to risk-benefit considerations, post-approval requirements, and modified post-market surveillance commitments.

NMRAs in LMICs should use reliance FRPs. The World Health Organization (WHO) defines reliance as "the act whereby the regulatory authority in one jurisdiction takes into account and gives significant weight to [i.e., totally or partially rely upon] assessments performed by another regulatory authority or trusted institution…in reaching its own decision" [1, p. 243]. As this definition implies, a reliance pathway should be used when a product has been evaluated and authorized by an SRA or another competent NMRA,[2] or if the product is WHO prequalified, and the regulatory reports are made available to the concerned NMRA.

Because regulatory systems can be very resource intensive, NMRAs should consider regulatory reliance on technical requirements for dossiers and review outcomes from other competent NMRAs. Reliance will bring efficiency to the regulatory processes to expedite availability of and access to medicinal products to treat serious, life-threatening conditions in public health emergencies and for unmet medical needs. NMRAs can accomplish reliance by the following:

- Establishing a reliance mechanism with relevant and competent NMRAs with an equal or advanced regulatory setting or both (i.e., maturity level 3 and higher, including SRAs) for obtaining and sharing regulatory information;
- Eliminating duplicate reviews of a product that other reliable NMRAs have already reviewed;
- Performing joint reviews among member states to optimize individual capacities;

[2] Stringent regulatory authority means a regulatory authority that is:
a) A member of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) before October 23, 2015, namely: the U.S. Food and Drug Administration, the European Commission, and the Ministry of Health, Labor, and Welfare of Japan, also represented by the Pharmaceuticals and Medical Devices Agency; or
b) An ICH observer before October 23, 2015, namely: the European Free Trade Association, as represented by Swissmedic and Health Canada; or
c) A regulatory authority associated with an ICH member through a legally binding mutual recognition agreement before October 23, 2015, namely: Australia, Iceland, Liechtenstein, and Norway.

- Strengthening their regulatory system specifically for the market authorization function; and
- Developing a value-added approach to streamlining the timely availability of and access to essential, lifesaving medicinal products.

Use of reliance mechanisms is crucial for NMRAs in LMICs because they generally do not have the resources needed to conduct a complete review with potentially limited data in an expedited timeframe. Instead, to ensure timely product review and authorization, using good reliance practices leverages the reviews conducted by SRAs that possess the technical, financial, and human resources required. Redundant reviews or arbitrary additional requirements imposed by NMRAs in LMICs exacerbates inequities in access to medicines products by:

1. Restricting or delaying access to essential, lifesaving medicinal products.
2. Redirecting resources (financial, human, and technical) that could otherwise be spent on process and procedures specific to the country of context and that ensure the quality of available products.

Although using reliance pathways is an efficient way for NMRAs in LMICs to maximize their available resources, it can still be critical to perform minimal review and oversight of the applications to ensure sameness in the medicinal product and evaluate issues that are specific to LMICs and their country context. It is also important for NMRAs to work toward reducing differences in dossier requirements, for example, through harmonization and reliance initiatives that have begun in various regions. Harmonization initiatives between countries help facilitate reliance mechanisms within the harmonization network, as regulators are assured that the review practices and submission requirements in the NMRA used for reliance are the same as or equivalent to the approving NMRA. During a health emergency or for an unmet medical need specifically, NMRAs should allow as much flexibility as possible in these submission requirements without affecting the risk to the public.

Purpose

The primary purpose of the model dossier is to expedite availability and access to essential or lifesaving medicinal products in health emergencies or for unmet medical needs. To meet this purpose, the intended uses and audiences include:

- As a model dossier applicable to various approval pathways that NMRAs can adapt for use and implementation during a health emergency or for an unmet medical need.
- As guidance for manufacturers to navigate different approval pathways to facilitate dossier compilation and submission.
- To provide an adaptive common technical document (CTD) format that would be acceptable in a health emergency or for an unmet need for a majority of NMRAs in LMICs.
- To highlight redundant and noncritical review requirements when using reliance pathways that hinge on reviews conducted by SRAs.

Using the Model Dossier

In a public health emergency or for an unmet medical need, an NMRA is likely restricted to the regulatory framework already in place (if any), which could be a lengthy review process. To overcome this concern, a model dossier was designed to provide guidance for an NMRA to adapt existing FRPs for their country context, specifically considering adherence to their regulatory mandates. The guidance may also assist NMRAs in informing the manufacturers/applicants or market authorization holders or importers of different applicable FRPs and dossier requirements for a given public health emergency or unmet medical need. Manufacturers/applicants may also reference the model dossier when submitting a dossier for expedited review to obtain timely review and authorization or approval across multiple jurisdictions or countries.

This guidance first outlines legal and regulatory considerations for adopting FRPs and provides a recommendation for harmonizing dossier submission formats. It then provides specifics for alternative designations or approval pathways that SRAs use, followed by proposed pathways for LMICs to use.

Emergency use authorization (EUA) is the first pathway addressed, and the guidance provides an overview of the model that SRAs use, followed by models that LMICs can adopt. The model dossier then describes requirements and variations for designations or pathways that SRAs use for FRPs. Although the terminology varies across regulatory agencies, the following terms are used to distinguish between the possible designations or pathways:

- Accelerated approval
- Breakthrough therapy designation (BTD)
- Fast track
- Priority review

These terms follow criteria and specifics defined by the U.S. Food and Drug Administration (U.S. FDA; [2]), however, the subsequent sections also note when other regulatory agencies use different terminology to identify the designations or pathways they use. These pathways are important to discuss because NMRAs in LMICs need to understand the available FRPs that SRAs use for approving medicinal products so they can be aware of limitations, alternative data requirements, or post-approval expectations. For example, if an SRA granted an accelerated approval, the NMRA using reliance should ensure that an applicant is required to inform them of any changes in the submission data or original approval the SRA granted. Examples include updates to available clinical data generated as part of a post-marketing requirement or changes in the approved indication. However, it is not recommended that NMRAs in LMICs recreate these pathways. Instead, they should use the model dossier to facilitate reliance FRPs that use SRA reviews assessed via an alternate FRP. For that reason, the model dossier also outlines the following reliance FRPs available for LMICs to adopt:

- Abridged review
- Collaborative procedures for accelerated registration
- Regional regulatory harmonization and reliance
- Recognition

Annex 1 outlines the fundamental dossier submission data requirements for the reliance FRPs to enable implementation by an NMRA and provides guidance to manufacturers that chose to use any of the available FRPs. **Annex 2** includes a decision tree that outlines the suggested FRP to use considering the eligibility criteria discussed in the following sections.

It is critical that NMRAs do not impose arbitrary and unnecessary requirements, such as country-specific clinical trials or product lot release testing that are reasonably accepted as coming from a reliable source. Imposing specific clinical trials or lot release testing takes time and effort, requiring specialized human and financial resources that are typically unavailable in resource-constrained settings, thus hampering timely access to lifesaving medicinal products.

To aid in understanding what review may be performed when using FRPs, the model dossier outlines the specific areas that NMRAs in LMICs should consider for review. It also outlines how to handle variable requirements in structured product labeling (SPL) or summary of product characteristics (SmPC) package inserts.

Legal and Regulatory Considerations

Medical countermeasures are necessary to diagnose, prevent, or treat disease conditions during public health emergencies such as a pandemic. Medical products (including medicinal products, vaccines, diagnostic kits, and medical equipment) are required to respond to new emergencies effectively, including pandemics or threats. To facilitate the availability of these medical products (including medicinal products specifically), it is necessary for regulatory authorities to have legal and regulatory instruments that they can use during public health emergencies to allow authorization of medicinal products when regular approval pathways restrict timely availability. Many regulatory authorities may also have strategic national stockpiles to address emergency preparedness. Similarly, regulatory authorioties should establish regional strategic stockpiles of mutually authorized and lifesaving medicines and vaccines to facilitate distribution to specific countries with active health emergency needs [3]. Such collaborative effort reduces the burden on individual countries to establish a strategic national stockpile and enables flexibility to target resources to countries as the resources are needed.

Because of NMRAs' role in ensuring public health, including in an emergency, a majority of them do have medical countermeasures and associated regulations to address these issues. In some situations, specific sections in the legislative acts or rules authorize them to address such a situation. For example, in the United States, EUA authority is granted under section 564 of the Food, Drug, and Cosmetic Act, which specifies use of expanded access authorities for investigational products and several authorities related to the emergency use of approved medical countermeasures [4].

Because the development and review process for medicinal products can be lengthy, regulatory authorities provide several avenues to expedite the review process to increase access to lifesaving medicinal products—for example, products for the treatment or prevention of serious diseases or conditions. An FRP that is widely used to fulfill an unmet need or improve existing therapies is to grant fast track designation along with an accelerated approval or priority review [2]. These mechanisms entitle the sponsor or applicant to have increased communication with the regulatory authorities, use of alternate clinical endpoints to show efficacy, and/or decreased review timelines. In certain emergencies, regulatory authorities may temporarily authorize unapproved products or authorize products for unapproved uses through an EUA.

The intent of any regulatory framework is to function effectively and efficiently to support medicinal product development, the submission of market authorization applications, regulatory reviews, and availability of medicinal products to benefit public health [5]. The recent COVID-19 pandemic exposed the need for expedited regulatory pathways designed to accelerate regulatory assessments specifically in LMICs.

Most regulatory submissions are in CTD format when manufacturers submit them for SRA assessment. The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) format is accepted internationally.

CTD Requirements: ICH versus ASEAN

Numerous initiatives aim to harmonize the submission format and contents of market authorization applications of medicinal products to reduce the burden on industry to develop dossiers [6].

ICH developed the ICH CTD as a harmonized format for dossier development to support medicinal product applications submitted to ICH member states [7, 8, 9, 10]. The agreement to compile all information regarding quality, safety, and efficacy into a single format has streamlined regulatory review procedures leading to a uniform electronic submission and thus creating an efficient review procedure. The ICH CTD became the mandatory format for new drug applications submitted to U.S. FDA, European Medicines Agency (EMA), and Japan's Pharmaceuticals and Medical Devices Agency (PMDA). Other countries have accepted and introduced this format in their premarket evaluation and registration of drug products, and WHO uses this format in its dossier submission requirements for prequalification of medicinal products. Although this format and associated guidelines were initially intended for new medicinal products, countries have adopted it for all medicinal products, including generics. **Annex 3** includes a brief description of the various modules of the ICH CTD.

The Association of Southeast Asian Nations (ASEAN) adapted the ICH CTD to generate the ASEAN CTD (ACTD) [11], for medicinal product applications to ASEAN member states (Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, the Philippines, Singapore, Thailand, and Vietnam). The ACTD establishes a standard format for registration that simplifies communication between regulatory bodies and applicants. **Annex 4** includes a brief description of the four parts of the ACTD.

Comparison Between ICH CTD and ACTD

The contents of the two CTD formats are generally the same, but the organization of the content varies. To assist with a review using either submission format, the model dossier compares the two CTD formats and outlines the differences to help a regulator find information easily, regardless of their familiarity with how the specific dossier format is organized. It will also assist a manufacturer in developing a dossier in either format by providing a map showing where each requirement should be organized in the CTD model.

The ICH CTD has 5 modules, and the ACTD consists of parts I through IV. Modules 3 through 5 correspond to parts II through IV, respectively. In the ACTD, the summaries of the quality (part II), nonclinical (part III), and clinical (part IV) are at the beginning of each part of the ACTD sections, and these are in module 2 of the ICH CTD. ACTD does not have an XML backbone

but instead has an overall table of contents and section-specific table of contents similar to what is often seen in the non-eCTD electronic submission format of the ICH CTD.

Annex 5 proposes a model of ICH CTD module 1 (ACTD part I) with the minimum necessary application information that a regulator could adopt without specified module 1 requirements. It is recommended that regional NMRAs work to harmonize module 1 requirements to streamline dossier submissions to multiple countries. The module 1 proposed in the model dossier can be used as template that can be modified during the harmonization efforts.

Annex 6 compares the remaining sections of the two CTD formats to aid regulators and manufacturers in understanding the differences between application dossiers that may be submitted using either format to meet the intended markets' regulatory requirements. Although these are not the exclusive submission formats used globally, they are the most prominent and should be acceptable to any regulator in an emergency or urgent situation.

Facilitated Regulatory Pathways

Enabling Mechanisms

Using FRPs requires carefully considering the available resources and procedural requirements. Regulators created alternate procedural mechanisms to facilitate the demands of FRPs. The following sections describe two mechanisms that global regulators commonly use: presubmission meetings and rolling reviews.

Presubmission Meetings or Requirements

Before receiving application dossier submissions for FRPs, NMRAs may allow or require presubmission meetings or prior approval from the agency to submit a dossier using an FRP. This generally includes submission and discussion of a preliminary data package and risk management plan. This mechanism allows regulators to evaluate the preliminary data and provide input on the dossier to ensure complete submissions and facilitate FRPs.

The criteria and requirements for a presubmission meeting or prior approval for submission will depend on the agency and intended pathway. For example, while the U.S. FDA does not require presubmission activities for their available approval pathways, the agency strongly encourages pre-EUA activities before submitting an EUA application and consultation during product development before an accelerated approval pathway submission [4, 12]. By contrast, requests for expedited pathway designations (fast track, breakthrough therapy, and priority review) do not require consultation before submitting a request [12]. EMA allows an applicant to submit a letter of intent before making an application for conditional marketing authorization, but an applicant is allowed to request a conditional marketing authorization at the time of submission [13]. The Australian Therapeutic Goods Administration's (TGA) newly developed provisional approval pathway encourages a presubmission meeting and requires provisional determination before submitting a dossier for registration [14].

Generally, these strategies are employed during a full review process using an FRP, anticipating exceptions in data requirements (e.g., emergency use or accelerated approval). However, the strategies could be adopted to enable reliance FRPs. NMRAs should use

presubmission communications only if deemed necessary to ensure complete applications or to facilitate an expedited review.

Rolling Review

The rolling review process is a dynamic and adaptable approach that can accelerate the availability of important medicinal products significantly, particularly when timely access is critical. The process has been introduced for various FRPs by Brazilian Anvisa, EMA, Health Canada, Singapore Health Sciences Authority, the U.K. Medicines and Health Care Products Regulatory Agency (MHRA), National Medical Products Administration (NMPA) of China, Japan PMDA, Swissmedic, TGA, U.S. FDA, and WHO [12, 15, 16, 17, 18, 19, 20].

A rolling review consists of multiple rounds of data submission and associated review cycles, allowing a regulator to review key portions of an application before a complete dataset is available. When implementing a rolling review process, regulators should consider several procedural aspects to ensure its effectiveness and efficiency, including:

- **Design and documentation**: Develop clear and comprehensive guidelines and standard operating procedures for the rolling review process. Document key milestones, roles, responsibilities, and decision criteria.
- **Early engagement**: Encourage early engagement with the manufacturer to facilitate a mutual understanding of expectations, data requirements, and timelines. Establish communication channels for ongoing dialogue.
- **Data submission plan**: Specify the format, content, and timeline for data submissions. Ensure that the manufacturer provides data in a structured and organized manner to facilitate efficient review. The submission plan should cover all data planned for submission, and a regulator should be sure that at complete dataset is submitted at the end of the rolling review process.
- **Regular meetings**: Schedule regular meetings between regulators and the manufacturer to discuss progress, address questions, and provide feedback. These meetings can include milestone reviews and issue resolution sessions. Applicants and sponsors may also have access to early consultation with certain agencies.
- **Review timelines**: Establish clear timelines for the review process, including deadlines for data submissions, milestone reviews, and decision-making. Monitor progress and adjust timelines as needed.
- **Prioritization**: Define criteria for prioritizing rolling review applications, especially during public health emergencies. Consider factors such as the medical product's potential to address unmet needs or its relevance to the emergency.
- **Feedback mechanisms**: Implement mechanisms for regulators to provide timely feedback to the manufacturer on data quality, completeness, and compliance with regulatory requirements.
- **Regulatory flexibility**: Allow for regulatory flexibility in data requirements and submission formats to accommodate the dynamic nature of rolling reviews.

Generally, using a rolling review process is necessary only for an FRP without a complete dataset available at submission, which requires providing additional data to the regulators later in the review process or during another review cycle. A rolling review should not be necessary for a reliance FRP because the SRA's review was completed. This does not include any post-approval requirements the approving SRA specified.

Emergency Use Authorization Pathways

EUA Pathways [21]

Full EUA: *Used as the first line of authorization, in which a thorough review of all available data is conducted.*

Abridged EUA: *Used when an SRA evaluated and authorized a product under a full EUA, and an NMRA has the capacity to evaluate specific aspects of the dossier.*

Reliance EUA: *Used when an SRA evaluated and authorized a product under a full EUA, and the regulatory reports are made available to the concerned NMRA.*

Promoting the Quality of Medicines Plus (PQM+), in collaboration with the University of Washington, developed a series of guidance documents focused on EUAs of therapeutics, vaccines, and diagnostics to aid NMRAs as they develop a regulatory framework for EUA pathways and build their capacity for the corresponding regulatory oversight [21, 22, 23]. *Proposed Model to Build Capacity for Emergency Use Authorization for Therapeutics: Guidance for National Medicine Regulatory Authorities* thoroughly reviews important considerations and implementation examples of EUAs for therapeutics with broad applicability [21]. The guidance includes a high-level approach to adopting EUA mechanisms, including the need for establishing a regulatory framework, different pathways to consider, managing authorized products, and the need for additional therapeutics, along with activities an NMRA should undertake before, during, and after a health emergency. This section summarizes portions of the EUA guidance that apply in the context of the model dossier and expands on certain elements concerning post-approval expectations, timeline for authorization, and expectations for transitioning to a full authorization. The model dossier also explains the submission pathways and data packages necessary for timely reviews using FRPs during a health emergency and for unmet medical needs.

The term “emergency use authorization” has been applied broadly to any authorization pathway that is used during a health emergency [21]. The various pathways differ in terminology, scope of use, submission requirements, and approach. This makes it challenging for NMRAs as they develop EUA requirements to align with regional and international regulators and for manufacturers seeking EUA approval in various countries. The EUA models that SRAs implement generally include complete CTD submission requirements, with flexibility in reporting timelines and limited exceptions for post-authorization data submission. These full-review EUA models are not realistic for LMICs, especially considering their resource constraints, so alternate EUA models should be established by NMRAs within LMICs to ensure timely access to quality, safe, and effective treatments.

Expanding on pathways outlined in *Emergency Use Authorization for Therapeutics: Guidance for National Regulatory Authorities* [21], PQM+ compared three EUA models (full EUA, abridged EUA, and reliance EUA) and provides context for when each should be used. The abridged EUA and reliance EUA models specifically are proposed for LMICs’ adoption based on an evaluation of their regulatory framework and capacity. This does not preclude using other reliance mechanisms, such as a collaborative registration procedure or mutual recognition procedure, but the purpose is to help NMRAs clearly outline a specific EUA process that reflects their country’s context.

Criteria for Use of an EUA Pathway

An EUA pathway should be used for an unmet medical need during a public health emergency, including the diagnosis, prevention, or treatment of a disease or condition. Local regulations define the criteria for when to use an EUA pathway and generally requires a public health emergency declaration to justify its use. However, an example of when a pathway used in a public health emergency is available for other contexts or without an emergency declaration includes an EMA-issued conditional marketing authorization intended for treating, preventing, or diagnosing seriously debilitating or life-threatening diseases, including for orphan medicines or during a public health emergency [13]. The WHO Emergency Use Listing Procedure (EUL) lists the following criteria that must be met: [24].

- 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 it is reasonable to consider the product for an EUL assessment—e.g., there are no licensed products for the indication or for a critical subpopulation (e.g., children);
- Existing products have not been successful in eradicating the disease or preventing outbreaks (in the case of vaccines and medicines);
- The product is manufactured in compliance with current good manufacturing practices (GMP) in the case of medicines and vaccines and under a functional quality management system in the case of in vitro devices; and
- The applicant undertakes to complete the development of the product (validation and verification of the product in the case of in vitro devices) and apply for WHO prequalification once the product is licensed.

Risk-Based Considerations

As with any expedited authorization pathway that allows exceptions in the data requirements, a regulator must assess the benefit of immediate availability of the medicinal product versus the risk of an evaluation based on limited data. An NMRA will conduct this benefit–risk assessment during the full evaluation and will guide any post-authorization requirements. Use of the abridged or reliance EUA pathways will also rely on the approving SRA's benefit–risk assessment. An NMRA should not repeat a benefit–risk assessment, but it should understand limitations in the authorization and be aware of the additional data as part of the post-authorization requirements.

When an EUA pathway is used for an unmet medical condition during a public health emergency, the regulatory authority expects a minimal data submission based on the benefit–risk assessment before its approval. The data should follow the ICH CTD or ACTD format, including data on quality, non-clinical, and clinical studies. ICH CTD module 1 (ACTD part I) should include essential information about the medicinal product, its indication, and its proposed use, including a concise summary of the benefit–risk assessment. It should also highlight any additional risk management measures undertaken because of the emergency.

Minimum-quality data includes a concise description of the medicinal product's composition, manufacturing processes, and process controls. It should focus on critical quality and process attributes, analytical procedures, and analytical method validations (specifically for non-compendial methods). If data for long-term stability under recommended temperature conditions are not available, the NMRA should consider data from accelerated studies and stress studies conducted for the active drug substance and medicinal product. The submission should

highlight any deviations or modifications made because of the emergency. A post-authorization commitment should cover any additional manufacturing process validations or long-term stability studies required.

Clinical requirements may be adjusted during a review of a medicinal product when using an EUA pathway. Clinical trials may be combined—for example, a phase 1/2 or phase 2/3 clinical—or conducted in parallel, such as initiating a phase 3 trial before conclusion of the phase 2 trials, based on preliminary or interim trial results. During a typical medicinal product development process, each trial is conducted, completed, and evaluated before progressing to the next phase trial. In addition, regulatory review may be based on preliminary clinical trial data from preplanned interim results. Although an EUA may be issued based on interim clinical trial results, continual review will occur as data are made available and until all clinical requirements are met. During the COVID-19 pandemic, the U.S. FDA issued guidance for the design of clinical trials to support potential medicinal products [25].

Full EUA

The full EUA pathway is used as the first line of authorization, in which a thorough review of all available data is conducted. This type of authorization requires complete data submission with limited exceptions (such as long-term stability data) based on a benefit–risk assessment of the disease and propoposed therapy. Because of resource constraints in LMICs, a full EUA assessment is generally conducted only by SRAs in high income countries. Although a full EUA model is unrealistic for many LMICs to adopt, it is important for regulators in LMICs to understand the approaches and requirements for adopting models that subsequently rely on these assessments. Thus, the following sections summarize key points and include information specifically from International Coalition of Medicines Regulatory Authorities member countries with well-defined and established full EUA pathways for therapeutics, including clear regulatory mandates, processes, submission requirements, and post authorization requirements. (All European Union countries are included under the EMA).

Dossier Requirements

Applicants are expected to fulfill the CTD requirements to the extent possible at submission and should also include details for planned or ongoing studies (particularly clinical studies or stability studies), a rationale for any missing data, and a timeline for submission of pending data. The regulatory agency then conducts a full review, with missing data considered during the overall benefit–risk assessment.

Applicants are also expected to ensure enhanced transparency to health care providers and patients through clear descriptions of the authorized indications and conditions of use. The U.S. FDA uses fact sheets that align with U.S. FDA–approved package inserts or instructions for use [26]. The EMA requires the SmPC and package leaflets to include notification of the conditional marketing status and the specific obligations that will be reviewed annually [13].

Post-Approval expectations

Regulatory agencies have outlined general post-market requirements for EUAs, but additional requirements may be imposed based on the benefit–risk analysis conducted during the assessment process. Generally, applicants are required to continually monitor and report safety and efficacy data from ongoing and long-term clinical trials, in addition to post-authorization risk management and pharmacovigilance plans. A pharmacovigilance plan is required for any therapeutics approval, and it may be expanded for a product granted EUA based on the

available pre-authorization data. Additional EUA-specific post-approval expectations include periodic reporting of real-world safety and efficacy data (Singapore Health Sciences Authority [27]), adverse event reporting via the Yellow Card reporting system (MHRA [28]), and black triangle on the package to encourage patient reporting on adverse events; and an Australia-specific annex to the EMA risk management plan as applicable (TGA [29]).

Abridged EUA

The abridged EUA pathway is used when an SRA has evaluated and authorized a product under a full EUA, and an NMRA has the capacity to evaluate specific aspects of the dossier. Examples of regulators with an abridged EUA pathway include Anvisa, Food and Drug Authority Ghana, MHRA, PMDA, and TGA [14, 28, 30, 31]. NMRAs should not require any changes or additions to the dossier content submitted to the authorizing SRA or WHO, and the aspects reviewed in an abridged EUA assessment should focus on areas of concern in the regional and country contexts (such as stability data or clinical data for specific at-risk populations).

An abridged pathway could also be used if changes between the dossier submitted to the reviewing NMRA and the dossier submitted to the SRA are minimal. Manufacturers should be discouraged from making any changes to dossier content, but NMRAs may allow limited flexibility for health emergencies or unmet medical needs. In this case, regulators should review the changes to ensure that they do not affect the quality, safety, and efficacy of the medicinal product. An application should be rejected if changes in the dossier content are extensive or are likely to affect the quality, safety, or efficacy (for example, a change in excipients to decrease production cost). An NMRA should allow changes only when it has the capacity to adequately assess their impact on the product's quality, safety, or efficacy. **Annex 1** outlines the fundamental dossier requirements.

Reliance EUA

The reliance EUA pathway is used when an SRA has evaluated and authorized a product under a full EUA, and the regulatory reports are made available to the concerned NMRA. Use of this pathway focuses on limiting the number of redundant reviews conducted by NMRAs and providing approval pathways for NMRAs that lack the capacity to review complete dossiers. NMRAs using a reliance EUA pathway should limit review to aspects that specifically affect LMICs (for example, sufficient stability data that reflects their environment), discussed further in the section, *Priority Review Areas for LMICs*. **Annex 1** outlines the fundamental dossier requirements.

Duration of EUA and Mechanism for Transition to Full Approval

Annex 7 summarizes EUA timelines and available mechanisms for transition to full approval in the SRAs described. The duration of authorization does not apply if the granting agency cancels, revokes, or otherwise terminates an EUA before the end of the EUA period. This generally occurs when the benefit–risk assessment is no longer favorable, when the emergency declaration is revoked, or when the product is granted authorization under a full approval pathway.

When using an abridged or reliance EUA pathway, the duration of an EUA will depend on the local regulations, but it should not exceed the timeframe of the authorization granted in the approving SRA. Ideally, an NMRA will follow the same terms and conditions (including duration) as required by the referenced market authorization used for the abridged or reliance EUA.

Full Approval Pathways

Full Approval Pathways [2]

Accelerated approval: Approval is based on surrogate endpoints that are reasonably likely to predict clinical benefit.

Breakthrough therapy designation: Expedites the drug development and review process through early engagement (starting during phase I trials), eligibility for fast track pathway features, and additional agency support. Designation is granted based on preliminary clinical evidence showing improvement in a clinically significant endpoint.

Fast track: Accelerates development processes and review through more frequent agency engagement, rolling review, and eligibility for accelerated approval and priority review.

Priority review: Decreases the approval timeline through application of an expedited review clock.

Note: A product may qualify for one, multiple, or all pathways listed.

Regulatory authorities in developed countries implement various FRPs that are intended to facilitate and expedite development and review of new medicinal products to address unmet medical needs in the treatment of serious or life-threatening conditions. These FRPs help ensure that therapies for serious conditions are available as soon as authorities conclude that the therapies' benefits justify their risks. This depends on the seriousness of the condition and the availability of alternative treatments. Generally, complete datasets are expected as with a regular full approval pathway. Typically, mechanisms such as presubmission meetings and rolling reviews are used to shorten review timelines. If approvals are made while confirmatory data are generated (such as for accelerated approval), the NMRA will continually review the data to ensure that the therapies' benefits continue to justify their risks. The European Federation of Pharmaceutical Industries and Associations compiled a summary of various expedited programs or pathways adopted for products addressing unmet medical needs [32].

For this guidance, FRPs discussed are identified by the following terms:

- Accelerated approval
- BTD (breakthrough therapy designation)
- Fast track
- Priority review

These individual programs (also referred to as designations or pathways as appropriate) may be used concurrently. For example, a medicinal product that receives a fast track designation with the U.S. FDA may also be eligible for accelerated approval or priority review if it meets the specified criteria [12].

Accelerated Approval

Accelerated approval pathways are available from many regulatory authorities, such as U.S. FDA [12], Health Canada (as part of a notice of compliance with conditions pathway [33]), EMA (as part of the conditional approval program [13]), and others of the developed world to ensure that promising medicinal products for serious life-threatening or debilitating illnesses reach

patients in a timely manner through use of surrogate endpoints[3]. *Accelerated approval allows the use of surrogate endpoints that are reasonably likely to predict clinical benefit*. It can take a long time to complete clinical trials that show a new medicinal product's effect on irreversible morbidity or mortality or other clinical benefits compared with standard treatment. This is why surrogate endpoints can be used to evaluate the predicted efficacy of a medicinal product earlier than would be possible if complete clinical trials were required, thus ensuring that promising therapies are available to patients as early as possible. Manufacturers are required to conduct post-marketing trials to verify the medicinal product's clinical benefit.

Information available from regulatory agencies helps drug developers understand the endpoints that have been used successfully in the approval or license of medicinal products. The acceptability of surrogate endpoints for use in medicinal product development programs depends on various factors, such as the disease studied, patient population, therapeutic mechanism of action, and availability of current treatments. Each program is evaluated on a case-by-case basis, and the data required will be specific to the medicinal product and indication.

Breakthrough Therapy Designation

BTD is an approach used to expedite the development and regulatory evaluation of medicinal products intended for the prevention or treatment of serious or life-threatening conditions and those addressing unmet medical needs or improving existing therapies. The process involves providing significantly increased guidance and closer communication between the NMRA and the sponsor or manufacturer during the medicinal product development program as early as phase 1 clinical studies.

Qualifying criteria vary depending on the NMRA but generally center on preliminary evidence using a clinically significant endpoint, as medicinal products are expected to be at the beginning stages of development. For example, the EMA includes the BTD under the priority medicines (PRIME) designation [34], and the sponsors should present proof-of-concept data, early clinical data, or both. Then EMA will actively assist during the drug development program. The U.S. FDA requires clinical data showing improvement over available therapy on clinically significant endpoints [12]. In both cases, the agencies require evidence showing that the medicinal product may demonstrate substantial improvement on at least one clinically significant endpoint measuring an effect on irreversible morbidity or mortality or symptoms that represent serious consequences of the disease. Because of that and to enhance the efficiency of drug development programs, both the EMA and U.S. FDA encourage pharmaceutical companies to request a BTD in parallel with or at any stage throughout the medicinal product development process. However, it is recommended before initiating later-stage clinical trials if preliminary clinical evidence indicates that the product offers advantages over existing treatments. For example, U.S. FDA specifically recommends that BTD is applied for no later than the end-of-phase-2 meetings to benefit from the provisions of BTD [12].

Most benefits of BTD occur before submission of a product dossier, with the intention of decreasing the product development timeline and ensuring that adequate evidence is generated before dossier submission. Although neither BTD's nor PRIME's ultimate intention is to accelerate the product approval process (because regular full approval is expected), the product is likely to qualify for different expedited review pathways such as accelerated approval or priority review. The clinical evidence needed to support BTD is preliminary and therefore not

[3] A surrogate or intermediate clinical endpoint is a laboratory measurement, radiographic picture, physical sign, or other measure that has been established as reasonably likely to predict clinical benefit but is not itself a measure of clinical benefit.

sufficient to establish safety and effectiveness for purposes of marketing authorization approval. The SRA will review the complete data package generated during the medicinal product development to determine whether the medicinal product meets the safety, quality, and efficacy requirements before receiving marketing authorization.

Dossier Requirements

Products that are assisted through a BTD generally submit complete CTDs to support the medicinal product's evaluation unless the medicinal product also qualifies for another pathway such as accelerated approval. Even though NMRAs in LMICs are not encouraged to perform a full review for products that have applied for and received BTD, it is critical to be aware of this pathway that SRAs use in various countries and regions such as China, the European Union, and the United States.

Annex 8 summarizes BTD-relevant information, similarities, and differences in the submission requirements.

Fast Track

A fast track program enables accelerated development processes and review of essential and life-saving new medicinal products or new indications for existing medicinal products.. Fast track is applied to medicinal products being developed for diagnosing, preventing, and/or treating serious conditions for which no existing therapy is available or which may be potentially better that the available product or products in terms of patient tolerance, safety, effectiveness, and quality. Although benefits will vary among regulators, for this definition, benefits of a fast track program include:

1. Increased interactions (meetings and written communications) between manufacturers and regulators in the medicinal product development process.
2. Expanded, iterative, and expedited scientific advice.
3. Early appointment of rapporteur (as applicable to the agency).
4. Eligibility for other expedited review pathways such as accelerated approval or priority review.

Using the fast track program does not alter the submission requirements, and the normal review process is followed unless the product is also granted accelerated approval or priority review (which generally occurs). The EMA will also hold a submission readiness meeting specifically to aid manufacturers in compiling a complete dossier and to address regulatory challenges before dossier submission. The U.S. FDA [12] implemented a fast track program, and EMA's fast track program is called PRIME [34]. Regulatory agencies also use the term "fast track" to define pathways with criteria and benefits that are different from those discussed here. For example, TGA uses "fast track" to refer to both priority review and provisional approval pathways [35].

Priority Review

A priority review program shortens the approval timeline by applying an expedited review clock. For example, U.S. FDA commits to complete a review in six months instead of its standard 10-month review cycle [12]. EMA has provisions for an accelerated assessment of 150 evaluation days versus 210 evaluation days [36]. Medicinal products that received a fast track designation or BTD, or those under evaluation for accelerated approval can also be granted priority review if the relevant criteria are met. Additionally, regulatory authorities such as Health Canada [37],

TGA [35], MHRA [38], and many emerging market countries have also adopted priority review pathways with appropriate procedures and guidelines available.

To meet priority review criteria, the manufacturer should demonstrate that the medicinal product provides a statistically significant and clinically relevant improvement in efficacy or decrease in risk such that the overall benefit–risk profile is improved over existing therapies on the market. For example:

- The medicinal product shows improvement in one or more of the serious outcomes of the condition on which the effect is claimed.
- A beneficial effect is shown on a serious symptom or manifestation of the condition for which there is no existing therapy.
- A clinical benefit is demonstrated for individuals who are unable to tolerate or are unresponsive to existing therapies.
- Combined use with an existing therapy or therapies is not feasible because of safety or efficacy considerations.
- The new medicinal product can provide clinical benefits that are similar to existing therapies but avoid serious toxicity present in existing therapies.

The dossier submission requirements are not altered if a medicinal product is granted priority review, but expedited mechanisms such as a rolling review may be used.

Reliance Pathways

Reliance Pathways [1]

Abridged review: Used when at least one reference or competent benchmark authority has registered a medicinal product, and resources are conserved by not reassessing the full scientific supporting data.

Collaborative procedures for accelerated registration [39]**:** Used when an SRA has approved a medicinal product, or the product is WHO prequalified. Ensures registration within a predefined timeline.

Regional regulatory harmonization [6]**:** Initiatives center on creating standard technical requirements within a region or group of countries. Harmonization efforts support use of reliance by establishing common standards and collaborative networks among NMRAs.

Recognition: An agency automatically accepts a regulatory decision made by another NMRA, SRA, or WHO (e.g., WHO prequalification or EUL decision) without needing additional technical evaluation by the recognizing entity.

A reliance pathway is used when an SRA or another competent NMRA has evaluated and authorized a product, or the product is WHO prequalified, and the regulatory reports are made available to the concerned NMRA.

NMRAs in developed countries use the FRPs outlined in the previous section (specifically accelerated approval, BTD, fast track, and priority review) when conducting full reviews. Because these pathways still require a full review of the dossiers submitted, they are not recommended for LMICs to adopt because it is most efficient to use reliance FRPs to maximize available resources. However, it is important for regulators in LMICs to be aware of the different processes and associated criteria to be assured of the safety, efficacy, and quality of an approved medicinal product, and to understand potential limitations or post-approval

expectations associated with the approval. Any medicinal product that an SRA approved, regardless of the use of an FRP, should qualify for review in an LMIC through one of the reliance FRPs described in this section. **Annex 1** outlines the fundamental dossier requirements for each pathway.

Abridged Review

Abridged review is performed when at least one reference or competent benchmark authority has registered a medicinal product, and resources are conserved by not reassessing the full scientific supporting data. This reliance model focuses on aspects that must be evaluated specifically for the local environment, and an abridged assessment is conducted in relation to the use of the product under local conditions, focusing on aspects of quality (such as stability), benefit–risk assessment for the local medical practice or culture, and patterns of disease.

WHO Collaborative Registration Procedures for Accelerated Registration

To shorten the registration times and maximize limited resources in LMICs, *WHO implemented the collaborative registration procedures (CRP) for accelerated registration* [39] *to register WHO-prequalified* [40] *and SRA-approved medicinal products and make them available to patients within predetermined timelines.* WHO and SRAs have fully assessed medical products for quality, safety, and efficacy before approval or prequalification. In addition, SRAs and WHO use various mechanisms to continue to monitor quality while the medical products are on the market. With CRP, an NMRA can rely on an SRA's or WHO's assessment of the medicinal product and use the data the manufacturer submitted to WHO or SRA. CRP also builds the capacity of NMRAs through exposure to best practices in regulatory systems, inspection approaches, scientific evaluations, and review processes implemented by WHO and SRAs. It also fosters regulatory harmonization by requiring the ICH CTD, eliminating extraneous requirements, streamlining submission to multiple NMRAs, and encouraging collaborative assessment processes in regional networks. CRP is specifically used for medicinal products that SRAs have approved are WHO prequalified.

The WHO CRP process involves sharing assessment reports and inspection outcomes with the NMRA of the country that elected to participate in CRP, allowing more efficient decision-making. An important aspect of CRP is that NMRAs commit to making registration decisions within a specified timeframe after receiving access to the shared information. This collaborative approach enhances efficiency and reduces duplication of regulatory efforts while ensuring that the medicinal products meet international standards. NMRAs must first sign up to participate in the WHO CRP to ensure timely approval and registration of vital essential medicinal products. The steps in the CRP process are as follows:

1. A country's NMRA signs up to participate in CRP.
2. NMRA nominates focal persons who will have access to the WHO secure internet-based platform.
3. Applicants (manufacturers) voluntarily express interest in applying for the procedure.
4. The applicant submits the same dossier as the one that WHO approved for prequalification or approved by an approving SRA as applicable.
5. Applicants authorize WHO or an SRA to share its assessment and inspection outcomes for the specific medicine product or products with the NMRA in which registration is sought.

6. WHO or an SRA shares the assessment and inspection reports with the NMRA via a secure internet-based platform.
7. The designated focal person obtains the information.
8. NMRA makes an independent decision within 90 days after receiving access to the assessment and inspection reports and informs the applicant and WHO or SRA as appropriate within 30 days of their decision.

The NMRAs should confirm the sameness of the dossier submitted, and the applicant or manufacturer should communicate and justify any changes. The NMRA should be alert to possible differences, for example, changes in the excipients that may affect the performance of the finished pharmaceutical product (FPP); sources of the active pharmaceutical ingredient (API), including the manufacturing sites; and primary container materials that may affect the quality of the FPP.

Regional Regulatory Harmonization and Reliance

Regional regulatory harmonization initiatives center on creating standard technical requirements within a region or group of countries, including legislation, regulatory requirements, guidelines, procedures. Harmonization initiatives facilitate reliance mechanisms through common standards established across the member states and collaborative networks that develop trust among NMRAs (e.g., through joint review processes).

The Caribbean Regulatory System is an example of regional harmonization. It uses a regional reliance mechanism that trusts regulatory authorities associated with the Pan American Health Organization (PAHO) and the European Union, and WHO prequalification to accomplish the marketing authorization function more efficiently. The trusted NMRAs play a vital role in providing guidance and expertise to assist the small states in the Caribbean Community to make informed decisions regarding which medicines should be recommended for authorization in the regional market [41].

The Joint Assessment Coordinating Group, formed by the ASEAN Pharmaceutical Products Working Group, facilitates joint reviews of medicinal products for ASEAN member states [42]. This effort allows regulators from different NMRAs to work together, maximize resources, and learn from each other. Various regional harmonization efforts on the African continent have developed similar activities, including the Eastern African Community [43], the Economic Community of West African States [44], and the Southern African Development Community through its regulatory work-sharing initiative ZaZiBoNa [45].

Recognition

Recognition is a reliance pathway by which one NMRA accepts the regulatory decision of another NMRA, SRA, or WHO (e.g., WHO prequalification or EUL decision) without needing additional technical evaluation by the recognizing entity [1]. Recognition can be viewed as a subset or more stringent form of reliance. In most cases, recognition involves reviewing only selected components, such as certificates or reports issued by the trusted NMRA or institution. The foundation of recognition rests upon demonstrating sameness between the regulatory requirements of the reference regulatory authority and those of the relying authority. Recognition represents one of the most expedited review pathways and often demands formal and legally binding provisions. Thus, it is crucial for regulatory authorities to establish recognition agreements that delineate compliance standards while ensuring access to quality-

assured medicines. These agreements also specify the type of recognition applied among the NMRAs, which may be either unilateral or mutual.

Unilateral recognition. In numerous instances, particularly when recognition occurs between a regulatory authority in an LMIC and an SRA or WHO, the nature of this recognition may not be mutual but rather unilateral (without reciprocity). In such cases, a country chooses to formally acknowledge assessments conducted by another NMRA or WHO without a strict requirement for full harmonization of regulations between the relying and the reference regulatory authorities. Trust can be established without an exhaustive examination of the trusted NMRA's capabilities, often relying on reputation because of resource constraints. The WHO Annex 10 on good reliance practices specifies, "The relying authority remains independent, responsible, and accountable for the decisions taken, even when it relies on the decisions, assessments, and information of others" [1, p. 243].

Mutual recognition. Mutual recognition typically relies on formal, legally binding agreements. Establishing these agreements demands a significant investment in time and resources because both regulatory systems might undergo a thorough mutual assessment to demonstrate their equivalency before an agreement can be established successfully. According to the Organisation for Economic Co-operation and Development definition, a mutual recognition agreement is a "principle of international law whereby states party to mutual recognition agreements recognize and uphold legal decisions taken by competent authorities in another member state. Mutual recognition is a process which allows conformity assessments…carried out in one country to be recognized in another country" [46].

These agreements may include specific provisions, such as sectoral annexes pertaining to the mutual recognition of inspections for GMP, and batch certification of both medicinal products and vaccines where relevant. The scope of each agreement can vary and encompass different product and activity categories.

Fully operational mutual recognition agreements allow authorities and their counterparts to:

- Rely on each other's GMP inspection system.
- Share information on inspections and quality defects.
- Waive product batch testing on import into their territories, if applicable [47].

Examples of Applications of Recognition Mechanisms

Applications processed through a reliance or recognition pathway must incorporate a manufacturer-signed assurance of conformity. It attests that the product and its packaging align in every aspect, including but not limited to qualitative and quantitative formulation, the facilities involved in manufacturing both the FPP and the API, stability profiles, summary product characteristics, and labeling, among others. Any deviations or exceptions from the product approved by the regulatory authority on which the mutual recognition agreement relies should be identified explicitly [1]. PAHO issued guidance that includes a sample assurance of sameness letter [48]. Some examples of successful implementation of recognition agreements include the following:

- The European Union introduced the mutual recognition procedure in 1995 to enable member states to mutually recognize marketing authorizations. For years, the results of inspections evaluating GMP have been exchanged under initiatives such as the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme and through mutual recognition agreements [49]. This system relies on a unified

assessment process, allowing assessment reports from any agency within the European Union network to serve as a basis for trust by other regulatory bodies. This arrangement is made possible by a robust, shared legal framework and standardized regulatory criteria to which all European Union countries adhere, fostering a climate of trust and recognition [50].

- The Mexican Federal Commission for Protection against Sanitary Risk unilaterally recognizes marketing authorizations from certain reference regulatory authorities [51].

Importance of the Application of the Recognition Mechanism in LMICs

LMICs should strongly consider collaborating to implement recognition mechanisms, especially within the same region where demonstrating the equivalency of regulatory systems is more feasible. Recognition agreements offer multiple advantages to regulatory authorities, primarily streamlining resource management and minimizing redundant activities such as cross-territory inspections. This optimization allows NMRAs to concentrate on high-risk products and other critical priorities within their jurisdictions. Furthermore, recognition can facilitate pharmaceutical trade, enhancing the availability of medicines to patients by eliminating the need for retesting products upon importation.

Trust serves as a foundational element in the development of recognition agreements, highlighting the importance of countries taking initial steps to establish harmonization tools. These tools may include common international standards, standardized report formats, and information sharing through public availability or communication channels. Before formalizing reliance arrangements, NMRAs could potentially benefit from peer-to-peer work, such as joint inspections and collaborative audits of each other's work. These collective efforts would build confidence in the systems and procedures of the respective NMRAs.

Priority Review Areas for LMICs

When using a reliance FRP, the technical content of the dossier submitted must be the same as what was submitted to the SRA or WHO and should be updated to reflect any post-approval or post-prequalification variations. However, manufacturers may alter certain aspects such as product presentation, labeling, and storage conditions, based on the national or regional requirements, so it is important for NMRAs using reliance pathways to confirm the sameness of the dossier submitted. Some of the critical areas that require confirmation for sameness include but are not limited to the following:

- The composition of the finished medicinal product (qualitative and quantitative).
- The manufacturing sites for the API and the FPP.
- The manufacturing processes for the API and FPP.
- The specifications for the excipient or excipients, API/drug substance, and the FPP.
- The clinical studies, including bioequivalence studies, and the contract research organization site or sites, if applicable.

Any differences between the dossiers should be clearly stated and justified. Areas in which differences could be acceptable include:

- Product presentations but same packaging materials.
- National or regional labeling requirements.

- Storage conditions and shelf life, which is normally based on the zone classification for the country.

The authorizing SRA or WHO should first review and approve variations or amendments to applications before submitting to the NMRA to ensure that the sameness of the product is maintained.

Selection of Approval Pathway

This guidance presented different FRPs used to expedite both drug development and regulatory review of marketing applications by SRAs. However, NMRAs in LMICs are not encouraged to replicate these pathways. Instead, they should become familiar with the FRPs and ensure that they understand the processes and procedures that SRAs use for medicinal product approvals. Medicines approved through FRPs have the same standards as medicines approved under a full review process. These pathways are intended to enable SRAs to collaborate with applicants to generate pertinent data and prioritize the review of applications for drugs that could represent a new therapeutic option for numerous patients.

Advantages of Adopting Facilitated Regulatory Pathways

Timelines are shorter for registration or market authorization processes.

Provides accelerated access to patients with the greatest need for specific medicinal products.

Regulatory efforts are reduced.

Provides assurance/warranty that medicinal products meet international quality, safety, and efficacy standards.

LMICs can focus their resources on high-risk activities.

When considering medicinal product approval in LMICs, an integral aspect is adoption of reliance FRPs that leverage SRA reviews or form agreements with other regional agencies. NMRAs and manufacturers also need to identify and select the most efficient and effective authorization or approval pathway. Some key considerations include:

- The circumstances under which the pathway will be applied, such as during health emergencies or to address unmet medical needs. In such situations, it is important for NMRAs to select the appropriate FRP. Prolonged standard reviews can be detrimental, especially when these medicines could potentially treat or prevent life-threatening conditions, and the population urgently requires access to them before formal approval.
- Whether the legal framework permits the NMRA to use the FRP. As discussed in the *Legal and Regulatory Considerations* section, regulatory authorities must have legal and regulatory instruments to invoke during public health emergencies that enable authorization of new medicinal products or new uses for existing ones. The FRPs available are contingent on the prevailing regulatory framework. For instance, if an EUA process conflicts with existing statutory laws, a country may need to amend the statutory law before implementing an EUA framework.
- The benefit–risk assessment conducted by the SRA and any conditions for authorization or approval. NMRAs should avoid requesting additional information, such as local clinical trials or lot release testing, and instead ensure that applicants are obligated to inform them of any changes in the original approval granted by the authorizing SRA.

Annex 2 includes a decision tree that outlines the suggested FRP to use, considering the eligibility criteria.

Variable Requirements in Structured Product Labeling and SmPC Package Inserts

Many regulatory authorities have regulations and guidelines that outline requirements for SmPC package inserts and SPL for prepackaged medicinal products subject to their acts and regulations. Administration and enforcement of the act or regulations is an important consideration for regulatory authorities, even in emergency or urgent situations.

Ensuring that the SPL and SmPC package insert requirements comply with these requirements is challenging for many regulatory authorities, particularly in cases of EUAs for medicinal products. Regulatory authorities provide guidance to assist in making decisions on labeling and packaging requirements during an emergency. For example, U.S. FDA provides general recommendations and procedures that apply to authorization of the emergency use of certain medicinal products under sections 564, 564A, and 564B of the Federal Food, Drug, and Cosmetic Act as amended, or added by the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 [26]. The act's provisions, described in section II of the guidance, include key legal authorities to sustain and strengthen national preparedness for public health, military, and domestic emergencies involving chemical, biological, radiological, and nuclear agents, including emerging infectious disease threats such as pandemic influenza.

When exporting emergency use drugs to LMICs, the SPL requirements may differ from those for domestic use. It is crucial to consult with legal experts, regulatory authorities, and stakeholders familiar with the destination country's regulations to ensure compliance with local labeling requirements in emergency situations.

The following options and possibilities for product labeling and packaging during the emergency are suggested for LMICs:

- Translation: Ensure that the drug label is translated into the destination country's official language or languages so that health care professionals and patients can understand the information provided and use it properly and safely.
- Essential information: Consider including on the label only the information essential to meeting local requirements, which may involve removing nonessential details to make the label simpler and easier to understand.
- Stick-on labels: Consider using stick-on labels that contain the necessary information per the local requirements instead of completely relabeling the medicine. These labels can be attached to the original packaging, making it easier to comply with specific regulations without extensive relabeling.
- Supplemental inserts: Include supplemental inserts in the packaging or in a pouch attached to the outside of the package that provide necessary information about the drug, including dosage instructions, contraindications, and potential side effects. In certain situations, retail pharmacies disseminate information (approved by regulatory authorities) to patients when dispensing the drug.

- Collaboration with local authorities: Work closely with local regulatory authorities to determine the specific labeling requirements for emergency use drugs in the destination country. Ensure compliance with local regulations while addressing time constraints.
- Clear instructions for use: Ensure that the label provides clear instructions for use, including dosage, administration, and storage conditions, which will help health care professionals and patients use the medication safely, even if it does not meet all other labeling and packaging requirements.
- Documentation in English: Consider including relevant documentation in English in addition to translating the label into the local language. This can facilitate communication and understanding with international organizations, suppliers, or health care professionals who may be involved in the emergency response.

It is essential to consult the NMRA's specific regulatory guidelines and requirements to ensure compliance with the labeling and packaging regulations. Additionally, working closely with the local regulatory authorities and relevant stakeholders can help ensure that the modified label meets all necessary requirements for imported products during a specific emergency.

Annexes 9 through 12 provide overviews of two WHO documents and additional guidance regarding labeling and packaging:

- Summary of the WHO standard SPL requirements for medicines (**Annex 9**).
- Overview of WHO Recommended Patient Information Leaflet (**Annex 10**).
- Provisions and Procedures for Emergency Use Medicines sent to LMICs (**Annex 11**).
- Modifying Label of Medicines for Export to LMICs - Pros and Cons (**Annex 12**).

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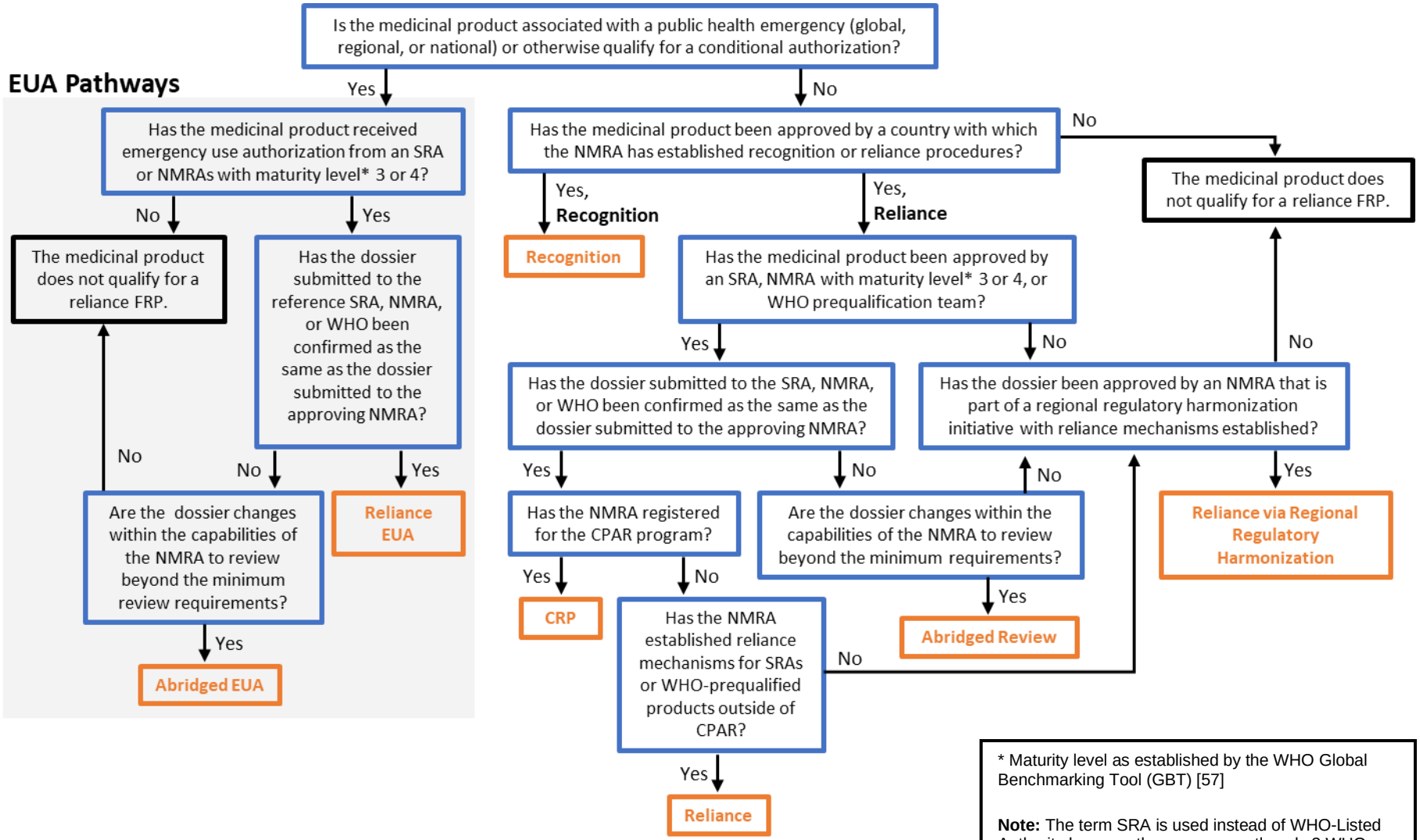
Annex 1: Model Dossier Requirements by Reliance Facilitated Regulatory Pathway

Application Package Contents	Reliance FRPs					
	Reliance EUA	**Abridged EUA**	**Recognition**	**Reliance**	**CRP**	**Abridged Review**
Module 1 (ICH CTD) / part 1 (ACTD); application form	Yes	Yes	Yes	Yes	Yes	Yes
SRA- or WHO-approved package insert	Yes	Yes	Yes	Yes	No †	Yes
SRA- or WHO-approved label *or* fact sheet for product recipients and caregivers and fact sheet for health care providers (as applicable)	Yes	Yes	Yes	Yes	Yes	Yes
Proposed risk management and post-marketing surveillance plans	Yes	Yes	Yes	Yes	No †	Yes
Assurance of sameness	Yes	Yes	Yes	Yes	No †	Yes
Certificate of the responsible SRA's or WHO's decision	Yes	Yes	Yes	Yes	No †	Yes
Assessment reports of the responsible SRA(s) or WHO	Yes	Yes	Yes	Yes	No †	Yes
Evidence of quality and good manufacturing practices compliance (GMP certificate)	No*	Yes	No	No*	No †	Yes
CTD quality, nonclinical, and clinical overviews (module 2 of ICH CTD or parts II–IV of ACTD)	No*	Yes	No	No*	No	Yes
Full dossier as required by national law and/or regulations (e.g., CTD modules 2–5)	No	No	No	No	Yes (same as submitted to SRA or WHO)	No ‡
Minutes from presubmission meeting(s) as applicable	Yes	Yes	No	No	No	No

* These components may be required depending on the level of reliance
† These are made available by the SRA or WHO via CRP procedures
‡ Specific components may be necessary if there have been changes to the dossier

Annex 2: Decision Tree for Reliance Facilitated Regulatory Pathways



* Maturity level as established by the WHO Global Benchmarking Tool (GBT) [57]

Note: The term SRA is used instead of WHO-Listed Authority because there are currently only 3 WHO-listed authorities [58]. They should be considered in the same way as SRAs.

Annex 3: Description of ICH Common Technical Document Organization

Module 1 (Regional)

Module 1 covers administrative and product information specific to each regional requirement, designed by each regulatory authority independently. Information in this module includes a cover letter, table of contents, application form, product information, expert information, environmental risk assessment, pharmacovigilance, and clinical trial information, among others.

Module 2 (Summaries)

Module 2 includes summaries of the data included in module 3 (quality), module 4 (nonclinical), and module 5 (clinical). No single document explains the content of module 2 for the registration of pharmaceuticals for human use. The documents for modules 3, 4, and 5 include a section on the information that must be provided in module 2.

Module 3 (Quality)

Information and data on quality are required under this module. A summary of these data should be included in the quality overall summary (QOS). Some regulatory authorities, including the WHO prequalification program, also require a final quality information summary (QIS) after the review is completed. Many guidelines from various regulatory authorities and WHO are available to aid applicants in appropriately providing information and justification of the quality data on the drug substance and the drug product.

The ICH guideline M4Q(R1) [8] should be consulted to determine the best placement for information in module 3 along with the appropriate references made to the position of the information in alternate sections. This placement of the data will ensure the appropriate location of the information and justification to permit efficient assessment of quality information.

Although most of the countries and regions are using module 3 along with all the relevant guidelines, many countries (particularly LMICs) are still not fully adopting all data requirements. Some of these differences are in process validation, method verification, stability, and product development.

Information on the data requirement in module 3 includes information on the drug substance/API and drug product. The drug product information required in module 3 includes the method of manufacturer, characterization and control of drug substance, reference standards, container closure system, and stability.

The drug substance information is usually available in the drug master file of the API manufacturer. Regulatory authorities expect a complete master file (open/close part) to be available for the assessment of drug substance from the manufacturer of the API or the drug substance. If the master file is not available, this information is required to be submitted in the dossiers under the drug substance. The drug master file system is well established in many SRA countries, WHO, and European Directorate for the Quality of Medicines and Health Care (EDQM). The EDQM, after performing the complete assessment (review, testing, and GMP compliance of the site) issues certification of suitability (CEP). Most LMICs do not have a well-established drug master file review system for drug substance.

The following section summarizes information and the data required for the drug substance:

DRUG SUBSTANCE

S.1 General Consideration/Information

S.2 Manufacture

In general, regulatory authorities expect data on the manufacture of the API, including the facility involved in the manufacture, packaging, and testing, along with their addresses and location. Furthermore, a flow diagram of the synthetic process(es) should be provided that includes chemical structures (reflecting stereochemistry where applicable) of the API starting materials, and intermediates (including reagents and solvents). The level of detail required in the manufacturing description depends on the significance of the process parameters in determining product quality.

S.3 Characterization

Elucidation of structure and other characteristics confirmation of structure, based on the synthetic route and spectral analyses, should be presented, including isomerism and polymorph data interpretation. All information on impurities, including the actual impurity arising from the synthesis and degradation of products using ICH guidelines, should be part of this information.

S.4 Control of Drug Substance

Using the ICH Q6A guideline, the specification of the drug substance, including the critical quality standards as justified by the manufacturer, should be included to control the drug substance. If a manufacturer's standard is used where there is a compendial standard, the controls on purity and potency (i.e., assay) should be at least as stringent as compendial monographs. Where the drug substance is a solvate or a hydrate, specifications for the solvated drug substance should include a range for the percent content by weight of the solvent supported by data.

Specifications are critical quality standards that are proposed and justified by the manufacturer and authorized by regulatory authorities as conditions of acceptance. The assay should be clearly specified as a free acid/base or salt. The specifications should include tests, acceptance criteria, and reference to analytical methods in a manner that clearly identifies the methods used.

Analytical methodologies for testing the drug substance must be supplied. Module 3 should include in-house analytical processes used for regular testing. Although HPLC/UPLC is commonly used to determine drug-related impurities, other chromatographic techniques such as GC and TLC can also be used if suitable and warranted. Analytical validation information, including experimental data for the analytical procedures used for testing the drug substance, should be provided. Validation reports for the analytical procedures employed for routine testing should be included.

S.5 Reference Standards or Materials

Information on the reference standards or reference materials used for testing of the drug substance should be provided. The source(s) of the reference standards or materials used in the testing of the drug substance should be included. Primary reference standards can be obtained from official sources such as those recognized in the compendia.

A secondary reference standard (e.g., working standards) should be standardized against the compendial reference standard or other primary reference standard. The secondary reference standard should be fully characterized to confirm identity (IR and UV spectra), purity, and potency (chromatograms). Copies of certificates of analyses should be provided for the primary and secondary reference materials. If additional purification steps are used to increase the purity of an API for generating a reference standard, this should be described.

S.6 Container Closure System

A description of the container closure system (CCS) should be provided, including identity of materials of construction for the primary packaging and a brief specification. It is generally acceptable to perform identification by IR certificates of compliance from vendors to confirm suitability of the CCS for the proposed drug substance, whether the product is packaged under an inert atmosphere or if desiccants are added, if applicable.

S.7 Stability

The goal of stability testing is to provide data on how the quality of a drug substance fluctuates over time under the effect of various environmental factors such as temperature, humidity, and light to determine a retest/expiry period for the drug substance and storage settings.

ICH stability guidelines provide guidance on conducting stability studies. It is expected that the manufacturer of an API performs stability studies on the drug substance and provide this information to regulators in the drug master file.

P. DRUG PRODUCT

The information and the data required for drug product is summarized below:

P.1 Composition of the Drug Product

Description of the dosage form: Information should include the physical description, strengths, and any other characteristics (for example, “Product is available as a yellow, oval, immediate-release, film-coated tablet, score line on one side, and available in two strengths”).

Composition, i.e., list of all components of the dosage form and their amount on a per unit basis (including overages, if any). The function of the components and the reference to their quality standards (e.g., compendial monographs or manufacturer’s specifications) should be specified. The composition should express the quantity of each component on a per unit basis (e.g.. milligrams (mg) per tablet, mg per milliliter (mL), mg per vial). All components used in the manufacturing process (including water) should be specified.

Any overages used should be clearly indicated. Using an overage amount of drug substance to compensate for degradation during manufacture or a product’s shelf life, or to extend the shelf life, is not acceptable. Overages are allowed only to compensate for any manufacturing losses. Data to support overages should be provided. All components should be identified by their proper or common names and associated quality standards. If an excipient used is available in more than one grade, their grades should be specified.

P.2 Pharmaceutical Development

This section should include information on research and development performed in establishing the proposed dosage form, formulation, manufacturing process, and container closure system, and microbiological attributes. Any extra information relevant to pharmaceutical development or the criticality of a product or process should also be included in the document.

The pharmaceutical development section should comprise aspects that define the drug product's quality target product profile (QTPP) in terms of quality, safety, and efficacy. Typical quality attributes and process parameters vary for different dosage forms. Some attributes could be critical and require additional characterization by the manufacturer on a case-by-case basis.

P.3 Manufacture

The name, address, and responsibility of each manufacturer—including contractors, production sites, and facilities that are involved in manufacturing, packaging, and testing of the finished product—should be clearly specified. The manufacturing facility involved in sterilization of primary container closure systems using gamma radiation should also be included.

P.4 Control of Excipients

The specifications for excipients should be provided. This would include the specifications for all excipients, including processing aids that do not appear in the final drug product (e.g., solvents, nitrogen gas, silicone for stoppers). If the standard claimed for an excipient is a compendial monograph, it is sufficient to state that the excipient is tested according to the requirements of that standard, rather than reproducing the specifications found in the compendial monograph.

If a manufacturer's standard is claimed for compendial API, the testing should be at least as stringent as specified in the monograph. The analytical procedures used for testing the excipients should be provided for the non-compendial monograph. There is no need to submit copies of the monograph in the application. Analytical validation information for an in-house method should be provided. Compendial methods do not require full validation but should include verification of data.

P.5 Control of Drug Product

The drug product's specifications are required and should be provided by the manufacturer of the FPP. Specifications should also include both release and shelf-life specifications for assay. Controls on purity (such as limits on specific degradation products and total degradation products) and potency should be as stringent as the most stringent of those listed in the relevant compendial monographs, particularly when the manufacturer's standard is used. The potency of the active ingredient should be clearly stated as an acid/base or active moiety in the assay.

The specifications of sterile powders and their reconstituted solutions should be provided. In accordance with ICH Q6A, periodic test schedules (also known as skip lot testing) or alternate testing frequencies (also known as sunset testing) that have been proposed for stability study batches should be included.

The risk of a batch failing will determine the number of batches required to support reduced testing (for example, reduced microbial testing for a solid oral product will require less justification than reduced residual solvent testing for granulated products). In the specification discussion, any suggestion for alternate testing frequencies or periodic test schedules should be made with full justification.

P.6 Reference Standards or Materials

Information on the reference standards or reference materials used for testing of the drug product should be provided.

P.7 Container Closure System

A description of the container closure systems should be provided, including the identity of materials of construction of each primary packaging component and specifications. The specifications of the primary packaging in direct contact with the drug product and any secondary packaging should include description, identification, critical dimensions, and drawings, etc.

P.8 Stability

The purpose of stability testing is to provide evidence on how the quality of a drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a shelf life for the drug product and recommended storage conditions.

Module 4 (Safety; nonclinical study reports)

The ICH guideline M4S(R2) [9] should be consulted to determine the best placement for information in module 4 along with the appropriate references made to the position of the information in alternate sections.

Module 4 describes the format and organization of the nonclinical (pharmacotoxicological) data relevant to the application. It comprises three main sections: table of contents, study reports, and literature references. The table of contents lists all the nonclinical study reports and indicates the location of each study report in the CTD format.

The second section (4.2), Study Reports, is made up of three subsections: Pharmacology, Pharmacokinetics, and Toxicology. These subsections also have subsections under them: Pharmacology has four, and Pharmacokinetics and Toxicology each has seven. The section on toxicology has some subsections with sub-subsections. The module ends with the third section for literature references.

Module 5 (Efficacy; clinical study reports)

The ICH guideline M4E(R2) [10] should be consulted to determine the best placement for information in module 5 along with the appropriate references made to the position of the information in alternate sections.

Module 5 should contain all clinical study reports. Section 5.1 includes the table of contents, and section 5.2 includes the tabular listing of all clinical studies. Section 5.3 is broken down into subsections based on the type of clinical study. Section 5.4 is available for any relevant literature references.

The first subsection in section 5.3 is specific to biopharmaceutic studies, including bioavailability, bioequivalence, in vitro-in vivo correlation, and associated analytical methods. The second, third, and fourth subsections should include pharmacokinetic studies using human biomaterials, human pharmacokinetic studies, and human pharmacodynamic studies, respectively. The fifth section should include reports of relevant controlled clinical trials,

uncontrolled clinical trials, analysis of data from multiple trials, and any other clinical studies. The sixth section should include reports of post-marketing experience, and the final section should contain case report forms and individual patient listings.

Annex 4: Description of ASEAN Common Technical Document Organization

Part I: Administrative Data

This section covers the Association of Southeast Asian Nations Common Technical Document's (ACTD) general table of contents. It offers a thorough review of the material contained in each part and contains the Administrative Data area, which includes documents such as application forms, labels, and packaging inserts. Part I concludes with the Product Information section, which contains important information regarding the pharmaceutical product, such as mechanism of action and adverse effects.

Part II: Quality

The purpose of Part II is to ensure that the pharmaceutical product meets the required quality standards. It starts with the Quality Overall Summary, which gives detailed summaries on the quality aspects of the data. This part also contains all the detailed information of the quality aspects of the active pharmaceutical ingredient and product.

Part III: Nonclinical

Part III begins with the Nonclinical Overview of the pharmaceutical product's nonclinical data. The Nonclinical Written Summaries and Nonclinical Tabulated Summaries that follow provide thorough information regarding the nonclinical studies undertaken.

Part IV: Clinical Document

Part IV starts with a Clinical Overview of the pharmaceutical product's clinical data. The Clinical Summary follows, which provides a synopsis of biopharmaceutics, clinical pharmacology investigations, clinical effectiveness, and clinical safety. There are also tabular lists of all clinical trials and clinical study reports, and a list of significant literature references.

Annex 5: Proposed Module 1 (ICH CTD) or Part I (ACTD)

Module 1 / Part I			
Date of Submission:			
Section A: Applicant Information			
Company Name:			
Address:			
Country:			
Telephone:			
Fax:			
Email:			
Section B: Authorized Local Representative Information			
Representative Name:			
Company Name:			
Address:			
Country:			
Telephone:			
Fax:			
Email:			
Section C: Regulatory Action Requested			
Select the applicable regulatory action requested and provide the additional information indicated (as applicable):	[ ]	**New Marketing Authorization**	
	[ ]	**Variation to Existing Authorization**	
		Existing Authorization Reference Number:	
	[ ]	**Renewal of Authorization**	
		Existing Authorization Reference Number:	
	[ ]	**Emergency Use Authorization**	
	[ ]	**Abridged Authorization**	

	[ ]	**Collaborative Registration Procedure**	
		Reference Agency:	
	[ ]	**Reliance**	
		Reference Agency:	
	[ ]	**Regional Reliance**	
		Reference Agency:	
	[ ]	**Mutual Recognition**	
		Reference Agency:	
	[ ]	**Other (Specify):**	

Justification of Approval Pathway

Manufacturing and Marketing Authorization(s)/International Registration Status				
	Please list all applicable	1	2	3
Authorized	Country			
	Date of Authorization			
	Proprietary Name			
	Authorization Number			
Refused	Country			
	Date of Refusal			
	Reason for Refusal			
Withdrawn (by applicant after authorization)	Country			
	Date of Withdrawal			
	Proprietary Name			

	Reason for Withdrawal			
Suspended/revoked (by competent authority)	Country			
	Date of Suspension/Revocation			
	Proprietary Name			
	Reason for Suspension/Revocation			

Section D: Product Information		
Finished Pharmaceutical Product Information		
Proprietary Name		
INN, Common or Nonproprietary Name		
Dosage Form (e.g., tablet, capsule, solution, etc.)		
Strength(s) (e.g., 100 mg, 200 mg)		
Route of Administration (e.g., oral, intravenous, topical, etc.)		
Product Description		
Prescribing Information		
Category of Distribution	[ ]	Prescription Only
	[ ]	Pharmacist-Initiated Medicine
	[ ]	Over-the-Counter Medicine
Nature and Content of Container		
Country of Origin		

Therapeutic Indication(s)	Specified Population
1.	
2.	
3.	
4.	

Manufacturer 1	Name	
	Address:	
	Manufacturing Activities	
	Site Registration/License Number	
Manufacturer 2	Name	
	Address	
	Manufacturing Activities	
	Site Registration/License Number	
Manufacturer 3	Name	
	Address	
	Manufacturing Activities	
	Site Registration/License Number	
Please provide any additional details relevant to the finished pharmaceutical product.		
Active Substance(s) Information		
Active Substance 1	Name	
	Manufacturer	
	Manufacturers Address	
	Grade/Source	
Active Substance 2	Name	
	Manufacturer	
	Manufacturers Address	
	Grade/Source	
Active Substance 3	Name	
	Manufacturer	
	Manufacturers Address	

	Grade/Source	
Active Substance 4	Name	
	Manufacturer	
	Manufacturers Address	
	Grade/Source	
Please provide any additional details relevant to the active substance.		
Storage and Distribution Sites		
Storage Site 1	Name	
	Address	
	Storage Conditions	
	Site Registration/License Number	
Storage Site 2	Name	
	Address	
	Storage Conditions	
	Site Registration/License Number	
Distribution Site 1	Name	
	Address	
	Storage Conditions	
	Site Registration/License Number	
Distribution Site 2	Name	
	Address	
	Storage Conditions	
	Site Registration/License Number	
Please provide any additional details relevant to the storage and distribution sites.		

Section E: Stability		
Description of Shelf-Life Stability Study		
Proposed Shelf Life		
Proposed Shelf Life (after reconstitution or dilution)		
Description of Storage Condition Stability Study		
Proposed Storage Conditions		
Proposed Storage Conditions (after reconstitution or dilution)		
Section F: Attachments		
Proof of Payment of Application Fees	[ ] Yes [ ] No	Additional information:
GMP Certificate(s) of Compliance for All Manufacturing Sites	[ ] Yes [ ] No	Additional information:
Reference Agency Marketing Authorization (as applicable)	[ ] Yes [ ] No	Additional information:
Assessment Reports from Reference Agency (as applicable)	[ ] Yes [ ] No	Additional information:
Proposed Package Insert	[ ] Yes [ ] No	Additional information:
Proposed Label	[ ] Yes [ ] No	Additional information:
	[ ] Yes	Additional information:

Fact Sheet for Product Recipients and Caregivers and Fact Sheet for Health Care Providers (as applicable)	[ ] No	
Assurance of Sameness (as applicable)	[ ] Yes [ ] No	Additional information:
Proposed Risk Management and Post-Marketing Surveillance Plan	[ ] Yes [ ] No	Additional information:
Section G: Declaration		
I hereby declare that the information provided in this application form is accurate and complete to the best of my knowledge. I understand that any false or misleading information may lead to regulatory actions.		
Applicant Signature:		Date:
Please attach all required supporting documents per the Common Technical Document (CTD) format, and include this completed application form with your submission.		

Annex 6: Comparison between ICH CTD and ACTD

Summaries and Overviews

ICH CTD - Module II			ACTD – Parts II, III, IV			
Section	**Sub-section**	**Details**	**Part**	**Section**	**Sub-section**	**Details**
2.1 Common Technical Document Table of Contents (Modules 2-5)	TOC (paper only)		Part II, Part III, Part IV (Section A)			
2.2 CTD Introduction						
2.3 Quality Overall Summary	Introduction		Part II (Section B)			
	2.3.S.1	From 3.2.S.1		S.1	1.1	Nomenclature
					1.2	Structure
					1.3	General Properties
	2.3.S.2	Information on the manufacturer		S.2	2.1	Name and address of the manufacturer
		A brief description of the manufacturing process (including, for example, reference to starting materials, critical steps, and reprocessing) and the controls that are intended to result in the routine and consistent production of material(s) of appropriate quality			2.2	The description of the Drug substance manufacturing process and process control that represents the applicant's commitment for the manufacture of the Drug substances
		A flow diagram, as provided in 3.2.S.2.2				
						Information on the manufacturing process, which typically starts with a vial(s) of the cell bank, and includes cell culture, harvest(s), purification and modification reaction, filling, storage and shipping conditions.

ICH CTD - Module II			ACTD – Parts II, III, IV			
Section	**Sub-section**	**Details**	**Part**	**Section**	**Sub-section**	**Details**
						Flowchart of manufacturing process, Description of batch identification system, Description of inactivation or detoxification process, Description of purification process Stabilization of active ingredient, reprocessing, Filling procedure, in process control
		A description of the Source and Starting Material and raw materials of biological origin used in the manufacture of the drug substance, as described in 3.2.S.2.3			2.3	Starting materials, solvents, reagents, catalysts, and any other materials used in the manufacture of the drugs substance indicating where each material is used in the process. Tests and acceptance criteria of these materials
						Control of source and starting materials of biological origin; Source, history and generation of the cell substrate; Cell banking system, characterization and testing; Viral safety evaluation.
		A discussion of the selection and justification of critical manufacturing steps, process controls, and acceptance criteria. Highlight critical process intermediates, as described in 3.2.S.2.4;			2.4	Critical steps: Tests and acceptance criteria, with justification including quality specifications and experimental data, performed at critical steps of the manufacturing process to ensure that the process is controlled
		A description of process validation and/or evaluation, as described in 3.2.S.2.5.			2.5	Process validation and/or evaluation studies for aseptic processing and sterilization

ICH CTD - Module II			ACTD – Parts II, III, IV			
Section	**Sub-section**	**Details**	**Part**	**Section**	**Sub-section**	**Details**
		A brief summary of major manufacturing changes made throughout development and conclusions from the assessment used to evaluate product consistency, as described in 3.2.S.2.6. The QOS should also cross-refer to the non-clinical and clinical studies that used batches affected by these manufacturing changes, as provided in the CTD-S and CTD-E modules of the dossier.			2.6	Description and discussion of significant changes made to the manufacturing process and/or manufacturing site of the Drug substance used in producing non-clinical, clinical, scale-up, pilot and if available, production scale batches.
						The development history of the manufacturing process as described in S 2.2.
	2.3.S.3	A summary of the interpretation of evidence of structure and isomerism, as described in 3.2.S.3.1, should be included. When a drug substance is chiral, it should be specified whether specific stereoisomers or a mixture of stereoisomers have been used in the nonclinical and clinical studies, and information should be given as to the stereoisomer of the drug substance that is to be used in the final product intended for marketing.		S.3	3.1	Confirmation of structure based on e.g., synthetic route and spectral analyses.
		A description of the desired product and product-related substances and a summary of general properties, characteristic features and characterisation data (for example, primary and higher order structure and biological activity), as described in 3.2.S.3.1, should be included.				Compendial requirements or appropriate information from the manufacturer; Details on primary, secondary and higher-order structure and information on biological activity, purity and immunochemical properties (when relevant).

ICH CTD - Module II			ACTD – Parts II, III, IV			
Section	**Sub-section**	**Details**	**Part**	**Section**	**Sub-section**	**Details**
		The QOS should summarise the data on potential and actual impurities arising from the synthesis, manufacture and/or degradation, and should summarise the basis for setting the acceptance criteria for individual and total impurities. The QOS should also summarise the impurity levels in batches of the drug substance used in the non-clinical studies, in the clinical trials, and in typical batches manufactured by the proposed commercial process. The QOS should state how the proposed impurity limits are qualified.			3.2	Summary of impurities monitored or tested for during and after manufacture of drug substance
		A tabulated summary of the data provided in 3.2.S.3.2, with graphical representation, where appropriate should be included.				
	2.3.S.4	A brief summary of the justification of the specification(s), the analytical procedures, and validation should be included.		S.4	4.1	
	2.3.S.5	Information from 3.2.S.5 (tabulated presentation, where appropriate) should be included.		S.5		Information on the reference standards or reference materials used for testing of the Drug substance.
						Compendial reference standard
	2.3.S.6	A brief description and discussion of the information, from 3.2.S.6 should be included.		S.6		Descriptions of the container closure systems.
	2.3.S.7	This section should include a summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions, the proposed storage conditions, retest date or shelf-life,		S.7		Stability Summary and conclusion

ICH CTD - Module II			ACTD – Parts II, III, IV			
Section	**Sub-section**	**Details**	**Part**	**Section**	**Sub-section**	**Details**
		where relevant, as described in 3.2.S.7.1.				
		The post-approval stability protocol, as described in 3.2.S.7.2, should be included.				Post approval stability protocol and stability commitment
		A tabulated summary of the stability results from 3.2.S.7.3, with graphical representation where appropriate, should be provided.				Stability Data
	2.3.P.1	Information from 3.2.P.1 should be provided		P.1		Dosage form and characteristics
						Accompanying reconstitution diluent (s) if any.
						Type of container and closure used for the dosage form and reconstitution diluent (s), if applicable.
		Composition from 3.2.P.1 should be provided				Name, quantity stated in metric weight or measures, function and quality standard reference.
	2.3.P.2	A discussion of the information and data from 3.2.P.2 should be presented.		P.2	2.1	Data on the development studies conducted to establish that the dosage form, formulation, manufacturing process, container closure system, microbiological attributes and usage instruction are appropriate for the purpose specified in the application.
					2.2	Active ingredient: Justification of the compatibility of the active ingredient with excipients listed in P1. In case of combination products, justification of the compatibility of active ingredients with each other.
						Literature data

ICH CTD - Module II			ACTD – Parts II, III, IV			
Section	**Sub-section**	**Details**	**Part**	**Section**	**Sub-section**	**Details**
						Excipients: Justification of the choice of excipients listed in P1, which may influence the drug product performance.
					2.3	Formulation Development: A brief summary describing the development of the finished product, (taking into consideration the proposed route of administration and usage for NCE and Biologics).
						Overages: Justification of any overage in the formulation(s) described in P1.
						Physicochemical and Biological Properties: Parameters relevant to the performance of the finished product e.g., pH, dissolution
					2.4	Selection and optimization of the manufacturing process
						Differences between the manufacturing process(es) used to produce pivotal clinical batches and the process described in P.3.2, if applicable
					2.5	Suitability of the container closure system used for the storage, transportation (shipping) and use of the finished product.
					2.6	Microbiological attributes of the dosage form, where appropriate
					2.7	Compatibility of the finished product with reconstitution diluent(s) or dosage devices. Literature data
	2.3.P.3	Information on the manufacturer		P.3	3.1	Name, address, and responsibilities of each manufacturer involved
					3.2	Name and quantities of all ingredients

ICH CTD - Module II			ACTD – Parts II, III, IV			
Section	**Sub-section**	**Details**	**Part**	**Section**	**Sub-section**	**Details**
		A brief description of the manufacturing process and the controls that are intended to result in the routine and consistent production of product of appropriate quality.			3.3	Description of manufacturing process and process control
					3.4	Tests and acceptance criteria
		A brief description of the process validation and/or evaluation, as described in 3.2.P.3.5			3.5	Description, documentation, and results of the validation and/or evaluation studies for critical steps or critical assays used in the manufacturing process.
						Viral safety information
		A flow diagram, as provided under 3.2.P.3.3				
	2.3.P.4	A brief summary on the quality of excipients, as described in 3.2.P.4, should be included.		P.4	4.1	Specifications for excipients
						Compendial requirements or appropriate information from the manufacturer
					4.2	Analytical procedures used for testing excipients where appropriate.
						Compendial requirements or appropriate information from the manufacturer
					4.3	Information regarding sources and or adventitious agents.
						Compendial requirements or appropriate information from the manufacturer

ICH CTD - Module II			ACTD – Parts II, III, IV			
Section	**Sub-section**	**Details**	**Part**	**Section**	**Sub-section**	**Details**
					4.4	For excipient(s) used for the first time in a finished product or by a new route of administration, full details of manufacture, characterization and controls, with cross reference to supporting safety data (non-clinical or clinical)
	2.3.P.5	A brief summary of the justification of the specification(s); Specification(s) from 3.2.P.5.1 should be provided		P.5	5.1	The specification(s) for the finished product.
		a summary of the analytical procedures and validation			5.2	Analytical procedures used for testing the finished product
					5.3	Information including experimental data, for the validation of the analytical procedure used for testing the finished product
						Non-compendial method
						Verification of compendial method applicability - precision & accuracy
					5.4	Description and test results of all relevant batches.
						Summary protocol of the production and control
		Characterisation of impurities should be provided.			5.5	Information on the characterisation of impurities
						Compendial requirements or appropriate information from the manufacturer
					5.6	Justification of the proposed finished product specification(s)
						Compendial requirements or appropriate information from the manufacturer

ICH CTD - Module II			ACTD – Parts II, III, IV			
Section	**Sub-section**	**Details**	**Part**	**Section**	**Sub-section**	**Details**
		A tabulated summary of the batch analyses provided under 3.2.P.5.4, with graphical representation where appropriate should be included.				
	2.3.P.6	Information from 3.2.P.6 (tabulated presentation, where appropriate) should be included.		P.6		Information on the reference standards or reference materials used for testing of the finished product.
						Compendial requirements or appropriate information from the manufacturer
	2.3.P.7	A brief description and discussion of the information in 3.2.P.7 should be included.		P.7		Specification and control of primary and secondary packaging material, type of packaging and the package size, details of packaging inclusion (e.g. desiccant, etc.)
	2.3.P.8	A summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions of the stability studies and analysis of data should be included.		P.8		Stability Summary and conclusion
		The post-approval stability protocol, as described in 3.2.P.8.2, should be provided				Commitment on post approval stability and monitoring
		Conclusions with respect to storage conditions and shelf-life and, if applicable, in-use storage conditions and shelf-life should be given.				Stability report : data demonstrating that product is stable through its proposed shelf life.
						Description of procedures to guarantee cold chain (where applicable)
		A tabulated summary of the stability results from 3.2.P.8.3, with graphical representation where appropriate, should be included.				

ICH CTD - Module II			ACTD – Parts II, III, IV			
Section	**Sub-section**	**Details**	**Part**	**Section**	**Sub-section**	**Details**
				P.9		In Vitro Comparative dissolution study as required
						In Vivo Bioequivalence study as required
	2.3.A.1	A summary of facility information described under 3.2.A.1 should be included.				
	2.3.A.2	A discussion on measures implemented to control endogenous and adventitious agents in production should be included.		A.1		A discussion on measures implemented to control endogenous and adventitious agents in production should be included.
		A tabulated summary of the reduction factors for viral clearance from 3.2.A.2, should be provided				A tabulated summary of the reduction factors for viral clearance, should be provided.
	2.3.A.3	Excipients				
	2.3.R	A brief description of the information specific for the region, as provided under "3.2.R" should be included, where appropriate.				
2.4 Nonclinical Overview		General Aspects	Part III (Section B)	1.1		General Aspects
		Content and Structural Format		1.2		Content and Structural Format
2.5 Clinical Overview	2.5.1	Product Development Rationale	Part IV (Section B)	1		Product Development Rationale
	2.5.2	Overview of Biopharmaceutics		2		Overview of Biopharmaceutics
	2.5.3	Overview of Clinical Pharmacology		3		Overview of Clinical Pharmacology
	2.5.4	Overview of Efficacy		4		Overview of Efficacy
	2.5.5	Overview of Safety		5		Overview of Safety
	2.5.6	Benefits and Risk Conclusions		6		Benefits and Risk Conclusions
	2.5.7	Literature References				
2.6 Nonclinical Written and Tabulated Summaries		Introduction	Part III (Section C)	1.1		Introduction

ICH CTD - Module II			ACTD – Parts II, III, IV			
Section	**Sub-section**	**Details**	**Part**	**Section**	**Sub-section**	**Details**
		General Presentation Issues		1.2		General Presentation Issues
	2.6.1	Introduction				
	2.6.2	Pharmacology Written summary		2.1	2.1.1	Pharmacology written summary
	2.6.3	Pharmacology Tabulated Summary (see Appendix B)			2.1.2	Pharmacology Tabulated Summary (See Appendix A)
	2.6.4	Pharmacokinetics Written Summary		2.2	2.2.1	Pharmacokinetics Written Summary
	2.6.5	Pharmacokinetics Tabulated Summary (see Appendix B)			2.2.2	Pharmacokinetics Tabulated Summary (see Appendix A)
	2.6.6	Toxicology Written Summary		2.3	2.3.1	Toxicology Written Summary
	2.6.7	Toxicology Tabulated Summary (see Appendix B)			2.3.2	Toxicology Tabulated Summary (see Appendix A)
2.7 Clinical Summary	2.7.1	Biopharmaceutic Studies and Associated Analytical Methods	Part IV (Section C)	1		Biopharmaceutic Studies and Associated Analytical Methods
	2.7.2	Clinical Pharmacology Studies		2		Clinical Pharmacology Studies
	2.7.3	Clinical Efficacy		3		Clinical Efficacy
	2.7.4	Clinical Safety		4		Clinical Safety
	2.7.5	Literature References				
	2.7.6	Synopses of Individual Studies		5		Synopses of Individual Studies

For additional details on differences with the nonclinical and clinical aspects for the overview and summary information, see the nonclinical and clinical sections that follow.

Quality

ICH CTD - Module 3					ACTD - Part II			
Section	**Sub-section**			**Details**	**Section**	**Sub-section**		**Details**
3.1	TOC (paper only)				A			
3.2	3.2S	3.2.S.1	3.2.S.1.1	Nomenclature	C	S.1	S.1.1	Nomenclature
			3.2.S.1.2	Structure			S.1.2	Structural formula
			3.2.S.1.3	General properties			S.1.3	General Properties
		3.2.S.2	3.2.S.2.1	Manufacturer(s)		S.2	S.2.1	Manufacturer(s)
			3.2.S.2.2	Description of Manufacturing Process and Process Controls			S.2.2	Description of Manufacturing Process and Process Controls
			3.2.S.2.3	Control of Materials			S.2.3	Control of Materials
			3.2.S.2.4	Controls of Critical Steps and Intermediates			S.2.4	Controls of Critical Steps and Intermediates
			3.2.S.2.5	Process Validation and/or Evaluation			S.2.5	Process Validation and/or Evaluation
			3.2.S.2.6	Manufacturing Process Development			S.2.6	Manufacturing Process Development
		3.2.S.3	3.2.S.3.1	Elucidation of Structure and other Characteristics		S.3	S.3.1	Elucidation of Structure and Characteristic
			3.2.S.3.2	Impurities			S.3.2	Impurities
		3.2.S.4	3.2.S.4.1	Specification		S.4	S.4.1	Specification
			3.2.S.4.2	Analytical Procedures			S.4.2	Analytical Procedures
			3.2.S.4.3	Validation of Analytical Procedures			S.4.3	Validation of Analytical Procedures
			3.2.S.4.4	Batch Analyses			S.4.4	Batch Analyses
			3.2.S.4.5	Justification of Specification			S.4.5	Justification of Specification

ICH CTD - Module 3					ACTD - Part II			
Section	**Sub-section**			**Details**	**Section**	**Sub-section**		**Details**
		3.2.S.5		Reference standards or materials		S.5		Reference Standards or Materials
		3.2.S.6		Container closure systems		S.6		Container Closure System
		3.2.S.7	3.2.S.7.1	Stability Summary and Conclusions		S.7	S.7.1	Stability Summary and Conclusion
			3.2.S.7.2	Post Approval Stability Protocol and Stability Commitment			S.7.2	Post-approval Stability Protocol and Stability Commitment
			3.2.S.7.3	Stability Data			S.7.3	Stability Data
	3.2.P			Drug product [name, dosage form, manufacturer]		P		Drug Product
		3.2.P.1		Description and composition of the drug product		P 1		Description and Composition
		3.2.P.2		Pharmaceutical development		P 2		Pharmaceutical Development
							P 2.1	Information on Development Studies
							P 2.2	Component of Drug Product
							P 2.3	Finished Product
							P 2.4	Manufacturing Process Development
							P 2.5	Container Closure System
							P 2.6	Microbiological Attributes
							P 2.7	Compatibility
		3.2.P.3		Manufacture		P 3		Manufacturer
			3.2.P.3.1	Manufacturer(s)				Manufacturer(s)
			3.2.P.3.2	Batch Formula			P 3.1	Batch Formula
			3.2.P.3.3	Description of Manufacturing Process and Process Controls			P 3.2	Manufacturing Process and Process Control

ICH CTD - Module 3					ACTD - Part II			
Section	**Sub-section**			**Details**	**Section**	**Sub-section**		**Details**
			3.2.P.3.4	Controls of Critical Steps and Intermediates			P 3.3	Controls of Critical Steps and Intermediates
			3.2.P.3.5	Process Validation and/or Evaluation			P 3.4	Process Validation and/or Evaluation
		3.2.P.4		Control of excipients [name]		P 4		Control of Excipients
			3.2.P.4.1	Specification(s)			P 4.1	Specification
			3.2.P.4.2	Analytical Procedures			P 4.2	Analytical Procedures
			3.2.P.4.3	Validation of Analytical Procedures				
			3.2.P.4.4	Justification of Specifications				
			3.2.P.4.5	Excipients of Human or Animal Origin			P 4.3.	Excipients of Human and Animal Origin
			3.2.P.4.6	Novel Excipients			P 4.4	Novel Excipients
		3.2.P.5		Control of drug product		P 5		Control of Finished Product
			3.2.P.5.1	Specification(s)			P 5.1	Specification
			3.2.P.5.2	Analytical Procedures			P 5.2	Analytical Procedures
			3.2.P.5.3	Validation of Analytical Procedures			P 5.3	Validation of Analytical Procedures
			3.2.P.5.4	Batch Analyses			P 5.4	Batch analyses
			3.2.P.5.5	Characterization of Impurities			P 5.5	Characterization of Impurities
			3.2.P.5.6	Justification of Specification(s)			P 5.6	Justification of Specification
		3.2.P.6		Reference standards or materials		P 6		Reference Standards or Materials
		3.2.P.7		Container closure system		P 7		Container closure system
		3.2.P.8		Stability		P 8		Product Stability
			3.2.P.8.1	Stability Summary and Conclusion				Stability Summary and Conclusion
			3.2.P.8.2	Post approval Stability				Post-approval stability protocol and stability commitment
								Stability Data
						P 9		Product Interchangeability

Nonclinical

ICH CTD - Module 4						ACTD - Part III				
Section	**Sub-section**	**Sub-section**	**Details**	**Sub-section**	**Details**	**Section**	**Sub Section**	**Sub Section**	**Sub Section**	**Details**
4.1	TOC (paper only)					A	TOC			
4.2	4.2.1 Pharmacology	4.2.1.1			Primary Pharmacodynamics	D	2 Pharmacology	2.1.1		Primary Pharmacodynamics / Immunogenicity Study
		4.2.1.2			Secondary Pharmacodynamics			2.1.2		Secondary Pharmacodynamics
		4.2.1.3			Safety Pharmacology			2.1.3		Safety Pharmacology
		4.2.1.4			Pharmacodynamic Drug Interactions			2.1.4		Pharmacodynamic Drug Interactions
	4.2.2 Pharmacokinetics	4.2.2.1			Analytical Methods and Validation Reports (if separate reports are available)		3 Pharmacokinetics	3.1.1		Analytical Methods and Validation Reports
		4.2.2.2			Absorption			3.1.2		Absorption
		4.2.2.3			Distribution			3.1.3		Distribution
		4.2.2.4			Metabolism			3.1.4		Metabolism (Inter-species Comparison)
		4.2.2.5			Excretion			3.1.5		Excretion
		4.2.2.6			Pharmacokinetic Drug Interactions (nonclinical)			3.1.6		Pharmacokinetic Drug Interaction (Nonclinical)
		4.2.2.7			Other Pharmacokinetic Studies			3.1.7		Other Pharmacokinetic Studies
	4.2.3 Toxicology	4.2.3.1			Single-Dose Toxicity (in order by species, by route)		4 Toxicology	4.1.1		Single-Dose Toxicity
		4.2.3.2			Repeat-Dose Toxicity			4.1.2		Repeat-Dose Toxicity
		4.2.3.3	Genotoxicity					4.1.3		Genotoxicity
				4.2.3.3.1	In vitro				4.1.3.1	In-vitro Reports

ICH CTD - Module 4						ACTD - Part III				
Section	**Sub-section**	**Sub-section**	**Details**	**Sub-section**	**Details**	**Section**	**Sub Section**	**Sub Section**	**Sub Section**	**Details**
				4.2.3.3.2	In vivo (including supportive toxicokinetic evaluations)				4.1.3.2	In-vivo Reports
		4.2.3.4	Carcinogenicity (including supportive toxicokinetic evaluations)					4.1.4		Carcinogenicity
				4.2.3.4.1	Long-term studies				4.1.4.1	Long Term Studies
				4.2.3.4.2	Short- or medium-term studies				4.1.4.2	Short or Medium Term Studies
				4.2.3.4.3	Other studies				4.1.4.3	Other Studies
		4.2.3.5	Reproductive and Developmental Toxicity					4.1.5		Reproductive and Developmental Toxicity
				4.2.3.5.1	Fertility and early embryonic development				4.1.5.1	Fertility and Early Embryonic Development
				4.2.3.5.2	Embryo-fetal development				4.1.5.2	Embryo-Foetal Development
				4.2.3.5.3	Prenatal and postnatal development, including maternal function				4.1.5.3	Prenatal and Postnatal Development
				4.2.3.5.4	Studies in which the offspring (juvenile animals) are dosed and/or further evaluated.				4.1.5.4	Studies in which the Offspring Are Dosed and/or Further Evaluated
		4.2.3.6	Local Tolerance					4.1.6		Local Tolerance
		4.2.3.7	Other Toxicity Studies (if available)					4.1.7		Other Toxicity Studies (if available)

ICH CTD - Module 4						ACTD - Part III				
Section	**Sub-section**	**Sub-section**	**Details**	**Sub-section**	**Details**	**Section**	**Sub Section**	**Sub Section**	**Sub Section**	**Details**
				4.2.3.7.1	Antigenicity				4.1.7.1	Antigenicity
				4.2.3.7.2	Immunotoxicity				4.1.7.2	Immunotoxicity
				4.2.3.7.3	Mechanistic studies (if not included elsewhere)					
				4.2.3.7.4	Dependence				4.1.7.3	Dependence
				4.2.3.7.5	Metabolites				4.1.7.4	Metabolites
				4.2.3.7.6	Impurities				4.1.7.5	Impurities
				4.2.3.7.7	Other				4.1.7.6	Other
4.3	Literature References					Section E	LIST OF KEY LITERATURE REFERENCES			

The following sections provide additional clarification for the comparison between the ICH CTD and ACTD regarding the nonclinical sections. The comparison shows very few differences.

Nonclinical Overview: *ICH Module 2.4 and ASEAN Part III Section B*

The difference found in the nonclinical overview is in the introduction to the subsections. ICH states that the number of pages for the section should not exceed 30, but ACTD does not mention the number of pages.

The second difference is in within the Content and Structural Format section. ICH refers to the last part of the structural format as a ***list of literature references,*** and ASEAN calls it a ***list of literature citations***.

Nonclinical Summary: *ICH Module 2.6 and ASEAN Part III Section C*

The ACTD and ICH CTD both require the same infrmoation however they are organized slightly differently. For example, the ICH CTD has separate sections for Pharmcology Written Summary (2.6.2) and Pharmacology Tabulated Summary (2.6.3), whereas the ACTD has an overall Pharmacology section (2.1) with subsections for the Written Summary (2.1.1) and Tabulated Summary (2.1.2).

In the Nonclinical Tabulated Summaries section, the recommended formats for the tables in this section are provided in Appendixes B and C for ICH, and ACTD presents these formats in Appendix A. The ICH Appendix B contains templates for preparing the tables, and Appendix C includes examples of the summary tables. ACTD does not mention examples of summary tables.

Nonclinical Reports: *ICH Module 4 and ASEAN Part III, Section D*

The ACTD states, “For ASEAN member countries, the Study Reports of this part may not be required for NCE [New Chemical Entity], Biotechnological Products and other Major Variation Products if the Original Products are already registered and approved for market authorization in Reference Countries” [11, pp. 4–5]. The ICH guideline does not make such requirements.

The ACTD does not require literature references in this section, though section 4.3 is titled ***Literature References*.**

Clinical

ICH CTD - Module 5				ACTD - Part IV			
Section	**Sub-section**		**Details**	**Section**	**Sub-section**		**Details**
5.1			Table of Contents	A			Table of Contents
5.2			Tabular Listing of All Clinical Studies	D			Tabular Listing of All Clinical Studies
5.3	5.3.1	5.3.1.1	Bioavailability (BA) Study Reports	E	1	1.1	Bioavailability (BA) Study Reports
		5.3.1.2	Comparative BA and Bioequivalence (BE) Study Reports			1.2	Comparative BA and Bioequivalence (BE) Study Reports
		5.3.1.3	In Vitro – In Vivo Correlation Study Reports			1.3	In Vitro – In Vivo Correlation Study Reports
		5.3.1.4	Reports of Bioanalytical and Analytical Methods for Human Studies			1.4	Reports of Bioanalytical and Analytical Methods for Human Studies
	5.3.2	5.3.2.1	Plasma Protein Binding Study Reports		2	2.1	Plasma Protein Binding Study Reports
		5.3.2.2	Reports of Hepatic Metabolism and Drug Interaction Studies			2.2	Reports of Hepatic Metabolism and Drug Interaction Studies
		5.3.2.3	Reports of Studies Using Other Human Biomaterials			2.3	Reports of Studies Using Other Human Biomaterials

ICH CTD - Module 5				ACTD - Part IV			
Section	**Sub-section**		**Details**	**Section**	**Sub-section**		**Details**
	5.3.3	5.3.3.1	Healthy Subject PK and Initial Tolerability Study Reports		3	3.1	Healthy Subject PK and Initial Tolerability Study Reports
		5.3.3.2	Patient PK and Initial Tolerability Study Reports			3.2	Patient PK and Initial Tolerability Study Reports
		5.3.3.3	Intrinsic Factor PK Study Reports				
		5.3.3.4	Extrinsic Factor PK Study Reports				
		5.3.3.5	Population PK Study Reports			3.3	Population PK Study Reports
	5.3.4	5.3.4.1	Healthy Subject PD and PK/PD Study Reports		4	4.1	Healthy Subject PD and PK/PD Study Reports
		5.3.4.2	Patient PD and PK/PD Study Reports			4.2	Patient PD and PK/PD Study Reports
	5.3.5	5.3.5.1	Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication		5	5.1	Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
		5.3.5.2	Study Reports of Uncontrolled Clinical Studies			5.2	Study Reports of Uncontrolled Clinical Studies
		5.3.5.3	Reports of Analyses of Data from More than One Study			5.3	Reports of Analyses of Data from More than One Study
		5.3.5.4	Other Clinical Study Reports			5.4	Other Clinical Study Reports
	5.3.6		Reports of Post-Marketing Experience				
	5.3.7		Case Report Forms and Individual Patient Listings				
5.4			Literature Reference	F			List of Key Literature References

A comparison between the ICH CTD and ACTD as it relates specifically to the clinical components shows very few, though distinct, differences between the two formats. The following section discusses the differences in the clinical overview, clinical summary, and clinical reports sections.

Clinical Overview: *ICH Module 2.5 and ASEAN Part IV, Section B*

One major difference in this section is in the Benefits and Risks Conclusions (ICH 2.5.6; ASEAN IV.B.6). Along with the sections found in the ACTD, the ICH CTD expanded the section with additional subsections, as follows:

2.5.6.1 Therapeutic Context

2.5.6.1.1 Disease or Condition

2.5.6.1.2 Current Therapies

2.5.6.2 Benefits

2.5.6.3 Risks

2.5.6.4 Benefit–Risk Assessment

A few minor additions in the ICH CTD requirements center mostly on data specific to the region, the intended population, or a foreign population. The following are specific additions to the ICH CTD by section with the corresponding ACTD section indicated.

- Section 2.5.1 (ICH) and IV.B.1 (ASEAN)
  - "Include a brief overview of the major therapies currently used in the intended population" [10, p. 2]
  - "Briefly describe plans for the use of foreign clinical data (ICH E5)" [10, p. 2].
  - "Regulatory guidance and advice (at least from the region(s) where the Clinical Overview is being submitted) should be identified, with discussion of how that advice was implemented. Formal advice documents (e.g., official meeting minutes, official guidance, letters from regulatory authorities) should be referenced, with copies included in the references section of module 5" [10, p. 2].
- Section 2.5.4 (ICH) and IV.B.4 (ASEAN)
  - "Support for the applicability to the new region of data generated in another region, where appropriate (ICH E5)" [10, p. 4].
- Section 2.5.5 (ICH) and IV.B.5 (ASEAN)
  - "Support for the applicability to the new region of data generated in another region, where appropriate (ICH E5)" [10, p. 5].

Clinical Summary*: ICH Module 2.7 and ASEAN Part IV, Section C*

One major difference between the two CTDs is in section 2.7.4.5 (ICH) and IV.C.4.5 (ASEAN). The ICH CTD includes two additional sections on Intrinsic Factors (2.7.4.5.1) and Extrinsic Factors (2.7.4.5.2), and the ACTD includes a section on Patient Groups (IV.C.4.5.1)

The clinical summary section also has three minor additions in the ICH CTD compared with the ASEAN CTD:

- Section 2.7.2.3 (ICH) and IV.C.2.3 (ASEAN)
  "PK studies that were performed to determine whether foreign clinical data could be extrapolated to the new region (see ICH E5). The result of the studies and analysis of the similarity of the PK data between regions or races should be summarized in

this section. Such studies that use PD biomarkers (but do not evaluate clinical efficacy) may similarly be summarized here. An independent subsection can be created to summarize these kinds of data" [10, p. 15].

- Section 2.7.3.2 (ICH) and IV.C.3.2 (ASEAN)
  "Narratives of any bridging studies using clinical endpoints, i.e., certain studies intended to evaluate the ability to extrapolate certain types of foreign clinical data to the new region (see ICH E5), should be included in this section. An analysis of the results of such studies, together with other information (e.g., PK and PD data) that addresses the ability to extrapolate the efficacy and safety results of foreign studies, should be performed if necessary. The conclusions of such an analysis should be noted at the start of Section 2.7.3.3.2, Comparison of Efficacy Results of All Studies, and the full report of the analysis should be provided in Module 5" [10, p. 18].
- Section 2.7.3.3.2 (ICH) and IV.C.3.3. (ASEAN)
  "The results from all studies designed to evaluate the drug's efficacy should be summarized and compared, including studies with inconclusive or negative results. Important differences in study design such as endpoints, control group, study duration, statistical methods, patient population, and dose should be identified" [10, p. 19].

***Clinical Reports**: ICH Module 5 and ASEAN Part IV, Section E*

Differences between the two CTD formats found within the clinical reports sections are minimal. The ACTD includes a few additional details related to vaccines in sections IV.E.3–5. Along with the same sections found in the ACTD, the ICH CTD is expanded with three additional sections:

5.3.6 Reports of Post-Marketing Experience

5.3.7 Case Report Forms and Individual Patient Listings

5.4 Literature References

Annex 7: EUA Timelines and Mechanisms for Transition to Full Approval

Regulatory Agency	Duration of Authorization	Additional Conditions (as applicable)	Mechanism for Transition to Full Approval
EMA [13]	1 year, renewed annually		Conversion to standard marketing authorization after obligations are fulfilled and complete data confirms risk-benefit assessment
Health Canada [33]	For the duration of an applicable Interim Order Respecting the Importation, Sale, and Advertising of Drugs (ISAD IO)	Use may continue following expiry of an ISAD IO with a Notice of Compliance (NOC) under the Food and Drug Regulations.	Application is submitted for full approval.
Singapore Health Sciences Authority [27]	For the duration of the declared emergency		Application is submitted for full approval.
MHRA [52]	Reviewed annually (conditional authorization) or indefinite (temporary authorization)		Conversion to standard marketing authorization after obligations are fulfilled and complete data confirms benefit risk assessment
NMPA [28]	Variable; no more than 5 years	Confirmatory trial should be completed within 4 years of conditional approval.	Submission of a supplemental application for full approval
Swissmedic [19]	Maximum of 2 years		Application for conversion and documentation for the fulfillment of conditions 90 days before expiry of temporary authorization
TGA [14]	2 years for initial registration, maximum of 6 years following renewals	Provisional approval will lapse in a specified timeframe if approval conditions imposed are not met.	Application is submitted for full approval (within 6 years of provisional approval).
U.S. FDA [26]	For the duration of the EUA declaration under which the product was authorized	Use may continue for patients if treatment began before termination or revocation (if deemed medically necessary).	Application is submitted for full approval.

Annex 8: Summary of Breakthrough Therapy Designation Criteria and Requirements

Regulatory Agency	Eligibility Criteria	When the Sponsor Should Submit the Request	Timeframe for Evaluation	Advantages for the Manufacturers	General Requirements
EMA [34, 53]	Medicines under development that target conditions with an unmet medical need for which no treatment option exists, or when they can offer a major therapeutic advantage over existing treatments	During the exploratory clinical trial phase or with preliminary clinical evidence in patients to demonstrate proof of concept	40 days	Enhanced support from EMA, tailored to the relevant stages of development, such as: - Presubmission meeting to discuss PRIME eligibility. - Early appointment of rapporteur. - Scientific advice from multidisciplinary group of experts. - Dedicated EMA point of contact. - Potential accelerated assessment.	Users should submit a request for eligibility to PRIME via the IRIS platform. Applicant's should provide justifications for claims of major public health interest, including all information specific to the unmet medical need, using the template provided by EMA.
NMPA [54, 55]	A drug that is intended to prevent and treat a serious disease or diseases that highly affect the quality of life. There should be sufficient preliminary clinical evidence to demonstrate that the medicine is significantly clinically superior to other existing treatments.	At phase 1/2 and no later than the beginning of phase III of clinical trials	45 working days	- Prioritized resources for communication and intensive guidance on efficient drug development. - Potential priority review for new drug application.	The applicant must provide true, sufficient, and reliable data, materials, and samples to prove the safety, effectiveness, and quality controllability of the drug. For BTD: The applicant should submit a dossier for phase 1 clinical trials. For market authorization approval: Applicants should submit the dossier in ICH CTD format.
U.S. FDA [12, 56]	A drug that is intended, alone or in combination, to treat a serious or life-threatening condition. Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints.	With an Investigational New Drug application or after; ideally, no later than the end-of-phase 2 meeting	60 calendar days	- Frequent meetings with U.S. FDA to discuss drug development plan. - Guidance on clinical trials design and drug development. - Option for expedited review (e.g., rolling data submission). - Assignment of a cross-disciplinary project lead.	A sponsor should submit a request for BTD to Module I, Section 1.12.4, "Request for Comments and Advice," of the eCTD. A concise summary of information supporting the BTD request should be submitted, including the description of the preliminary clinical evidence that the drug may demonstrate substantial improvement over available therapies.

Annex 9: Summary of the World Health Organization Standard Structured Product Labeling Requirements for Medicines [59]

1. Name of the medicinal product: The label should clearly display the name of the medicine.

2. Statement of active substance: The label must include the active substance(s) present in the medicine and the quantity or strength of the active substance(s).

3. List of excipients: The label should list any excipients or inactive ingredients present in the medicine.

4. Pharmaceutical form and contents: This information includes the form of the medicine (such as tablets or capsules) and the quantity of tablets or capsules in each pack.

5. Method and route of administration: The label should specify the recommended method and route of administration (e.g., oral use, topical application).

6. Special warning for storage: The label must provide instructions regarding the storage conditions necessary to maintain the efficacy and safety of the medicine.

7. Special Warnings for Children: A warning should be included to indicate that the medicine must be stored out of the reach and sight of children.

8. Expiry date: The label should clearly display the expiry date of the medicine.

9. Special precautions for disposal: If necessary, the label may include instructions for the proper disposal of unused medicines or waste materials derived from the medicine.

10. Name and address of the supplier: The label must provide the name and address of the pharmaceutical company or supplier.

11. WHO reference number: If applicable, a WHO reference number may be included.

12. Manufacturer's batch number: The label should display the batch number assigned by the manufacturer.

13. General classification for supply: The label must indicate the classification of the medicine, such as whether it is subject to medical prescription or available over the counter.

14. Instructions on use: The label may include specific instructions on how to use the medicine.

15. Minimum particulars on blister or strips: Each blister or strip should include specific information such as the name of the medicinal product, name of the supplier, expiry date, and batch number.

Note: This summary may not cover all possible labeling requirements. It is always recommended to refer to the specific guidelines and regulations of the regulatory authority in each country.

Annex 10: Overview of World Health Organization Recommended Patient Information Leaflet [60]

The World Health Organization (WHO)-recommended patient information leaflet provides crucial information about the medicine and its uses, following the guidelines set by the WHO Prequalification Team, Medicines. Overall, it covers essential details about the medicine, its uses, dosage, administration, possible side effects, storage, and disposal. The leaflet begins with general instructions, urging patients to read the entire leaflet carefully before taking the medicine and to keep the leaflet for future reference.

Before giving the medicine to a child, patients are advised to inform their health care provider about all the other medicines the child may be taking, including antibiotics and certain treatments for metabolic disorders.

The leaflet provides instructions on administration of the medicine, including the recommended dosage for different age groups and how to administer medicines.

It also includes information about possible side effects. Patients are instructed to tell their health care provider if they experience any serious side effects or side effects not listed in the leaflet.

The leaflet provides storage and disposal instructions, emphasizing the need to keep the medicines out of the reach of children, protect medicines from light and moisture, and not to dispose of them in wastewater or household waste. Unused medicines should be returned to the pharmacist.

The leaflet includes contact information for the medicine’s supplier and manufacturer for any additional information or inquiries about the product.

Annex 11: Provisions and Procedures for Emergency Use Medicines Sent to LMICs

Labeling requirements for emergency use drugs exported to low- and middle-income countries (LMICs) may differ from the requirements for domestic use. Modifications to the original label depend on the specific regulations of the exporting country and the emergency situation. The following are some requirements to consider when modifying the label:

1. Product name: The product name may need to be translated into the LMIC's local language to ensure clarity and accuracy in communication.

2. Regulatory information: Include the necessary regulatory information specific to the exporting country and the emergency use authorization granted, which may include reference to the specific regulatory agency and emergency use approval number.

3. Dosage and administration information: Ensure that the dosage and administration instructions are provided clearly and in a manner that health care professionals in the receiving country can easily understand. Consider translating it into the local language if necessary.

4. Warnings and precautions: Include any specific warnings or precautions for the intended population in the LMICs. Warnings and precautions may include information regarding contraindications, potential adverse effects, or special considerations.

5. Storage and handling instructions: Provide clear instructions on storage conditions, shelf life, and any special handling requirements, especially if the drug requires specific temperature control or protection from light.

6. Batch or lot information: Display the batch or lot number clearly on the label for traceability and quality control purposes.

Annex 12: Modifying Label of Medicines for Export to LMICs: Pros and Cons

Drugs exported to low- and middle-income countries (LMICs) for emergency use may have labeling requirements that differ from those for domestic use. If the need for the drug is urgent, and there is not enough time to revise the original label, it may be necessary to add an extra label that meets the local LMICs' requirements. Importantly, the decision to add an extra label should be made in consultation with regulatory authorities and experts, weighing the benefits against potential risks and prioritizing patient safety and regulatory compliance.

The following are the pros and cons of modifying the medicines label:

Pros

1. Compliance with local regulations: Adding an extra label that meets the local LMICs' requirements ensures compliance with the exporting country's specific regulations, which helps facilitate the import and use of the drug in emergency situations.

2. Ensures patient safety: The extra label can provide important information about the drug's dosage, administration, and potential side effects that are relevant to the local population. This promotes patient safety and reduces the risk of adverse reactions or improper use of the drug.

3. Improves accessibility: The extra label with information that meets local requirements can facilitate the drug's accessibility and availability in emergency situations. This helps health care providers make informed decisions and ensures that patients receive timely and appropriate treatment.

Cons

1. Potential confusion: Adding an extra label to the original packaging may lead to confusion among health care providers and patients. The additional label must not contradict or obscure important information from the original label because it could compromise patient safety.

2. Incomplete information: The extra label might not include the complete information provided on the original label, especially if added in a rush. This can result in a lack of comprehensive information about the drug's indications, contraindications, and precautions.

3. Lack of standardization: Adding an extra label may result in a lack of standardization across different batches or shipments of the same drug, which can make it challenging to track and monitor the use of the drug, potentially affecting quality control and post-market surveillance.