A regulatory plan for a TB vaccine: points to consider

Version 1

About EDCTP

The European & Developing Countries Clinical Trials Partnership (EDCTP) is a public– public partnership between 14 European and 16 African countries, supported by the European Union.

EDCTP's vision is to reduce the individual, social and economic burden of poverty-related infectious diseases affecting sub-Saharan Africa.

EDCTP's mission is to accelerate the development of new or improved medicinal products for the identification, treatment and prevention of infectious diseases, including emerging and re-emerging diseases, through pre- and post-registration clinical studies, with emphasis on phase II and III clinical trials. Our approach integrates conduct of research with development of African clinical research capacity and networking.

About TBVI

The Tuberculosis Vaccine Initiative (TBVI) aims to support, integrate, translate, and prioritise R&D efforts to discover and develop new TB vaccines that are accessible and affordable for all. In an effort to optimise the discovery and development of new TB vaccines and biomarkers, TBVI facilitates and supports the generation of new knowledge and exchange among R&D partners. TBVI creates an enabling environment for consortium members to promote knowledge sharing through scientific meetings and workshops, publication in scientific and non-scientific journals, formal and informal networking.

This document was developed by TBVI, in collaboration with Olga Rovira (Kontivax), as one of the deliverables of the project 'Development of tools and documents to support coordination of EDCTP TB-vaccine funded research', which is part of the EDCTP programme support by the European Union. The document reflects the views of the authors. The European Union is not liable for any use that may be made of the information contained herein.

We gratefully acknowledge the contribution from all EDCTP-funded TB vaccine projects to the development of this document.

For more information about this document, please contact the EDCTP Secretariat at info@edctp.org.

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1 Introduction

In the development of a TB vaccine numerous elements will have to be considered in a variety of expertise areas such as non-clinical; clinical and chemistry, manufacturing and controls (CMC). While the three areas will constantly intertwine, it is the development stage which will mark the relevance of their contribution towards evidencing and supporting a positive benefit/risk outcome of the candidate vaccine. Once registered, aspects related to vaccine availability, pharmacovigilance and life-cycle activities will come forward.

TB vaccine developers are nowadays assisted by The TB Vaccine Development Pathway [Ref.1], which presents an assessment process on how to develop a TB vaccine. This tool is based on stage gates, from discovery to implementation. For each of these stage gates, relevant guidance covering all the development functions is provided with the aim to identify key activities that, upon successful completion, will allow the candidate vaccine to further advance to its next stage of development.

As part of this long and complex journey, the regulatory function will be present to provide a cohesive developmental framework for the three areas mentioned earlier, i.e. non-clinical; clinical and CMC. It will guide developers with principles to follow in order to ensure adherence to predefined requirements which, in return, will enable successful vaccine development and registration. The final goal is to facilitate availability of a safe and effective TB vaccine in those world areas where it is needed.

Early enough during clinical development, TB vaccine developers are advised to author a regulatory plan. Such a plan will define the regulatory strategy applicable to their TB candidate vaccine. It will thus set down the path to follow in order to obtain regulatory approval (i.e. registration or licensure) in the targeted regions. Its content should always be in line with the vaccine's target product profile (TPP). Initial guidance to draft a TB vaccine TPP can be obtained in the World Health Organization (WHO) Publication on Preferred Product Characteristics (PPC) for New Tuberculosis Vaccines [Ref.2]). The regulatory plan will also go hand-in-hand with the clinical development plan (CDP) which will ultimately define the key countries/regions for which regulatory submission and approval requirements will need to be addressed. Screening of applicable guidelines should be done and documented in the plan to have an overview of potential challenges and/or risks ahead that may necessitate mitigation strategies. When deviating from established guidelines appropriate justification and risk mitigation should be provided. A description of proposed interactions with regulatory authorities should be included in the regulatory plan too, possibly identifying key agencies to consult, topics to be discussed and the best timing to do so.

Worldwide there are so called "stringent regulatory authorities" (SRA) which are regulatory bodies recognised to adhere to internationally accepted standards, notably those defined within the ICH regulations (The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use). Registration/licensing procedures are well described by these SRAs and follow defined review processes and timelines that can be consulted in their corresponding websites [see examples of two SRAs in Ref.3 and Ref.4]. In addition, some SRAs have in place expedited regulatory pathways aiming at supporting the applicant with their product development and/or registration. In this context, it is recommended to also screen those expedited pathways and to evaluate whether the TB candidate vaccine would benefit from such approaches. Examples of expedited pathways available worldwide at e.g. the European Medicines Agency (EMA) or the United States Food and Drug Administration (US FDA) are listed in **Table 1**. While the majority focus on reducing overall review timelines at the time of registration, there are still some which aim at reinforcing dialogue with the applicant already from very early stages of development.

In addition to the expedited pathways described in Table 1, there are two additional mechanisms that may be of interest to TB vaccine developers (see also section 4.4); i) Article 58 of Regulation (EC) No 726/2004 establishes a mechanism whereby the European Medicines Agency (EMA) may give a scientific opinion, in the context of cooperation with the World Health Organisation (WHO), for the evaluation of certain medicinal products for human use intended exclusively for markets outside the European Union, and ii) Swissmedic's

Marketing Authorisation for Global Health Products (MAGHP) aims to improve and accelerate access to health interventions and therapeutic products in low- and middle-income countries (LMICs), with a focus on sub-Saharan Africa. The MAGHP procedure enables both a Marketing Authorisation in Switzerland while engaging WHO and NRAs in the review and approval process.

Table 1: Expedited (development and registration) pathways from worldwide SRAs

Regulatory authority	**Expedited pathway (can be expedited development or expedited registration)**
EMA (European Union, EU)	Priority Medicines Scheme (PRIME)
	Accelerated Assessment
	Conditional Approval
	Exceptional Circumstances
US FDA (United States of America, USA)	Fast track designation
	Accelerated approval
	Priority review
	Breakthrough therapy
Health Canada (Canada)	Priority review
	Notice of Compliance with Conditions ("Conditional")
Swissmedic (Switzerland)	Fast track
TGA (Australia)	Priority review
	Provisional approval
PMDA (Japan)	Sakigake
	Priority review

Tuberculosis remains a disease endemic in many low- and middle-income countries, amongst others on the African continent. Vaccine supply to those countries is very often undertaken by United Nations (UN) agencies who require vaccine pre-qualification (PQ) by WHO as a prerequisite. Therefore, TB developers should also contemplate in their regulatory plan timely interactions with WHO to assess their candidate vaccine against WHO programmatic suitability as well to best plan for PQ filing [see Ref.2; Ref.5].

Finally, the regulatory plan should be a living document that is revised and updated as clinical development progresses.

This document intends to provide some guidance to be considered when drafting a regulatory plan for a TB candidate vaccine. In the Annex, a regulatory plan template with precise directions on how to draft such a plan is provided. Both documents present different regulatory perspectives and mechanisms that are available today for TB vaccine developers to reflect on the best possible regulatory option applicable to their investigational vaccine programme. They should be read in conjunction.

The guidance and the template documents cover clinical development and registration phases. Post-approval activities remain out of scope. Throughout the documents' sections, strategic insights have been favoured over operational activities proper to the conduct of clinical trials.

Beyond the guidance included here, TB vaccine developers will find a wealth of relevant regulatory guidelines publicly available which are strongly recommended to be consulted. Due to their high number and to the broad spectrum contemplated in this document, the provision of a list with all those guidelines has been intentionally avoided and only a few key web links are provided (see Section 8). They are to be regarded as a starting point in the research of regulatory insights.

In order to have a quick overview on how a regulatory plan could look like, a standard table of contents (TOC) is presented in Section 2. Each of the topics listed in the TOC will be further elaborated in the subsequent sections of this document, i.e. Section 3 to Section 7.

The regulatory plan template is accessible in the Annex and it follows the same TOC.

2 Standard structure of a regulatory plan

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3 Regulatory plan: Overview

This section of the regulatory plan will be providing general background information related to:

- TB disease
- Main characteristics of the TB candidate vaccine being developed
- Definition of the development stage for the TB candidate vaccine
- Brief description of the intended regulatory strategy
- Competitors' landscape

4 Regulatory plan: TB vaccine development path

This section is the core of the regulatory plan. It is divided into 4 sub-sections according to key stage gates foreseen during standard clinical development: Phase 1, starting with first-in-human (FIH); Phase 2, including proof-of-concept (POC); Phase 3, addressing efficacy; and registration. Within each sub-section, it is recommended to address separate regulatory areas in relationship to non-clinical, clinical, CMC and procedural aspects, as needed. This will facilitate identification of key project activities to be undertaken and their timings, potential risks and mitigation strategies. For each of the areas mentioned, it is suggested to perform a screening of relevant guidelines in line with the applicable development stage and to evaluate the level of alignment. In case of deviations to those guidelines, it is desirable to document a brief justification. Refer also to the regulatory risk register at the end of the regulatory plan.

4.1 Phase 1 first-in-human / Phase 1

A first-in-human (FIH) clinical trial will assess the safety and reactogenicity profile of the TB candidate vaccine under development. This trial represents a very first and early safety evaluation in human subjects. Usually it will be conducted in healthy adult volunteers, especially if vaccination is intended for disease prevention versus treatment. Due to this trial being the first attempt testing the candidate vaccine in human volunteers, it is highly likely that the clinical knowledge of the vaccine is non-existent at this stage. Consequently, it is paramount to rely on previously performed non-clinical studies and particularly those that are assessing the toxicological profile of the vaccine. Sufficient preclinical information should therefore be available to support the vaccine dose and schedule to be tested safely in humans. In addition, knowledge gathered by testing the vaccine in relevant animal models will have provided a preliminary understanding on the immunological response(s) elicited by the vaccine and the potential benefit it represents.

Because the FIH is usually conducted with healthy adult volunteers, selection of the country and clinical site in which the study will be run is wide open. It is highly advisable to conduct the FIH trial in a region/country where a well-established regulatory authority/agency is present with capacity to evaluate clinical trial applications (CTA) in a robust way and in a clinic or research centre with experience in the conduct of Phase I trials. Clear and reliable submission and approval processes together with regulatory expertise are expected to be in place at those agencies. Such processes will ensure ethical conduct of the clinical investigation and appropriate protection of subjects while facilitating the sponsor's activities towards study approval, as a prerequisite to start the trial. In this respect, it is recommended the sponsor organises a meeting with the local agency in charge of regulatory approval, well ahead of CTA submission. This will be an opportunity to introduce the new TB candidate vaccine, do a check of the data package available in view of local requirements, clarify possible pending questions or even discuss with regulators some items not fully endorsed by the sponsor yet. Multiple topics can be discussed and agreed with the agency that can help the sponsor in de-risking the early stage vaccine programme. Examples of those are: manufacturing process and specifications, vaccine characterisation analytical methods, stability indicating tests, preclinical plan and toxicology, summary of clinical synopsis, etc. The sponsor is equally advised to identify whether additional requirements need to be fulfilled as part of the CTA, should the vaccine product be considered a genetically modified organism (GMO). This is particularly relevant in the European Union region, which has country-dependent legislations for GMOs. Depending on the type of agency chosen, the meeting will also represent a means to engage with regulators for future interactions during clinical development.
Once FIH has been successfully conducted, additional Phase 1 studies may be performed to further support the vaccine's safety profile. Those studies may be conducted in the targeted population, which will imply a transition of the clinical development plan to areas where TB is endemic such as the African continent, India, The Philippines or China, to list a few. As a secondary objective, Phase 1 studies may also be designed to obtain a preliminary estimation of the vaccine's immunogenicity profile. This is a complex undertaking especially relevant in the development of a TB vaccine, in lack of established correlates of protection.

For regulatory purposes, the vaccine to be used in clinical trials can be generally called "investigational medicinal product (IMP)". The IMP material intended for FIH/Phase 1 should be representative in terms of composition/manufacturing process to the one used in pivotal non-clinical studies, especially in toxicology studies. This will reduce uncertainty regarding safety considerations, which is a key element at this stage of development. IMP batches to be used in clinical trials should be produced according to Good Manufacturing Practices (GMP) applicable in the manufacturing region as well as in line with GMP rules in place in the clinical trial region. Characterisation and release testing of the IMP should be performed to an extent that allows sufficient product knowledge and safety reassurance. Quantity, purity, identity, and biological activity are regarded mandatory quality attributes to test and to fall within predefined acceptance criteria. Equally important is the collection of information about raw materials and their origin as well as materials coming into contact with the vaccine during manufacturing, in particular those of human or animal origin. It is recommended to evaluate the risk with regards to potential contamination with adventitious agents such as transmissible spongiform encephalopathies (TSEs), viruses, bacteria, mycoplasma or fungi. Knowledge should be gathered about product genetic stability, heterogeneity, degradation/stability profile or product- and process-related impurities. Compliance to Pharmacopoeias from main regions (i.e. European Pharmacopoeia,

Ph. Eur.; United States, USP) or to Technical Report Series (TRS) issued by the World Health Organization (WHO) is strongly recommended.

4.2 Phase 2 / Phase 2 proof-of-concept

In general, clinical development of a TB vaccine is subject to a stepwise approach in which knowledge is being accumulated as research advances. Small early studies will provide the basis to define subsequent trials, which are larger and more complex. Phase 2 studies are exploratory trials that intend to assess the adequacy of the candidate vaccine in the targeted indication and population, thereby supporting proof of concept for the vaccine candidate. Dose regimen, i.e. vaccine dose and schedule, is studied in depth at this stage together with other clinical parameters that will facilitate preparation and definition of Phase 3 clinical endpoints. A control group is usually included in Phase 2 trials and randomization to either vaccine candidate or control applied. Safety continues to be monitored and characterized as needed, especially if age de-escalation is foreseen or a different age population is assessed in Phase 2 as compared to Phase 1.
Should children be part of the TB vaccine target population, it is time to assess potential requirements in terms of paediatric investigation plans (for the EU)/paediatric study plan (for the USA).

With regards to non-clinical work, the focus at this stage will be placed on further characterization of TB-relevant immune responses, for example with challenge/protection non-clinical studies. Also, investigations on potential correlates of protection might be conducted with relevant animal models. Additional toxicity studies may be appropriate to further explore special considerations of the TB candidate vaccine or the indication/population (for example, developmental and reproductive toxicity (DART) studies if the candidate vaccine is to be used in women of childbearing potential or pregnant women).

For many investigational TB vaccines, a Phase 2 development stage will require embarking into multiregional clinical trials, possibly in a special population such as children. This is inevitably adding higher complexity to the CTA submission process due to potentially different local regulatory requirements and/or timelines for approval. It is therefore recommended to do a thorough check of those requirements aiming at collecting a CTA baseline package that can fit all targeted regulatory authorities as much as possible. Indeed, not doing this could, for example, lead to the undesirable result of having different versions of a clinical protocol intended for the one and same study. Thus, it is regarded important, as in the previous Phase 1, to keep on interacting with a reference agency (possibly an SRA) that can support the applicant throughout the whole development. In parallel, it is considered worth to start interacting with other agencies and/or organisations relevant for the vaccine clinical development program such as WHO.
The clinical trial material will be evolving during Phase 2 since optimisation of the manufacturing process is expected to occur, potentially including a working cell bank (WCB) step in the drug substance process (if not applied during Phase 1), a first scale-up exercise and refinement of the control strategy, based on the identified critical quality attributes (CQA). Changes to vaccine drug product formulation may also be needed in favour of a more stable formulation and/or due to antigen/excipients compatibility. Also, the pharmaceutical presentation may need to be adapted (i.e. frozen drug product versus lyophilized drug product). Characterisation of the vaccine will be pursued towards a better antigen and product understanding. The strategy for quality control testing for both release and stability monitoring should be reinforced by adding new tests, refining existing ones and improving their qualification status. Compliance to Pharmacopoeias from main regions (i.e. Ph. Eur.; USP) or to TRSs issued by WHO continues to be strongly recommended. In addition, it will be time to assess the programmatic suitability of the candidate vaccine for the WHO pre-qualification (PQ) process [Ref.2; Ref5] and identify which actions need to be undertaken for full compliance with requirements.

Because significant changes will be applied and the IMP tested in Phase 2 proof-of-concept will likely differ from the IMP tested in previous trials (initial Phase 2 or Phase 1), comparability exercises should be conducted and will be regarded as critical to demonstrate there is no adverse impact on the safety, quality or efficacy of the vaccine due to changes. A comparability exercise will primarily collect CMC information prior- and post-change. Depending on the nature of the change(s), it may be needed to extend such an exercise further to include non-clinical assessments.

At this stage, it will also be the time to refine the regulatory strategy to follow in order to register the TB vaccine. As part of this exercise multiple elements will need to be considered such as: country of vaccine manufacturing; identification of regions/countries for which the vaccine is intended; vaccine supply and procurement mechanisms as well as conditions for purchase; involvement of an SRA during clinical development and under which regulatory procedural mechanism, etc.

4.3 Phase 3 efficacy / Phase 3

The clinical development of the TB vaccine will pursue into Phase 3 studies which aim at demonstrating vaccine efficacy and/or the ability to prevent clinical disease, especially if there is lack of immune correlates of protection. Phase 3 efficacy studies are large pivotal trials statistically powered and designed to assess the final vaccine (formulation; dose/schedule) in endemic areas in view of licensure. Other pivotal trials performed during this stage gate may be relevant such as those which evaluate the use of the vaccine in a special population (specific safety aspects), the consistency in vaccine manufacturing or the co-administration with other vaccines already included in the Expanded Program for Immunization (EPI), only to list few examples. All the clinical data collected during this period will be key to start drafting the TB vaccine label to be registered.

Once Phase 3 clinical studies are completed, efforts will be invested to draft a risk management plan (RMP, in EU)/risk evaluation and mitigation strategy (REMS, in USA) that will encompass any post-marketing approval clinical study needed to characterize a potential safety risk arising from Phase 3 results or any other trial seen necessary as part of pharmacovigilance (PV).

If not done during Phase 2, non-clinical work will focus now on potential additional toxicity studies that are needed to address a specific population (for example, DART studies if the candidate vaccine is to be used in women of childbearing potential or pregnant women). The sponsor should make sure that toxicology studies available today are still covering the use of the candidate vaccine in the clinical setting for Phase 3 trials. Pivotal efficacy trials will require a high number of participating clinical sites spread across multiple countries. As a consequence, the CTA process will remain complex due to possibly different local requirements. Recommendations as described in the previous Phase 2 remain valid for this phase too: doing a thorough check of requirements and approval timings for countries involved in the trial and collecting a CTA baseline package. Also, interactions with an SRA are seen as very valuable to discuss final designs of clinical trials, CMC activities planned to be undertaken during Phase 3 and procedural aspects for later registration.

At phase 3, the final vaccine formulation (vaccine composition and dose) should have been defined in order to be tested in pivotal studies. In that respect, the more advanced vaccine CMC features are when starting Phase 3, the less risk it entails to adopt later changes that could potentially alter the efficacy and/or safety of the final vaccine. Yet, there will be changes/activities that the applicant will only be implementing as Phase 3 is ongoing. Scaling-up to commercial scale; finalisation of the associated control strategy and full process validation; demonstration of manufacturing process consistency; setting up the final testing strategy (quality control release and stability monitoring) including definition of commercial specifications and shelf-life are some of the examples that the applicant will need to reflect upon and to decide on the best time to execute. Whenever changes will be integrated, comparability studies will need to be performed to review and assess the impact on product quality; these can be CMC-based, with or without further non-clinical and clinical comparability depending on the likelihood those changes could impact efficacy/safety.
The regulatory strategy for registration of the TB vaccine should be finalised at this stage, if not done already, to leave the registration phase to the preparation of the different dossiers/applications.

4.4 Registration

This is the stage at which the application (Marketing Authorisation Application (MAA); Biologics License Application (BLA), Art58 dossier, etc.) is prepared in order to register first the TB vaccine in the country of manufacturing. This will allow a subsequent prequalification of the vaccine by WHO, which is a requirement

from UN agencies to supply low- and middle-income (LMI) countries. To do so, a tailored PQ file ("product summary file", PSF) will need to be prepared and submitted for WHO review and acceptance. In case the applicant has opted for the Art58 mechanism in the European Union (EU), WHO will be already involved in the first review performed by the EMA Committee for Medicinal Products for Human Use (CHMP) and the Pharmacovigilance Risk Assessment Committee (PRAC). Regulators, experts and observers from National Regulatory Authorities (NRAs) in LMI countries are invited to participate in the Art58 procedure too. These represent efforts to facilitate PQ and subsequent registration at the national level in the target countries. Both the first application approved in the country of manufacturing (usually approved by an SRA) and the PQ status will be key to explore collaborative registration in the targeted countries with WHO support. Similarly to Art58, a registration pathway specifically intended for the sub-Saharan African region is available in Switzerland. The so-called Marketing Authorisation for Global Health Products (MAGHP) procedure enables both a Marketing Authorisation in Switzerland while engaging WHO and NRAs in the review and approval process. NRAs involved are expected to approve the product in a 90-day time window upon MAA receipt. Ultimately, the TB vaccine will need to be registered in the targeted country in which the vaccine will be used. The registration phase will therefore focus on the preparation of documentation for the different applications and the preparation of meetings with the multiple regulatory stakeholders involved as part of the TB vaccine regulatory strategy.

Following ICH guidelines [Ref.6], the preferred dossier format adopted for registration purposes by most RAs is the so called "Common Technical Document" (CTD) which enables electronic submission (eCTD) from the applicant directly to the regulatory body/agency via secured submission portals. The eCTD is well defined into 5 different modules dedicated to specific disciplines, as listed in **Table 2** below. Within each of the modules an arborescence structure is set with separate folders named according to ICH conventions. Modules 2 to 5 are common for all regions while module 1 is region-specific.

Table 2: eCTD format for application dossier

CTD Module	Module heading
Module 1 (m1)	Administrative information and prescribing information
Module 2 (m2)	Summaries
Module 3 (m3)	Quality
Module 4 (m4)	Non-clinical study reports
Module 5 (m5)	Clinical study reports

In an initial dossier, non-clinical information will be populated in m4 and in m2. The applicant will need to submit relevant non-clinical study full reports supporting the vaccine to m4. The applicant is required to write summaries of the reports submitted to m4 and to place them into module 2.6 (m2.6 Nonclinical written and tabulated summaries). An overview of those summaries is also to be provided in module 2.4 (m2.4 Nonclinical overview).

Clinical information will be populated in m5 and in m2. The applicant will need to submit full clinical study reports to m5. In m2, a summary of these reports is to be presented. Such a summary justifies a positive benefit/risk for the use of the vaccine in the intended population and it is to be placed into module 2.7 (m2.7 Clinical summary). An overview document is required too which will be provided in module 2.5 (m2.5 Clinical overview).

Quality information will be provided in m3 (m3 Quality) and in m2.3 (m2.3 Quality overall summary). M3 presents CMC information in an extensive way and follows a predefined CTD structure with separate folders for drug substance, drug product, facilities, excipients, etc.

Finally, administrative forms, prescribing information, GMP certificates, risk management plan (RMP) (in EU CTD) and other relevant documents will be included in module 1 (m1 Administrative information and prescribing information). The content of m1 is region-specific.

5 Regulatory plan: Risk register

The development of a TB candidate vaccine will carry along risks of different nature that may be impacting the regulatory environment of the vaccine. As part of risk management, the sponsor/applicant is advised to include in their regulatory plan a section that details such risks and, most importantly, how to mitigate them. It is advised to identify first each risk and to score it as low, medium or high depending on the probability of occurrence and the impact it could cause. This will determine the level of action and measures to take proactively as part of the mitigation strategy.

6 Regulatory plan: List of references

The TB developer is recommended to keep a list of relevant references (literature publications, guidelines, internal company documents, etc) that is easily accessible whenever regulatory documents will need to be written.

7 Regulatory plan: Document's history

The regulatory plan is a living document that is revised and updated as clinical development of the TB candidate vaccine progresses. This section helps to track the history of the document and it is also a means of keeping a record of relevant regulatory changes occurring throughout the development of the TB vaccine.

8 Sources of information

(last accessed July 2020)

Ref.1 The TB Development Pathway
Ref.2 WHO Preferred Product Characteristics for New Tuberculosis Vaccines
Ref.3 European Medicines Agency (EMA)
Ref.4 United States Food and Drug Administration
Ref.5 The WHO prequalification of vaccines procedure
Ref.6 ICH Guidelines (The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use)
Ref.7 WHO TB website

List of Abbreviations

AVAREF	African Vaccine Regulatory Forum
BLA	Biologics License Application
CDP	Clinical Development Plan
CHMP	Committee for Medicinal Products for Human Use
CMC	Chemistry, Manufacturing and Controls
CP	Centralised Procedure
CTA	Clinical Trial Application
CTD	Common Technical Dossier / eCDT electronic submission
CQA	Critical Quality Attribute
DART	Development and reproductive toxicology
EMA	European Medicines Agency
EOP2	End of Phase 2
EPI	Expanded Program for Immunization
EU	European Union
FIH	First in Human
GAVI	Global Alliance for Vaccine and Immunization
GLP	Good Laboratory Practice
GMO	Genetically Modified Organism
GMP	Good Manufacturing Practice
GRevPs	Good Review Practices
IMP	Investigational Medicinal Product
LMI	Low- and Middle- Income
MAA	Marketing Authorisation Application
NRA	National Regulatory Authority
OMCL	Official Medicine Control Laboratory
PIP	Paediatric Investigation Plan
PL	Package Leaflet
PLCM	Product Lifecyle Management Document
PoC	Proof of Concept
PPC	Preferred Product Characteristics
PRAC	Pharmacovigilance Risk Assessment Committee
PQ	WHO prequalification process
PRIME	Priority Medicines Scheme
PSF	Product Summary File
PSP	Paediatric Study Plan
PV	Pharmacovigilance
REMS	Risk Evaluation and Mitigation Strategy
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SRA	Stringent Regulatory Authority
TOC	Table of Contents
TPP	Target Product Profile
TRS	Technical Report Series
TSEs	Transmissible spongiform encephalopathies
UN	United Nations
US FDA	United States Food and Drug Administration
VVM	Vaccine Vial Monitoring
WHO	World Health Organization