Annex 6

Good practices of national regulatory authorities in implementing the collaborative registration procedures for medical products

1. Background

In 2014, the 67th World Health Assembly resolution, WHA67.20, recognized that

> effective regulatory systems are an essential component of health system strengthening and contribute to better public health outcomes, that regulators are an essential part of the health workforce, and that inefficient regulatory systems themselves can be a barrier to access to safe, effective and quality medical products (*1*).

Nonetheless, regulators, globally, and in particular low- and middle-income countries, face an increasingly complex regulatory environment, with limited resources and a need to avoid duplication by communicating, collaborating, cooperating and forming coalitions to ensure product quality, safety and efficacy, as well as supply-chain security.

To this end, collaborative registration procedures (CRPs) with a view to accelerating national registrations and the regulatory life-cycle of products prequalified by the World Health Organization (WHO), or approved by reference stringent regulatory authorities (SRAs), have been developed and implemented (*2*, *3*). Based upon WHO's experience with the collaborative procedure for WHO prequalified pharmaceutical products and vaccines (*2*), and the pilot collaborative procedure of products approved by SRAs (*3*), it is possible to facilitate and accelerate national registration processes using this approach in the management of registrations and post-registration regulatory product life-cycle, based on reliance on the expertise and regulatory outcomes of recognized reference authorities.

Available assessment and inspection reports of reference SRAs or the WHO Prequalification Team (PQT), in addition to the registration dossiers, can facilitate and accelerate the adoption of national regulatory decisions by assuring national regulatory authorities (NRAs) of the positive benefit–risk of a product and its identical quality with the product already approved elsewhere, while allowing them to reflect their own judgement on the benefit–risk balance as it relates to their specific country situation and the legislation in place. This contributes substantially to savings in regulatory resources, improvements in the quality of regulatory decisions and faster availability of needed therapies for patients.

Nevertheless, it has been evident from experiences with the CRPs for products prequalified by WHO and pilot SRA collaborative registration, that it is critical to have clear NRA procedures to support acceleration of the availability of medical products, without compromising their quality, safety and efficacy, as well as providing an opportunity to harmonize dossier requirements and submission expectations.

Additionally, WHO has been facilitating regional collaborative procedures in the context of medicines regulatory harmonization in various regions. The regional mechanisms mobilize the existing regional resources to accelerate access to medical products through work-sharing and joint activities. These regional collaborative registrations have been established and supported in collaboration with their partners, in the East African Community, the Southern African Development Community, the Economic Community of West African States, the Caribbean Community and Common Market and the Association of Southeast Asian Nations. Similar initiatives are being developed for other regional economic communities and CRP can serve as an instrument to facilitate regional work-sharing.

2. Aims and objectives

This guideline is intended to serve as the NRAs' best practices model for implementing CRP and reliance and/or risk-based approaches in their overall marketing authorization system for medical products, and it should be read in conjunction with the full text of the collaborative procedures (*2*, *3*). The document also outlines the recommended approaches a NRA should take to process different types of applications, based on prior decisions and documentary evidence from the PQT, reference authorities and regional collaborative procedures.

The objectives of the document are to:

- describe the practical steps for NRAs to implement the collaborative procedure for prequalified products, SRA-approved products, or products from other reference authorities and regional harmonization;
- provide a resource for NRAs to effectively and efficiently implement collaborative reliance-based procedures for medical products, including vaccines.

This guideline is complementary to and consistent with the principles already elaborated in the draft guideline *Good regulatory practice: guidance for national regulatory authorities for medical products* (*4*). Furthermore, it supplements the guidance and best practices guidelines for marketing authorizations, which include *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for national medicines regulatory authorities* ("The Blue Book") (*5*), *Good review practices: guidelines for national and regional regulatory authorities* (*6*), and the *Guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for*

medical products regulatory decisions (*7*). These guidelines and best practices promote interagency communications, in order to facilitate greater regulatory convergence, thus increasing regulatory efficiency and quality of decisions, and improving patient access.

It should be remembered that WHO focal persons (as specified on the WHO website (*8*)) can be approached at any time, to provide additional explanations and assistance in the implementation of and practice of the collaborative procedure (Procedure) or other reliance approaches.

3. Scope

This guideline is focused mainly on the collaborative procedure for WHO-prequalified pharmaceutical products and vaccines and the collaborative procedure for pharmaceutical products and vaccines approved by SRAs. In addition, the principles, practical steps and tools described in this guideline may apply to a stand-alone setting outside the collaborative registration approach, for example, where the NRA specifies other authorities as reference authorities for its own reliance purposes. Although, the published Procedures apply for pharmaceutical products and vaccines, the general principles may also apply to medical devices, including in vitro diagnostics, for which the collaborative procedure guideline is under development.

This document provides recommendations to NRAs that are participating in the Procedures. Nonetheless, reliance or risk-based approaches follow the principles of good regulatory practices (GRP) and are also applicable and practised among the well-resourced and mature regulatory agencies. This enables a greater alignment and convergence with international standards for the NRAs, while they can also maximize efficient use of their own resources. Moreover, the NRAs are able to focus on value-adding activities and therefore reduce the burden of duplication of work done by trusted authorities and duplication of work for applicants/manufacturers.

In the case of national applications for registration of products assessed and prequalified by WHO or registered by reference authorities, it is possible that national applications can be submitted by other persons/legal entities that act on behalf of manufacturers with WHO-prequalified products or products approved by reference authorities. It is necessary to consider these options, and existing CRPs includes arrangements for such situations. If the applicant for national registration is not the same as the manufacturer with the WHO-prequalified or reference authority-approved product, the manufacturer with the WHO-prequalified or reference authority-approved product confirms to the NRA and WHO/reference authority by an authorization letter that the applicant is acting for, or pursuant to rights derived from, the manufacturer with the WHO-

prequalified or reference authority-approved product and that they agree with the application of the procedure in the country concerned.

Note: The CRPs cover initial registrations and variations/post approval changes.

4. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

abridged review. A limited independent assessment of specific parts of the dossier, or submission for suitability of use under local conditions and regulatory requirements, while relying on prior assessment and inspection outcomes from a reference authority or trusted institution to inform the local decision. The abridged review is based on assessment reports, and good manufacturing practices (GMP) inspection reports of reference authorities, plus specific parts of the *Common Technical Document* (CTD) (for example, stability data in Module 3 of the CTD (*9*)).

abbreviated review. See abridged review.

collaborative procedure (Procedure). The collaborative procedure to accelerate the national registration of prequalified pharmaceutical products and vaccines, or the collaborative procedure to accelerate the national registration of products approved by stringent regulatory authorities (*10*, *11*). The collaborative registration procedures cover initial registrations and post-registration variations/ post-approval changes.

dossier. The regulatory submission package submitted to the national regulatory authority as an application for marketing authorization in line with the applicable country requirements and requirements specified in the respective Procedure guidelines (*2*,*3*).

manufacturer. Any person or legal entity engaged in the manufacture of a product subject to marketing authorization or licensure; or any person or legal entity that is an applicant or holder of a marketing authorization or product licence where the applicant assumes responsibility for compliance with the applicable product and establishment standards.

participating authority or participating national regulatory authority. A NRA that voluntarily agrees to implement this collaborative procedure and accept the task of processing applications for registration of WHO-prequalified pharmaceutical products and vaccines, in accordance with the terms of the Procedure. A list of participating authorities is posted on the WHO/PQT website, for pharmaceutical products (*12*) and for vaccines (*13*).

recognition. The routine acceptance of the regulatory decision of another regulator or other trusted institution. Recognition indicates that evidence of

conformity with the regulatory requirements of country A is sufficient to meet the regulatory requirements of country B.

reliance. An act whereby a regulatory authority in one jurisdiction may take into account or give significant weight to work performed by another regulator, or other trusted institution, in reaching its own decision.

reference authority. A regulatory authority that agrees to provide outcomes of its regulatory expertise (especially assessment and inspection reports) to applicants/authorization holders or inspected manufacturers; agrees to sharing of these documents with national regulatory authorities; and provides, under specified conditions in line with the principles of the Procedure, support to other parties involved in the Procedure.

stringent regulatory authority. The authority as defined by the interim definition in 2017 (*10*) and updated in 2018 (*11*).

verification. The procedure by which a regulatory authority only validates the product or submission, and ensures that the product for local marketing is equal or similar to that approved by the reference authority or trusted institution. Verification may be on the basis of assessment reports, GMP inspection reports and/or a certificate of pharmaceutical product of a reference authority.

5. Key principles

5.1 Risk-based approach

It is regulatory best practice for NRAs to implement quality risk management (*14*). In this respect, the NRAs should allocate resources and a level of effort that is proportionate to the level of risk. For example, the quality, safety and efficacy of a product prequalified by WHO, or approved by a reference authority, may be considered demonstrated compared to a product with no such prior reviews and/or approvals; therefore, the level of effort required to reach a final regulatory decision by a NRA should be differentiated accordingly.

5.2 Optimum use of available resources

Assessment activities should be aligned with resources available to the NRA. In addition, NRAs should be able to recognize their capabilities, limitations and the most efficient and effective approach to ensure that the patients are served and protected with the available resources. This includes removing duplication and identifying elements in the benefit–risk assessment that are critical in the local context. For innovative products, this may mean bridging the benefit–risk assessment done by reference SRAs to the local population, suitability of use in the local context, or stability data that suit the local climatic conditions.

5.3 Ensuring the "sameness" of products

The core principle for collaborative registrations is to ensure identical products (or that where differences exist, these are clearly stated) between the NRA and the reference NRAs, regardless of the approaches or assessment activities conducted by the NRA. The same pharmaceutical product or same vaccine is defined in the Procedures (*2*, *3*), as characterized by:

- the same qualitative and quantitative formulation;
- the same manufacturing site(s)[1] for the drug substance and finished product, including specific block(s)/unit(s), manufacturing chain, processes, control of materials and finished product, and, in the case of vaccines, also by the same batch-release scheme;
- the same specifications for the excipient(s), drug substance and finished product;
- the same essential elements of product information for pharmaceutical products, and, in the case of vaccines, by the same product information, packaging presentation and labelling.

Notwithstanding the principle and definition of the same product under the Procedures, the general principles in this guideline may be applied in other cases where the information is partly the same, but some differences between the products exist and are clearly stated and acceptable to the NRA. In those cases, the NRA should take additional precautions or steps, such as full review of corresponding data not assessed by the reference NRA, or inspecting the additional sites, as the case may be, while relying on shared information where sameness is applicable.

5.4 Compliance with nationally legislated regulatory requirements

Submissions and documentary evidence should be consistent and they should comply with applicable national legal and regulatory requirements. Collaborative registrations, or reliance approaches, do not substitute compliance with applicable national requirements; however, NRAs are encouraged to update,

[1] The sameness of the manufacturing sites for active pharmaceutical ingredients (APIs) and finished pharmaceutical product (FPPs) means that the specific site must be approved by the PQT or reference authority for the specific product under consideration, and included as part of the marketing authorization in the reference country. Any additional sites, regardless of GMP status, are not acceptable under this procedure. Any changes or variations to include additional sites should be approved by the PQT or the reference authority before inclusion in the submission to the participating NRAs.

where applicable, any legal or regulatory requirements in line with international best practices and harmonized requirements.

5.5 Flexibility to allow national regulatory authorities to adapt to their situations

No one size fits all; the best practices should permit each NRA to adapt and suit their own circumstances; for example, the practical steps and tools should be applicable across the maturity levels of NRAs, national strategies or procedures. It should be remembered that internationally harmonized practices and standards facilitate work-sharing and improve the compliance of applicants/manufacturers.

6. Essential elements of a registration system (in the context of collaborative registration procedures)

6.1 National regulatory authority agreement to participate in collaborative procedures of WHO-prequalified pharmaceutical products and vaccines or products approved by stringent regulatory authorities

To responsibly decide on participation in the CRP, the management of interested NRAs should have a good understanding of the principles of the procedure (*2*, *3*) and be aware of its benefits and feasibility, as well as commitments that are associated with participation. Proper study of the procedure is necessary. It is useful to understand to what extent current practices and policies permit the implementation of the process and how the participation corresponds with the NRA's developmental plans. The NRA management should be especially assured that there are no legal barriers preventing participation or hampering effective implementation of the procedure. This is not normally the case, as the CRP only represents the availability of additional expertise for NRA consideration in its decision-making process. Any pending issues can be clarified with the WHO focal person prior to a formal agreement on participation.

To successfully operate the procedure from the beginning, and to be able to inform local applicants about registration in this respect, it is important to prepare registration pathways for prequalified and reference SRA-approved products and to consider the following factors, especially those presented next.

The selection of focal persons who are responsible for communication with WHO and with reference national regulatory authorities

Optimally, focal persons for the registration agenda should be selected among NRA technical staff who are experienced with the registration process, from the submission of applications to adoption of decisions, with post-registration

regulatory activities. They should also be able to communicate with colleagues who are responsible for the end-to-end registration process, including staff responsible for all administrative steps, inspection, post-approval changes, pharmacovigilance and laboratory testing.

Focal persons for inspection activities should preferably be experienced GMP inspectors who are involved in inspection planning and in communication with other departments in the NRA and inspectorates in other countries.

It is important that focal persons are motivated and able to communicate in English; and that they understand the NRA application tracking process and have access to the internet. It is up to the focal persons to regularly collect and communicate to WHO, or reference SRAs, the relevant Procedure-related information, and share such information obtained from WHO or reference SRAs with responsible NRA units.

National regulatory authority application tracking systems

NRAs should adapt existing tracking systems, or implement appropriate tracking systems for applications for registration, that enable easy identification and monitoring of progress and timelines of all applications considered under CRP and other NRA pathways. All the NRA staff that are responsible for different aspects of a product throughout the life-cycle management should have access to the tracking systems.

The adoption of provisions to organize the Procedure process and meet the prescribed timelines

This may include some adaptation of the application screening process; changes in assessment practice; recording of applications in NRA databases and tracking systems; new timelines for certain registration steps; modified staff responsibilities; and/or arrangements of technical committee meetings. Adequate resources should be available to implement the Procedure, especially with regard to the capacity of involved personnel, access to a shared network, and communication with WHO and reference NRAs. In line with GRP, the changes should be reflected in relevant standard operating procedures (SOPs) and staff should be appropriately trained in the Procedure, registration pathway, and the process for reliance on outcomes from other regulatory authorities or PQT , as well as risk management science (risk-based approaches) and change management.

Regulatory fees

Regulatory fees for the Procedure applications should be decided by the NRA and this information should be publicly available to the applicants.

Information to applicants

Manufacturers should be properly informed about the existence of the new process; scope of the products for which this is applicable; possible deviations from standard national requirements; differences from current registration practices; and the benefits that come with participation. An example of information to applicants for registration is included in Appendix 1. A focal person should be identified who would respond to Procedure-specific questions and assist those submitting their first Procedure applications.

Communication

When informing WHO about participation in the Procedure(s), the NRA should mention the date it is prepared to implement the Procedure(s) and to accept the first applications for this/these registration pathway(s).

MedNet is an information platform where WHO or SRA assessment and inspection outcomes, and additional confidential information, are shared. Focal persons are invited, by WHO, to this internet-based communication platform, after it receives a duly signed agreement for participation. Each focal person must create their personal access passcode, in order to enter the shared information site. If requested, WHO can assist in MedNet learning. In the case of regional cooperation, other information platforms can be used.

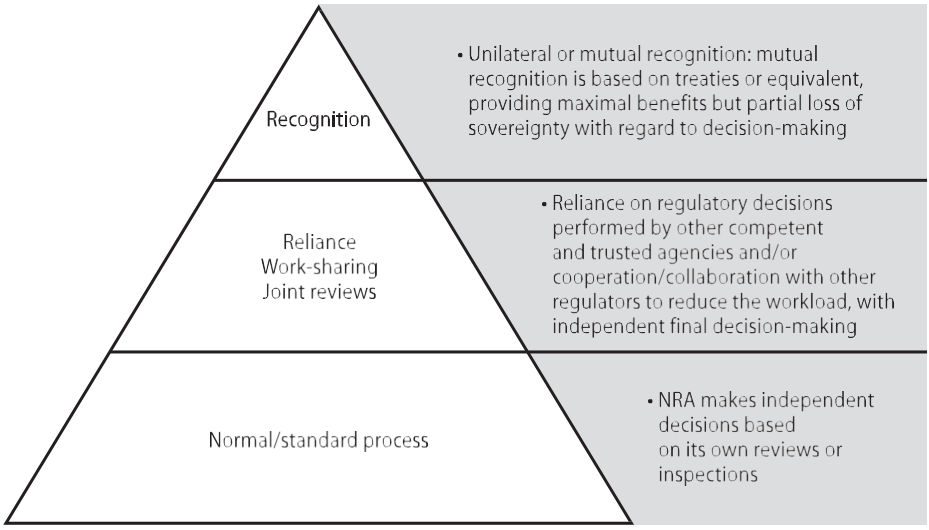
6.2 Registration pathways

NRAs should define and establish clear registration pathways, for example, for products with prior approval from reference SRAs; WHO-prequalified products; products through joint reviews or work-sharing; normal reviews; and fast-track mechanisms. This information enables manufacturers/applicants to select the most appropriate pathway and to provide the necessary documentary evidence applicable for each pathway as part of the dossier submission.

In-line with GRP, a robust registration system incorporates principles of good risk management that ensures that the level of control and resource allocation is proportionate to the level of public health risk associated with specific products. In this regard, NRAs should classify applications submitted for registration, based on the level of potential public health risk for each product. The risk class of a specific product may be determined by factors such as the route of administration; dosage form; formulation; development level (that is, new API or multisource product); competence of the companies, including compliance with regard to GMP; applicable WHO and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines, as demonstrated from past inspections; prior approval from reference authorities or WHO prequalification; and the scope of information available from the reference authorities or the PQT.

Fig. A6.1 shows an example of registration pathways for a NRA. At the base of the model is the normal registration pathway where the NRA independently performs all assessment and inspection activities in order to reach its own decision. Following this are different levels of cooperation or collaboration with other regulators, ranging from joint activities, work-sharing, reliance and, ultimately, recognition. It is important to note that the level of effort decreases as one goes up the pyramid, from independent full assessment at the base of the pyramid to complete reliance on decisions by others (recognition) at the top of the pyramid.

Fig. A6.1
Model for registration pathways for national regulatory authorities (NRAs)



NRAs may define the combination of these approaches and should clearly state the approaches applicable for collaborative registrations, that is, for products prequalified by WHO and for products approved by reference SRAs. NRAs should state the reference authorities for which recognition or reliance is applicable. It is suggested that where a list of reference authorities is stated, at the very least it should include the established reference SRAs.

6.3 Organization of assessment activities

NRAs should also consult the other applicable WHO publications that provide detailed arrangement for assessments (*5*, *6*).

A NRA has several options for organizing its assessment activities, based on its legal and regulatory framework, development plans and capabilities. The approaches described next may be adopted by the NRA.

Verification

Verification is not a scientific assessment but an administrative process to reach a regulatory decision, based on registration or authorization by a reference NRA or WHO prequalification. The NRA formalizes its decision by approving the product or submission and ensures the product for local registration and marketing conforms to the product as prequalified by WHO and approved by the reference NRA. This may require a policy, or a regulatory provision to facilitate the NRA to apply this approach. Verification should be applied where conformity with requirements of the reference authority or institution is sufficient to meet the requirements of the receiving authority or institution. This may apply to all or part of the submission.

Abridged/abbreviated review

Abridged/abbreviated review is a limited assessment of suitability of use under local conditions and regulatory requirements, while relying on prior assessment and inspection outcomes from the reference NRA or the PQT to inform the local decision. This approach focuses on value-adding activities in addition to the NRA's assessment activities and avoids duplication of the work already done by others. Desk review of inspection reports may be considered as a form of abridged/abbreviated review.

Note: These two options (verification and abridged reviews) are not mutually exclusive, as some NRAs may implement a combination of these approaches for the Procedures, where applicable. For example, some NRAs may recognize the PQT outcomes, since they address programmatic suitability for the countries for which prequalified products are mainly intended for use, while approvals from reference NRAs may require a combination of verification and abridged/abbreviated reviews to address the local context (e.g. benefit–risk in the local population; stability to allocate the storage conditions; shelf-life at the storage conditions prevailing in the country; risk management plans; and suitability of information for patients/health professionals, where applicable). Other special access mechanisms introduced by the reference SRA may address the local context in their review process, thereby enabling verification to be applicable in those cases.

The NRA should clearly identify the type of products and applications suitable for an abridged/abbreviated review or verification, as well as the abbreviated review timelines associated with those. To facilitate implementation, registration pathways, different templates and procedures, including SOPs, should

be in place to differentiate products or applications by the type of assessment to be conducted, that is, verification, abridged/abbreviated review, and /or full review. Additionally, the assessors should be trained accordingly. Sample templates for verification and abridged/abbreviated review are provided in Appendices 2 and 3, respectively.

Secondary review

NRAs may perform secondary reviews of the shared assessment and inspection outcomes from the PQT or reference NRA. Moreover, this approach may be essential where the NRA is involved or participates in the initial reviews, for example, joint reviews between the NRA and the PQT or in special access mechanisms by reference SRAs that have provisions for NRA participation. As a result, the NRA's input may be incorporated into the final decision of the PQT or the reference SRA, thereby facilitating a concurrent regulatory decision where a parallel submission has been made.

Full review

For full review, a NRA is capable, and has the resources and expertise, to carry out a full assessment of quality, preclinical and clinical data (safety and efficacy) of products with no prior approval elsewhere. This route is not recommended for the collaborative procedures, as it is considered a duplication of effort.

Verification, abridged review, and secondary reviews facilitate better resource management for the NRAs, shorten timelines compared with a full review and could improve the quality of the review. More importantly, the quality and availability of the full reports from the reference authorities are key to this process.

The NRA reserves the right to re-route any application to the normal review process if the application does not fulfil the intent of the verification or abridged/abbreviated or secondary review process, and the applicants should be made aware of this.

6.4 The effectiveness of risk-based review strategies

What metrics should be used to determine the effectiveness of risk-based review strategies in addressing the intended problems of volume, capacity and review effort, without compromising quality?

Timelines

NRAs should set timelines that take into account the level of reliance or different registration pathways, for example, recognition, reliance, work-sharing/joint reviews and full assessment. The timelines should be based on the NRA's existing

resources and benchmarking with other NRAs. Tracking mechanisms should be in place, and these should be able to track and account for the regulator's time and applicant's/manufacturer's time during the review process. Information on a predefined time for receipt of questions and provision of answers should be defined by the NRA. Typically, this is defined as 30 calendar days for the applicant/manufacturer to respond or provide additional information.

For the Procedures, the recommended timelines are specified in the Procedure, that is, the NRA should reach a decision within 90 days of the regulatory time and communicate such decision to the applicant within 30 days of reaching it. The NRAs are encouraged to streamline national processes as outlined in Sections 6.2 and 6.3.

The timelines are also affected by the quality of the submissions and the number of review cycles.

Other metrics

Other metrics that could be useful for reliance models or the Procedure include: the proportion of products approved/disapproved/withdrawn through these risk-based approaches, relative to the total approvals; the number of review cycles relative to completion of assessments; and review effort and quality of decisions.

The NRA should be able to track these metrics for each registration pathway, to assess the relative efficiencies and effectiveness of the adopted pathways; to evaluate not only accelerated decision-making, but also the impact on regulatory burden and quality of regulatory decisions; and to identify areas for improvement.

6.5 Steps of the common regulatory pathway

In principle, the CRP follows the key steps of a national registration process; however, certain steps can be simplified. According to NRA practice, the points presented next should be considered and incorporated into internal SOPs.

Procedure initiation

When the Procedure commencement date is announced by a NRA, the Procedure is applicable to new submissions to the NRA, or for products pending registration in the NRA. In situations where the applicant wishes to apply the Procedure to an application that is already pending within the NRA, the applicant should first update the dossier to ensure that the technical part of the information is the same as that approved by the PQT or reference NRA, and any deviations should be clearly stated. It is up to the NRA to decide whether or not it is more convenient to switch to the Procedure to complete the registration or to grant registration via the normal pathway, and inform the applicant accordingly (e.g. when the assessment is finished and registration is imminent).

Each applicant initiates the Procedure by submitting CRP-specific documents as part of a registration application. The correct fees should be paid and the date of receipt of the dossier/application recorded by the NRA.

Dossier format and content

Dossiers should be submitted in the appropriate format, as required by the respective NRAs, that is, hard copies, electronic format in portable document format (PDF), or electronic common technical document (eCTD), as applicable. Notwithstanding the submission format to the respective NRAs, the content of the dossier should enable verification of the sameness of the products as those of the PQT or the reference NRAs. The dossiers should be updated to include all variations approved by the PQT or reference NRA before the national submission. A current quality information summary (QIS or QIS-SRA(crp)) should be provided, where applicable, subject to exceptions in line with the PQT product-specific procedures. Additional NRA-specific documents should be included, such as application forms, product information and labelling in national format, if required. For detailed guidance on submission format and content, please refer to Section 4.2 in reference (*2*) and Section 4.1 in reference (*3*).

Screening to validate the application

The NRA should properly screen the applications, to ensure that the product is eligible for the Procedure and that all the required documentation is provided, as per the NRA procedures and CRP process. Use of a checklist is recommended (Appendix 4). The submission of the dossier should be recorded using the existing procedures for storage and management of applications. Formal deficiencies in the submitted application and the dossier should be communicated to the applicant, in line with the national practice. The screening should be performed quickly (e.g. within 2 days) and applicants should be given a defined time to respond (e.g. 30 days).

Decision on the Procedure and informing WHO

Having a complete valid CRP application, the NRA promptly decides whether or not to apply the Procedure, marks in its records that the product is being processed under the CRP, and promptly informs WHO accordingly. In the case that the NRA decides to register the product in line with the Procedure, the PQT or reference NRA shares assessment and inspection reports, typically within 30 days of receipt of the request and/or expression of interest from the applicant to participate in the CRP. This starts the 90-day regulatory period in which NRAs should decide on the registration in line with the Procedure.

Processing the application

To maximize the benefits of the PQT or reference NRA outcomes, the NRA is recommended to follow the risk-based review process, that is, to verify that the prequalified or reference NRA-approved product and national submissions are the same, and review country specific requirements, for example, prescribing and labelling information. The need for a special risk management plan follow-up should be considered. Appendix 2 is a template for verification, representing a simplified process to verify product similarity. Appendix 3 is a template for an abbreviated/abridged review, which includes verification of detailed requirements and limited scientific assessment to suit the local context, as required. Where applicable, as per country procedure, the report is tabled for consideration by a competent technical committee as soon as practicable, and within 90 calendar days of the Procedure.

Inspections

If the NRA inspectorate is involved in assessing compliance with GMP and other practices, and in data verification, the inspectors have available PQT or reference NRA inspection reports to facilitate the development of their judgement. It is advisable to organize a desk-review process instead of on-site inspections (*7*).

Laboratory testing

Preregistration laboratory testing of submitted samples is not recommended during CRPs. Instead, post-registration risk-based testing is recommended. The NRA should assess whether it is feasible to perform independent testing in its laboratories, or whether special arrangements or partnerships are necessary. WHO advice can be sought in relation to quality testing, and results from WHO-organized testing for prequalified products, including lot-release testing results for vaccines, can be shared. In other words, for vaccines, reliance on testing done by national quality control laboratories from reference authorities should serve as the basis for CRPs.

Product information

Prescribing and labelling information should be submitted in the standard national format. In the case of labelling, a mock-up presentation is normally sufficient instead of a definitive printed package of the product to be marketed, which may be difficult to produce before registration. Indications should be checked against national therapeutic guidelines, when applicable. The content of the product information should correspond to the information approved by the PQT or reference NRA. Different information content must be justified and can represent a deviation from prequalification or approval by the reference NRA.

For prequalified vaccines, the product information and labelling submitted to the NRA should be the same as that approved by the PQT.

Communication with applicants

After the NRA review process, issues to be communicated to WHO, the reference NRA, or the applicant are summarized and communicated through the normal communication procedures of the NRA. Should the applicant fail to respond in time or to provide other necessary cooperation, the NRA is entitled to terminate the procedure and to process the application in line with normal registration procedures. Such termination is communicated to the applicant and to WHO or the reference NRA.

Decision on registration and communication to WHO

The NRA may decide to refuse to register or issue a registration. Reasons for refusal and/or conditions for registration, including post-registration commitments, should be formally prepared and concurrently shared with the applicant and WHO within 30 days of the decision. The registration number, date, clock-stop days and – if applicable – deviations from the PQT or reference NRA decisions, should be notified to WHO and the reference NRA, as applicable.

Regulatory time measurement

The regulatory registration time for the purpose of the Procedure starts on the day on which the assessment and inspection reports are shared, or when a valid submission is received by the NRA (whichever is later), and ends on the date of registration. In the event of queries being raised, the clock should stop until the applicant has addressed the concern. Clock-stop time is not included in the registration time.

6.6 The focus of reviews in abridged/abbreviated assessments

The level of abridged review may vary depending on the type of product, for example, generic versus innovative product, or prescription versus non-prescription medicine, vaccines versus chemical entities, or the collaborative procedure, that is, based on WHO prequalification or reference NRA approval, or through special access mechanisms.

Quality review

Reliance is generally straightforward, as quality standards are often common across major jurisdictions, and those determined by the PQT or reference SRA are considered adequate for most NRAs. Nonetheless, applicant/manufacturer filing strategies may complicate reliance mechanisms, owing to potential

differences in indications and data and quality specifications for different markets. Notwithstanding this, the QIS or QIS-SRA(crp) is a useful document to facilitate the verification or abridged review for quality documentation, subject to exceptions as per Section 6.5, "Dossier format and content". It allows the applicant to clearly state differences, if any, for example, storage conditions and shelf-life for reference NRA approvals and easy verification of product sameness, thereby saving significant NRA resources in verification or abridged reviews. Verification or abridged reviews may focus on:

- *for APIs/drug substances*: general properties that enable identification of the potential impact of critical quality attributes on the performance of the finished product/drug product (e.g. pK_a, solubility, particle size distribution, polymorphism, where relevant); manufacturing site; manufacturing process (e.g. for APIs, purification crystallization, micronization; for drug substances, producing cell line, cell banks, purification methods, presence of viral inactivation steps); quality standards and specifications and test methods of the API/drug substance; container closure system; retest period; and storage conditions;
- *for biological substances*: the description of the molecule, including features such as glycosylation/post-translational modifications; "artificial" modifications (amino-acid substitutions, pegylation); and molecular size.
- *for FPPs/drug products*: description; unit and batch formula; production batch sizes; manufacturing site; manufacturing process; quality standards and specifications and test methods of the excipients and FPP/drug product; container closure system; shelf-life, including in-use period; and local storage conditions.

Note: In some cases, for example, approvals by reference SRAs, the NRAs may need to perform an additional independent review of stability data if the climatic conditions, or container closure system, and consequently the stability data, are not the same, but this does not preclude reliance on other quality aspects under the Procedure.

Clinical review

The NRAs should ensure the indications are consistent with national treatment guidelines, where applicable. For the collaborative procedure for reference SRA-approved innovative products, reliance tends to be more challenging, notwithstanding the same dataset that had been reviewed by the reference SRA, as the benefit–risk may not be identical in the different populations or settings. Additionally, with the adoption of various facilitated registration

mechanisms for innovative medicines, including conditional approvals or rolling submissions, the NRAs may not have similar registration pathways to facilitate approvals of such products. With this in mind, the concept of the bridging report (*15*) is recommended for the CRP for products approved by SRAs, to address differences in the target population relative to the population in the clinical trials; epidemiology and other features of the disease; concomitantly-used medicines; and, hence, the interaction potential; local therapeutic and diagnostic modalities; and other factors that can substantially lead to a different benefit–risk balance. A risk management plan should be reviewed from the point of view of local relevance.

Post-approval changes

Post WHO prequalification or reference NRA authorization, commitments should be considered and the relevant ones may be included in the local NRA registration decision. The applicants should be committed to reflect or at least notify post-approval changes. Deviations of the locally registered product from the PQT- or reference authority-approved product should be reported.

A model example of information, documentary evidence and assessment activity of a NRA applying the reliance model is provided in Appendix 5.

6.7 Managing product differences

Some differences could exist between the application dossiers, in particular for SRA-approved products. These should be clearly stated, and, in some cases, the NRA has to perform its own assessments of such data where the proposed changes were not covered in the original submission/assessment performed by reference SRA. Some common potential differences are highlighted below for illustrative purposes:

- different presentations without changing the packaging materials;
- regional labelling requirements;
- storage conditions and shelf-life.

Any change beyond the above would result in the product being considered different from the prequalified product or that approved by the reference NRA.

6.8 Managing variations/post-approval changes

Post-approval changes (variations) require significant resources for both manufacturers and the NRAs and pose a significant threat to the continued supply of quality-assured medicines and vaccines in the target countries. More

specifically, it is generally reported that it takes 2–4 years to complete approval of moderate to major change(s) in every country where a global product is registered. Consequently, these long regulatory approval timelines not only make the supply chain complex, with different versions of the product required to supply multiple countries, but also consume substantial resources for both manufacturers and NRAs.

To ensure the absence of deviations between the WHO-prequalified product, or reference NRA-approved product and the NRA-registered product, variations should only be submitted to the NRA after acceptance by the PQT or approval by reference NRAs, to ensure sameness of the products throughout the product life-cycle.

While it is expected that many NRAs have the expertise and capacity to review variations, there is significant risk associated with reviewing variations to a product approved by a different authority. Variations should be reviewed by the originating authority, to avoid the possibility/likelihood of different changes being accepted in the originating and receiving countries over time. This results in the product in the receiving country no longer being the same as that approved by the originating authority, that is, different from the product for which safety, efficacy and quality have been established.

The *WHO general guideline on variations to multisource pharmaceutical products* (*16*) provides a recommendation for expanding the capacity of individual NRAs through work-sharing and recognition of the decisions of other NRAs in the network, and convergence of regulatory requirements, thus avoiding unnecessary repetition of evaluations of the same variation by multiple NRAs.

Categorizations and management of variations

Variation terminology, fees and administrative requirements are subject to national regulations. Variations to the product that have been registered by the CRP registration pathway should first be submitted to the PQT or reference NRA for assessment. Post-approval variations differ, depending on the CRP route followed. The PQT will only categorize variations for prequalified products on a product-specific basis (*17*, *18*), while accepting SRA-approved variations and their categorization.

Once approved by the PQT or reference NRA, the applicant may implement the change and notify the NRA of such immediately (within 30 days). Variations submissions to NRAs should clearly indicate that the product has been registered by the CRP registration pathway, with same dossier, including any additional information based on PQT or reference NRA assessment, and evidence of such approval by submission of the "PQT or reference NRA approval letter" (for minor or major variations) or PQT or reference NRA acknowledgement

email (for notifications). The PQT or reference NRA will share the variation outcomes with the NRA, for variations that require prior approval.

To monitor the post-prequalification changes and to verify the compliance of manufacturers in submissions of variations, participating NRAs can benefit from visiting the PQT or reference NRA's website. WHO or reference NRA public assessment reports are continually updated with regard to the lists of approved variations.

The notifications that affect administrative information relevant to WHO or the reference NRA only are not included. Such administrative changes relevant for individual participating NRAs should be submitted in line with national legislation and guidance. As regards reference NRA-approved products, classification of variations may somewhat deviate from the PQT scheme, but similar principles of variation management should be followed, benefiting as much as possible from publicly available information.

Processing variations by the national regulatory authorities and communication to WHO

Like the assessment during the registration process, the NRA may consider performing verification based on the shared assessments of the variation by the PQT or reference NRA, instead of independent review, and issue an acknowledgement of receipt or approval within 30 days.

If a change is rejected by the NRA, this should be communicated to the applicant with an explanation for the rejection. As appropriate, there should be an opportunity for dialogue between the NRAs, WHO and the applicant, as necessary, with the aim of resolving the NRA's concerns with the application. Any significant deviations resulting in the NRA-registered product not being the same as the PQT- or reference NRA-approved product should be communicated to WHO and the reference NRA within 30 days, at which point the corresponding product is no longer considered to be in the CRP process.

Non-administrative changes submitted only to the NRA should not be approved or accepted unless justified. If the NRA decides to approve/accept a variation that is not approved or accepted by the PQT or reference NRA, the NRA should record the differences between the PQT- or reference NRA-approved and national product. The NRA informs WHO of such variations if they are major, for updates in the online list of products registered through the collaborative procedure. Depending on the nature of such variations, the product can be treated as different from the prequalified or the reference NRA product in the given parameters. As already discussed, in such cases when the NRA-registered product is no longer considered the same as the PQT- or reference NRA-approved product, the product is no longer considered to be in the CRP process.

6.9 Registration renewals: national regulatory authority and WHO actions

Renewals

The validity of registration and renewal of registration by the NRA will be based on the existing guidelines for renewal of registration of products applicable in each NRA. The renewal process represents a good opportunity to review whether all applicants' commitments were satisfied and to verify consistency (e.g. verifying all approved variations; requalification in the case of a prequalified pharmaceutical product; renewal or changes to the conditions of registration in the reference NRA are up to date for the nationally registered product) between the PQT, reference SRAs and national registration conditions.

Withdrawals, de-registrations, suspensions and de-listings

In cases where a prequalified product is withdrawn from prequalification by the manufacturer, it is suspended or de-listed by the PQT, who will then promptly, through the restricted-access website, and subject to the above-mentioned obligations of confidentiality and restrictions on use, inform the relevant participating NRA accordingly, providing the reasons for the withdrawal whenever required to do so. The same procedure applies for products registered through the collaborative procedure for SRA-approved products.

If a participating NRA de-registers or suspends the registration of a prequalified or SRA-approved product for any reason, the participating NRA informs the PQT or reference SRA thereof (together with the reason for this decision). The information should be provided without delay whenever product quality, safety or efficacy is concerned, and, in other cases, within 30 working days. A participating NRA is encouraged to consult the PQT or reference SRA before adopting a decision about de-registration or suspension of registration of a WHO-prequalified or SRA-approved product.

Other matters

In the event of a Notice of Concern (NoC) issued by the PQT or reference SRA for a site (GMP, good clinical practices [GCP] and good laboratory practices [GLP] issues) on a product registered under the procedure, the NRA should follow the position of the PQT or reference SRA, unless justified to decide otherwise. Reasons for not following the PQT or reference SRA decision should be communicated to the PQT or reference SRA.

References

1. Resolution WHA67.20. Regulatory system strengthening for medical products. In: Sixty-seventh World Health Assembly, Geneva, 19–24 May 2014. Geneva: World Health Organization; 2014 (http://apps.who.int/medicinedocs/documents/s21456en/s21456en.pdf, accessed 15 February 2019).
2. Collaborative procedure between the World Health Organization (WHO) Prequalification Team and national regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products and vaccines. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fiftieth report. Geneva: World Health Organization; 2016: Annex 8 (WHO Technical Report Series, No. 996; http://apps.who.int/medicinedocs/documents/s22405en/s22405en.pdf, accessed 15 February 2019).
3. Collaborative procedure in the assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fifty-second report. Geneva: World Health Organization; 2018: Annex 11 (WHO Technical Report Series, No. 1010; http://apps.who.int/medicinedocs/documents/s23456en/s23456en.pdf, accessed 15 February 2019).
4. Good regulatory practices: guidelines for national regulatory authorities for medical products. Geneva: World Health Organization; 2016 (working document QAS/16.686; https://www.who.int/medicines/areas/quality_safety/quality_assurance/GoodRegulatory_PracticesPublicConsult.pdf, accessed 15 February 2019).
5. Marketing authorization of pharmaceutical products with special references to multisource (generic) products: a manual for national medicines regulatory authorities (NMRAs), 2nd ed. Geneva: World Health Organization; 2011 (https://apps.who.int/iris/bitstream/handle/10665/44576/9789241501453_eng.pdf?sequence=1, accessed 15 February 2019).
6. Good review practices: guidelines for national and regional regulatory authorities. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, forty-ninth report. Geneva: World Health Organization; 2015: Annex 9 (WHO Technical Report Series, No. 992; http://apps.who.int/medicinedocs/documents/s21902en/s21902en.pdf, accessed 15 February 2019).
7. Guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fifty-second report. Geneva: World Health Organization 2018 (WHO Technical Report Series, No. 1010; http://apps.who.int/medicinedocs/documents/s23457en/s23457en.pdf, accessed 15 February 2019).
8. World Health Organization. Collaborative procedure for accelerated registration (https://extranet.who.int/prequal/content/collaborative-procedure-accelerated-registration, accessed 15 February 2019).
9. ICH harmonisation for better health. M4: The Common Technical Document (https://www.ich.org/products/ctd.html, accessed 15 March 2019).
10. Definition of stringent regulatory authority. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fifty-first report. Geneva: World Health Organization; 2017:34–5 (WHO Technical Report Series, No. 1003; https://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_1003_full-version.pdf?ua=1, accessed 15 February 2019).

11. Definition of "stringent regulatory authority". In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fifty-second report. Geneva: World Health Organization; 2018:43–4 (WHO Technical Report Series, No. 1010; https://apps.who.int/iris/bitstream/handle/10665/272452/9789241210195-eng.pdf?ua=1, accessed 15 February 2019).

12. World Health Organization. Essential Medicines and Health Products: prequalification of medicines (http://www.who.int/prequal/, accessed 15 February 2019).

13. World Health Organization. Immunization standards. Revised procedure for expedited review of imported prequalified vaccines for use in national immunization programmes (http://www.who.int/immunization_standards/vaccine_quality/expedited_review/en/, accessed 15 February 2019).

14. ICH harmonised tripartite guideline. Quality risk management Q4. Step 4 version. Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 2005 (https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf, accessed 15 February 2019).

15. Appendix 6: Requirements for provision of a bridging report for reference SRA-approved pharmaceutical product and vaccines for consideration of registration in participating countries. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fifty-second report. Geneva: World Health Organization; 2018: Annex 11 (WHO Technical Report Series, No. 1010; https://www.who.int/medicines/areas/quality_safety/quality_assurance/TRS1010annex11.pdf, accessed 16 February 2019).

16. WHO general guidance on variations to multisource pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fiftieth report. Geneva: World Health Organization; 2016: Annex 10 (WHO Technical Report Series, No. 996; http://apps.who.int/medicinedocs/documents/s22407en/s22407en.pdf, accessed 15 February 2019).

17. WHO guidelines on variations to a prequalified product. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, forty-seventh report. Geneva: World Health Organization; 2013: Annex 3 (WHO Technical Report Series, No. 981; https://www.who.int/medicines/areas/quality_safety/quality_assurance/Annex3TRS-981.pdf?ua=1, accessed 15 February 2019).

18. Guidance on variations to a prequalified vaccine. Geneva: World Health Organization; 2015 (http://www.who.int/immunization_standards/vaccine_quality/PQ_VXA_Variations_V7.pdf?ua=1, accessed 15 February 2019).

Appendix 1

An example of information to applicants for registration via the WHO collaborative registration procedure

Registration of WHO-prequalified pharmaceutical products and vaccines/products approved by stringent regulatory authorities (SRAs) through the collaborative registration procedure

Since [*date*], [*name of the NRA*] participates in the World Health Organization (WHO) collaborative registration procedure (CRP) for WHO-prequalified pharmaceutical products and vaccines/collaborative procedure in the assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities (SRAs), and accepts applications for registration in line with this procedure (hereinafter referred to as "the Procedure").

This Procedure serves to facilitate and accelerate the registration of products that have already been assessed and listed as prequalified by the WHO Prequalification Team (PQT)/SRAs. Detailed information about the CRP can be obtained at: https://extranet.who.int/prequal/content/collaborative-registration-faster-registration/ https://extranet.who.int/prequal/content/faster-registration-fpps-approved-sras

All applicants for national registration of WHO prequalified products/ SRA-approved products are encouraged to use this registration route. With this pathway, **finalization of the valid application is expected within 90 days of regulatory time**. Subject to [*name of the NRA*]'s previous agreement, the Procedure is also applicable to pending WHO prequalified products/SRA-approved products already in national registration. Specific arrangements may be necessary.

[*Name of the NRA*] reserves the right to use the standard national registration route or to switch to it during the CRP, in case of specific products (for example, products not included in national treatment/vaccination guidelines) or lack of the applicant´s cooperation.

Applicants wishing to use this registration route should:

1. Notify WHO/the SRA of their intention to use this Procedure for registration of a particular product by sending the appropriate notification form (Appendix 2/Appendix 3 Part B) to WHO/the SRA, as outlined on the WHO website. If the applicant for national registration is different from the manufacturer with a prequalified product/SRA-approved product, the

mutual agreement between the applicant and the manufacturer is necessary and the notification to WHO/the SRA has to be sent by the manufacturer.

2. Follow the national guidance to applicants for registration, available at [*insert reference for national guideline*]. More importantly, the following should be considered:

   a. The national Application form and requirements on samples and labelling stay in place.
   b. "WHO Collaborative Procedure"/"SRA Collaborative Procedure" should be indicated as the proposed registration pathway in the national application form or in the covering letter.
   c. The Expression of Interest form (Appendix 3 Part A/Appendix 7 of the Procedure), as outlined on the WHO website, has to be submitted.
   d. The technical content of the dossier has to correspond exactly to that submitted and currently approved by the PQT/SRA and as specified in the corresponding Procedure guidelines. The dossier has to be updated to reflect all post-prequalification variations approved by the PQT/SRA and accompanied by the appropriate current quality information summary (QIS)/QIS-SRA(crp). All variations still pending at the PQT/SRA have to be notified, and deviations from the prequalified product have to be clearly declared in the expression of interest form (Appendix 3 Part A/Appendix 7 of the Procedure).
   e. Additional, country specific requirements are: _____

3. A fee of _____ per product is charged for new applications considered under this procedure.

In situations where the applicant wishes to apply the Procedure to an application that is already pending with [*name of the NRA*], the applicant should first update the dossier to ensure that the technical part of the information is the same as that currently approved by the PQT/SRA, as applicable.

The post-prequalification variations should be submitted to [*name of the NRA*] within 30 days from the PQT/SRA approval. The PQT/SRA approval letter should be attached.

In case of questions/requests related to the CRP, the [name of the NRA] focal person's contact information is as follows: [*name of the NRA focal person for the CRP and their contact information*].

Appendix 2

Verification for product submitted under the WHO collaborative procedure

Note [*instructions on using the template*]**:** This template is provided for verification of products to be registered nationally through the WHO collaborative procedure for prequalified products, or products approved by reference stringent regulatory authorities (SRAs). National regulatory authorities (NRAs) are free to modify the template as they deem fit, to suit their specific requirements.

1. Product details

Dossier aspects to verify	
Proprietary product name	
International Nonproprietary Name (INN) of the active pharmaceutical ingredient (API)/ drug substance, strength, pharmaceutical form	
Applicant	
Date of application	
Application number (assigned by NRA)	
Type of product/registration	
Reference authority	
Declaration from the applicant	

2. Product quality

Dossier aspects to verify	Comments (including confirmatory statements of sameness)
Marketing status in reference SRA or WHO prequalification status	
Name and complete address of the applicant	

Table *continued*

Dossier aspects to verify	Comments (including confirmatory statements of sameness)			
Name and complete address (including specific unit/blocks) of the API/drug substance manufacturer(s)				
Name(s) and complete address(es) (including specific unit/blocks) of the manufacturer(s) of the finished pharmaceutical product(s) [FPP(s)] or biological drug products(s) (DP(s)), including the final product release if different from the manufacturer				
Description (visual appearance)				
Composition	**Component and quality standard**	**Function**	**Quantity per unit (mg)**	**%**
	Total			
Specifications for the finished product				
Container closure system (including pack sizes, container size or volume)				
Stability summary and conclusions (including the storage statement and shelf-life)				
Lot/batch-release documents				
Assessor's comments on the product quality				

3. Product information

Dossier aspects to verify	Comments
Is the information for the health-care professional provided as approved by the reference SRA or WHO Prequalification Team (PQT)?	
Is the information for the patient/user (patient information leaflet) provided as approved by the reference SRA or PQT?	
The information does not contradict national therapeutic guidelines	
Assessor's comments on the product information	

4. Labelling

The following minimum information appears on the label:

Dossier aspects to verify	Comments
Is the labelling of outer packaging (as final packaging or mock-up presentation) provided as approved by the reference SRA or PQT?	
Additional information on outer packaging as per national requirements	
Is the labelling of internal packaging (as final packaging or mock-up presentation) provided as approved by the reference SRA or PQT?	
Additional information on internal packaging as per national requirements	
Assessor's comments on the product labelling	

5. Applicant commitments to the WHO Prequalification Team or reference stringent regulatory authority

State any commitments by the applicant to WHO or to the reference SRA that may require follow up.

Examples:

- The applicant undertook to continue long-term testing of [*INN of API*] for a period of time sufficient to cover the whole provisional retest period [*period ending month/year*].

- The applicant undertook to continue long-term testing of [*FPP reference number, trade name [INN of API], strength, pharmaceutical form*] for a period of time sufficient to cover the whole provisional shelf-life [*period ending month/year*].
- The applicant committed that three consecutive production batches would be prospectively validated and a validation report – in accordance with the details of the validation protocol provided in the dossier – would be made available as soon as possible, for evaluation by assessors or for verification by the WHO inspection team.

6. General national regulatory authority review comments

7. Assessment of responses to [*list of questions/list of outstanding issues/request for supplementary information*]

For each question:

Question:

Response from the applicant:

Assessment of response:

Appendix 3

Abridged/abbreviated review for product submitted under the WHO collaborative procedure

***Note* [*instructions on using the template*]:** This template is provided as a recommended approach including a combination of the verification and abridged review of products to be registered nationally through the WHO collaborative procedure for prequalified products, or products approved by reference stringent regulatory authorities (SRAs). National regulatory authorities (NRAs) are free to modify the template as they deem fit, to suit their specific requirements. The assumption is that the NRA has access to the final assessment outcomes from WHO or the reference SRA in the form of assessment and inspection reports, including the quality information summary (QIS), to facilitate the abridged review. This template does not cover situations where the NRAs have no access to this confidential information in order to enable the verification of the specific product quality-related outcomes from WHO or the reference SRA. The different sections, for example, quality, clinical, product information and labelling, as well as risk management plans (RMPs), may be separated into different templates, especially where different teams/disciplines are involved in the review process.

1. Product details

Dossier aspects to verify	
Proprietary product name	
International Nonproprietary Name (INN) of the active pharmaceutical ingredient (API) or drug substance, strength, pharmaceutical form	
Applicant	
Date of application	
Application number (assigned by NRA)	
Type of product/registration	
Reference authority	
Declaration from the applicant	

2. Product quality

Dossier aspects to verify	WHO Prequalification Team (PQT) or reference SRA submission	NRA submission	Comments
Name and complete address of the applicant			
Name(s) and complete address (including specific blocks/units) of the manufacturer(s) of the finished pharmaceutical product(s) [FPP(s)] or biological drug products(s) (DP(s)), including the final product release if different from the manufacturer			
Drug substance or active pharmaceutical ingredient (name, manufacturer)			
Name of API/drug substance			
General properties that may affect the performance of the finished product (for example, polymorphism, solubility in physiological media)			

Table *continued*

Dossier aspects to verify	WHO Prequalification Team (PQT) or reference SRA submission	NRA submission	Comments
Name and address(es) (including specific blocks/units) of the manufacturer(s) of the API(s)/drug substance			
Control of the API/drug substance (including the specification reference number, version and date – the copy of the specification may be included as an attachment to the report)			
Analytical procedures (including the analytical procedure reference number, version and date – the copy of the analytical procedure may be included as an attachment to the report)			
Container closure system			

Table *continued*

Dossier aspects to verify	WHO Prequalification Team (PQT) or reference SRA submission				NRA submission				Comments
Stability summary and conclusions (including storage statement and re-test period)									
Finished pharmaceutical product (FPP)/drug product (DP)									
Description									
Composition	**Component and quality standard**	**Function**	**Quantity per unit (mg)**	**%**	**Component and quality standard**	**Function**	**Quantity per unit (mg)**	**%**	
	Total				**Total**				

Table *continued*

Dossier aspects to verify	WHO Prequalification Team (PQT) or reference SRA submission		NRA submission		Comments
Manufacturer (name, address (including specific block/unit) and responsibility)					
Commercial batch size and batch formula	**Proposed commercial batch size(s) (for example, number of dosage units)**		**Proposed commercial batch size(s) (for example, number of dosage units)**		
	Component and quality standard (and grade, if applicable)	**Quantity per batch (kg/ batch)**	**Component and quality standard (and grade, if applicable)**	**Quantity per batch (kg/ batch)**	
	Total		**Total**		

Table *continued*

Dossier aspects to verify	WHO Prequalification Team (PQT) or reference SRA submission	NRA submission	Comments
Narrative description of the manufacturing process (no need to compare the whole manufacturing process – one can just look at the blank master production document reference number, version and date, together with information on the site)			
Control of FPP/DP (state the specification reference number, version and date – a copy of the specification may be included as an attachment to the report)			
Analytical procedures (including the analytical procedure reference number, version and date–- a copy of the analytical procedure may be included as an attachment to the report)			

Table *continued*

Dossier aspects to verify	WHO Prequalification Team (PQT) or reference SRA submission	NRA submission	Comments
Container closure system (including pack sizes, container size or volume)			
Stability summary and conclusions (including the storage statement and shelf-life)			
Lot/batch-release documents			
Assessor's comments on the product quality			

3. Clinical safety and efficacy

Pharmacokinetic/safety/efficacy-related information used for PQT or reference SRA approval		
Type of study	"X" in appropriate box	Comparator product, where applicable
Bioequivalence/comparative pharmacokinetics		
Biowaiver based on Biopharmaceutics Classification System (BCS) biowaiver		
Additional strength biowaiver		
Clinical data		
Comparative pharmacodynamic and potential immunogenicity (for biologicals)		
Other (please specify)		
Assessor's comments on pharmacokinetic/safety/ efficacy-related information		

Bioequivalence/comparative pharmacokinetics			
Dossier aspects to verify	**PQT or reference SRA submission**	**NRA submission**	**Comments**
Study #			
Study title			
Clinical facility (or the contract research organization)			

Table *continued*

Bioequivalence/comparative pharmacokinetics			
Dossier aspects to verify	**PQT or reference SRA submission**	**NRA submission**	**Comments**
Bioanalytical laboratories			
Number of patients/volunteers			
Test product (name, manufacturer, batch number, batch size, location of multipoint dissolution data in physiological media and release media, if different)			
Reference product (name, manufacturer, source, batch number, expiry date)			
Results (geometric ratio and the 90% confidence intervals for the PK parameters)			
Assessor's comments on bioequivalence/comparative pharmacokinetics			

Relevant clinical studies			
Dossier aspects to verify	**PQT or reference SRA submission**	**NRA submission**	**Comments**
Study ID			
Number of study centres/ locations			
Design			
Study posology			
Study objective			
Subjects by arm entered/ completed			
Duration			
Population included in the study (age, sex, ethnicity, severity of disease)			
Diagnosis including criteria			
Primary endpoint			
Assessor's comments on relevant clinical studies			

4. Clinical data

Note: The benefit–risk profile of SRA-approved products in other markets could differ, as their use in other markets is not always considered in the SRA review process. In this respect, the SRA assessment does not always confirm the availability of data and questions that are relevant for use in other environments. For this reason, the SRA assessment reports can be considered incomplete. Therefore, the NRA has to address this local context or suitability in a local environment as part of the review process under the WHO collaborative registration procedure (CRP).

Product information	Comments
Proprietary product name	
International Nonproprietary Name (INN) of the API/drug substance, strength, pharmaceutical form	
Chemical class (new molecular entity [NME]/ therapeutic biological product, existing APIs/drug substance, new salt or ester, new dosage form, new combination product, amongst others)	
Pharmacological class	
Proposed indications, dosing regimens, age groups (confirm whether these are the same as approved by the reference SRA, WHO guidelines or national treatment guidelines)	
Existing alternatives to the proposed product for the same indication(s)	
Clinical pharmacology	
Justification for the dose/dose regimen (in the target population)	
Absorption, distribution, metabolism and excretion (ADME) (applicability in the target population, e.g. the pharmacokinetic effects of drug-demographic and drug-disease interactions, such as, renal impairment, hepatic impairment, should be described)	
Interaction studies (food and drug/drug interactions relevant for target countries that are not discussed in the SRA assessment report)	

Table *continued*

Product information	Comments
Pharmacodynamics	
Statistical methods for additional analysis, such as subgroup analyses and adjusted analyses	
Benefit–risk analysis	
Relevance of studied population for the target population (ethnicity, gender representation, age groups, etc.) as regards demonstration of safety and efficacy	
Relevance of SRA-approved conditions of use (proposed indications, dose and directions of use) as regards epidemiology and disease pattern in the target countries, as well as other implications for efficacy and safety, for example, feasibility of monitoring and precautionary measures (such as, microbial resistance testing or therapeutic drug monitoring) (applicants should have evaluated the effects of major demographic factors [e.g. age, sex, and race] and other predefined or relevant intrinsic and extrinsic factors on efficacy [such as, disease severity, prior treatment, concomitant illness, concomitant drugs, body weight, genetic variants, renal or hepatic impairment, microbial resistance]; regional differences may need to be considered with respect to multinational clinical trials)	
The adequacy of the directions for use	
The therapeutic role of a product and its recommended use according to relevant national and international treatment guidelines	
Other related quality issues, including but not limited to, storage conditions and conditions of administration and use	
Assessor's comments on clinical data	

5. Risk management plans

Note: The benefit–risk profile of SRA-approved products in other markets could differ, as their use in other markets is not always considered in the SRA review process. In this respect, the SRA assessment does not always confirm the availability of data and questions that are relevant for use in other environments. For this reason, the SRA assessment reports can be considered incomplete. Therefore, the NRA has to address this local context or suitability in a local environment as part of the review process under the WHO collaborative registration procedure (CRP).

Product overview	Comments
Proprietary product name	
International Nonproprietary Name (INN) of the API/drug substance, strength, pharmaceutical form	
Chemical class (new molecular entity (NME)/ therapeutic biological pro duct, existing API (generic) or similar biotherapeutic product, new salt or ester, new dosage form, new combination product, amongst others)	
Pharmacological class	
Proposed indications, dosing regimens, age groups (confirm whether these are the same as approved by the reference SRA, WHO guideline or national treatment guidelines)	
Risk management plan (RMP) was provided with the submission	
Epidemiology of the indications and target population (relevance of the clinical trial population to the intended target population [inclusions, exclusions, limited numbers, trial setting, use in special populations])	
Assessment of identified and potential risks (inclusion of all important risks related to the active substance, formulation, route of administration, target population, specific subpopulations and the potential for interaction from the safety specifications)	

Table *continued*

Product overview	Comments
Summary of planned pharmacovigilance activities (including post-authorization safety studies) (ongoing and planned studies in the post-authorization pharmacovigilance development plan in the target population)	
Plans for post-authorization efficacy studies (if applicable)	
Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)	
To what extent does the RMP approved by the reference SRA and applicant's commitments reflect the local situation or needs?	
Summary of the RMP	
Assessor's comments on the RMP	

6. Product information

6.1 Information for health-care professionals and corresponding sections of the patient information leaflet

***Note*:** The patient information leaflet (PIL) should fully mirror the information for health-care professionals in a user-friendly language and style. The review of the product information should take into account the local context, especially in cases where this was not accounted for in the reviews by the reference SRA. Moreover, WHO prequalification product information is specific to the expressions of interest (EOIs), that is, only taking into account the specific therapeutic indication in the EOI, while the NRA may consider broader therapeutic indications and national treatment guidelines.

Dossier aspects to verify	Comments
Is the information for the health-care professionals provided as approved by the reference SRA or PQT?	
Is the information for the patient/user (PIL) provided as approved by reference the SRA or PQT?	

Table *continued*

Dossier aspects to verify	Comments
Does the information contradict national therapeutic guidelines?	
Assessor's comments on the product information	

6.2 Labelling

The following minimum information appears on the label:

Dossier aspects to verify	Comments
Is the labelling of outer packaging (as final packaging or mock-up presentation) provided as approved by the reference SRA or PQT?	
Additional information on outer packaging as per national requirements	
Is the labelling of internal packaging (as final packaging or mock-up presentation) provided as approved by the reference SRA or PQT?	
Additional information on internal packaging as per national requirements	
Assessor's comments on the product labelling	

7. Applicant commitments to the WHO Prequalification team or reference stringent regulatory authority

State any commitments by the applicant to WHO or to the reference SRA that may require follow up.

Examples:

- The applicant undertook to continue long-term testing of [*INN of API*] for a period of time sufficient to cover the whole provisional retest period [period ending month/year].
- The applicant undertook to continue long-term testing of [*FPP reference number, trade name [INN of API], strength, pharmaceutical form*] for a period of time sufficient to cover the whole provisional shelf-life [*period ending month/year*].

- The applicant committed that three consecutive production batches would be prospectively validated and a validation report – in accordance with the details of the validation protocol provided in the dossier – would be made available as soon as possible for evaluation by assessors or for verification by the WHO inspection team.

8. General national regulatory authority review comments

9. Assessment of responses to [*list of questions/list of outstanding issues/request for supplementary information*]

For each question:

Question:

Response from the applicant:

Assessment of response:

Appendix 4

Additional information to be included in the screening checklist

Note **[*instructions on using the template*]:** This template only provides additional considerations during screening which is specific to the WHO collaborative procedure (hereinafter referred to as "the Procedure"). The assumption is that the national regulatory authority (NRA) has a standard dossier screening checklist to ensure a valid submission is provided by the applicants. This template provides additional considerations to assist the NRA in determining the suitable registration pathway and assessment level/type.

Dossier/product information
Dossier application/screening number
Applicant
Submission date
International Nonproprietary Name, strength, dosage form

Screening details

Description	Yes/no	Comments
Has the applicant submitted the applicable expression of interest (that is, cover letter and/or applicable appendices) for the Procedure?		
Has the applicant submitted a valid marketing authorization/registration data/prequalification letter from (*cross out where not applicable*): • WHO prequalification? • Reference stringent regulatory authority (SRA; specify)[1]? • Any other country?		

[1] The reference SRA is the one whose registration the applicant would like to be considered as acceptable for reliance; for example, a product could be manufactured in country A but registered in country B. Country B NRA therefore becomes the reference SRA. In some regulatory cases, the reference SRA could be the NRA in the country of manufacture.

Table *continued*

Description	Yes/no	Comments
Has the Applicant submitted the quality information summary (QIS), as approved/endorsed by the reference authority or WHO (*cross out where not applicable*): • the QIS (for prequalified products)? • the QIS-SRA(crp)?		
Has the applicant submitted the full assessment reports from the reference authority or institution[2]?		
Has the applicant submitted the full inspection reports from the reference authority or institution1?		
Has the applicant submitted the product information (information for health-care professionals and information for the patient/user), as approved by the reference authority or institution?		
Has the applicant submitted a bridging report, or justification for exemption, as applicable?		
Has the applicant submitted the risk management plan, if applicable/required?		
Has the applicant submitted the public assessment and inspection reports from the reference authority or institution, if applicable?		

[2] This information is required for information but not for a decision on the validity of the submission. Absence of the assessment or inspection reports in the submission from the applicant/manufacturer should not constitute a failed screening or invalid submission. For example, in the WHO Prequalification Team Collaborative Procedure, the assessment and inspection reports (unredacted) are shared directly between WHO and the NRA. This may apply for other reference authorities. Thus, in these cases, the applicant/manufacturer are not in possession of the reports for submission to the NRA.

Appendix 5

Example of a national regulatory authority reliance model approach: information, documentary evidence and assessment activity

Pathway	Assessment approach	Documentary evidence (supporting documentation)	Example of products	Comments
Recognition	No scientific assessment	• Certificate of pharmaceutical product (CPP) from reference stringent regulatory authority (SRA) • Public assessment and inspection reports • Assessment and inspection reports	• Products prequalified by the World Health Organization (WHO) • National regulatory authority (NRA) may specify the NRA(s) or institutions whose decision it recognizes	CPP is not applicable for prequalified products Similarity between the local context important for this pathway/ approach
Reliance				
a. WHO prequalification	Verification, or abridged reviews, secondary review, or a combination	• Signed agreements/ consent • Quality information summary (QIS) • Assessment and inspections reports from the WHO Prequalification Team (PQT) • WHO public assessment reports and WHO public inspection reports (publicly available from the PQT website)	Products prequalified by WHO	NRAs to review the product information for consistency with local treatment guidelines and policies; information shared directly from WHO

Table *continued*

Pathway	Assessment approach	Documentary evidence (supporting documentation)	Example of products	Comments
b. Reference SRA (special access mechanisms)	Verification, or abridged reviews, or combination of both	• Signed agreements/consent • QIS-SRA(crp) – endorsed by SRA • SRA assessment reports inspection reports • Public assessment and inspection reports (publicly available)	Products with scientific opinion or similar decisions to facilitate access in low- and middle-income countries	Scientific opinions, or similar SRA decisions consider the use in target settings (outside the SRA market)
c. Reference SRA	Combination of verification and abridged review	• Signed agreements/consent • QIS-SRA(crp) – endorsed by SRA • Bridging report, if applicable • SRA assessment reports, inspection reports • Public assessment and inspection reports (publicly available)	Products approved by SRA and marketed in SRA market	Information may be shared by the applicant/ manufacturer; SRA approvals do not necessarily consider use in other settings
d. Other reference NRAs	Abridged reviews	NRA assessment and inspection reports QIS-SRA(crp) (potential use if all stakeholders agree)	Products approved by NRAs recognized as reference by the NRA	Direct interaction between the NRAs; no WHO facilitation
Work-sharing/ joint reviews	Full assessment as primary reviewer or rapporteur, and secondary reviewer for other products	Primary assessment reports from rapporteur	All types of products, depending on the scope of the regulatory network	
Information-sharing	Full assessment and inspections	Memorandum of understanding (MoU) between NRAs for information sharing (non-binding)	All products in the scope of the MoU or agreements between the NRAs	

Appendix 6

Model acknowledgement or approval letter for variations of products registered through the WHO collaborative procedure

Application number _____

The Managing Director

[*Name of applicant*]

[*Address*]

[*Date*]

Attention: Regulatory Affairs Manager

Dear Sir/Madam,

I refer to the application dated [*date of application*] for variation of:

Proprietary name (trade name) _____

_____

Approved generic name(s) _____

_____

Strength(s) per dosage unit _____

Dosage form _____

Name of authorization holder* _____

[*Must be a person or legal entity in the country in which marketing is being authorized; this letter should normally be addressed to the marketing authorization holder]

Evaluation of the application has been completed following the WHO collaborative procedure (hereinafter referred to as the Procedure). Approval of the variation under [*name of legislation*] is granted, subject to the conditions in this letter and its attachments. This letter and its attachments constitute the approval. The date of approval is the date of this letter. In part, this approval relies upon your assurance that: **no variations have been made other than (i) those notified in this application; (ii) changes that are permitted without notification or prior approval according to the guidelines of [*name of the reference authority or institution*]; and (iii) the variation is as approved by [*name of the reference authority or institution*]**.

The conditions that apply are as follows:

General conditions applying to all products

- The product(s) must conform to all the details provided in your application and as modified in subsequent correspondence.
- The product(s) must conform to all the details as approved by [*name of reference authority or institution*] in line with the Procedure requirements.
- No further changes may be made to the product without prior approval, except for changes of the type listed in [*name of reference authority or institution*]'s policy on "Changes to pharmaceutical aspects of registered products that may be made without prior approval". The conditions in that policy apply.

[*OPTION 1: There is no objection to the concurrent supply of changed and unchanged product.*]

[*OPTION 2: The concurrent supply of the changed and unchanged product is considered unacceptable. You should use up all existing pre-variation stock before supplying the changed product.*]

Additional specific conditions applying to this product:

[*For example, "All batches of the finished product must comply with a limit of 0.5% for Impurity A"*]

[_____]

[_____]

If you have any doubt as to the meaning of this letter and its attachments, you should contact the undersigned prior to marketing the product.

Yours faithfully

[*Name*]

[*Signature*]

authorized person under [*name of legislation*]