Collaborative Procedure in the Assessment and Accelerated National Registration of Pharmaceutical Products Approved by Stringent Regulatory Authorities

Proposal of a mechanism to be piloted for selected medicines with interested pharmaceutical companies and national medicines regulatory authorities.

Comments to be forwarded to the World Health Organization, Prequalification Team, smidm@who.int

1. Definitions and acronyms

Facilitated registration procedure of SRA approved medicines (Procedure)
Registration procedure in which assessment and national registration of pharmaceutical products approved by stringent regulatory authorities (SRAs) is facilitated and accelerated by sharing of detailed assessment and inspection outcomes generated by a SRA.

Stringent regulatory authority (SRA)
A regulatory body which is: (a) a member of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) as specified on www.ich.org; or (b) an ICH observer, being the European Free Trade Association (EFTA), as represented by Swissmedic and Health Canada (as may be updated from time to time); or (c) a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time).

Participating SRA
SRA that agrees with provision of outcomes of its regulatory expertise (especially assessment and inspection reports) to applicants/authorization holders or inspected manufacturers, does not object to sharing of these documents with national medicines regulatory authorities and provides under specified conditions in line with principles of the Procedure a support to other parties involved in the Procedure. Detailed conditions of information sharing and support provided by participating SRAs are specified in Annex 2 to the Procedure and posted on the WHO/PQT web site (http://www.who.int/prequal/).

Participating authority or participating NMRAs
National medicines regulatory authority (NMRA) that voluntarily agrees to implement this collaborative procedure and accepts the task of processing applications for registration of medicines approved by SRAs in accordance with the terms of the Procedure. A list of participating authorities is posted on the WHO/PQT web site (http://www.who.int/prequal/).

Participating company
Pharmaceutical company, which is a holder of marketing authorization granted by SRA for a medicine that is intended to be submitted, has been submitted or has been granted a national registration by participating NMRAs in line with principles of the Procedure.

WHO Prequalification Team (WHO-PQT)

WHO organizational unit supporting – among other - the Procedure, collecting information about its performance, posting information related to the Procedure on its website and organizing in collaboration with interested stakeholders updates of the Procedure.

2. Background information

Management of diseases known to be of major public health relevance in countries with limited regulatory resources is often jeopardised by delayed access to new or otherwise needed therapies. Although many medicines successfully passed regulatory review process by internationally respected regulatory bodies, also known as the stringent regulatory authorities (SRAs), or even in addition were prequalified by WHO, local regulatory approvals tend to consume additional time, workload and resources of national regulatory authorities before these therapies can be available to patients.

In order to address this issue, WHO prequalification programme proposes a scheme for NMRAs and pharmaceutical companies (manufacturers) to facilitate registrations of medicines approved by the SRAs. The WHO itself recognizes the scientific evaluation of pharmaceutical products by stringent regulatory authorities as they apply similarly stringent standards for quality, safety and efficacy to those recommended by WHO.

Based on WHO experience with the Collaborative Registration of WHO ‑ Prequalified Pharmaceutical Products, it is possible to facilitate and accelerate national registration processes by provision of detailed assessment and inspection outcomes generated by respected regulatory bodies. Assessment and inspection reports of SRAs made available in addition to the registration dossiers can facilitate adoption of national regulatory decisions by assuring NMRAs about positive risk/benefit of a product and its identical quality with the product already approved elsewhere. Normally, publicly available versions of assessment and inspection outcomes do not provide sufficiently detailed information to adopt regulatory decisions and therefore detailed assessment and inspection outcomes that include commercially sensitive data must be shared. To make such information sharing possible is up to interested pharmaceutical companies, who have to provide consent with information exchange among reference SRA and NMRAs, to which a product is submitted for regulatory approval. Pharmaceutical companies benefit from accelerated and facilitated regulatory process. On the other side, it is up to interested NMRAs to provide sufficient assurance that shared data will be treated with necessary care and confidentiality.

It should be stressed that decision to apply the process for specific medicines is up to respective NMRAs, which retain the prerogative to conclude their assessment through sovereign decisions on medicine registration within their national jurisdiction.

---

2 In addition to medicines approved by conventional marketing authorization process, the Procedure is applicable to special 'approval' mechanisms like the scientific opinion process according to Art.58 of Regulation (EC) No 726/2004 in the EU.


4 In case of the Collaborative Registration of WHO ‑ Prequalified Pharmaceutical Products the assessments and inspections are organized by WHO, although WHO cannot be considered as a regulatory body.
In addition to facilitation of regulatory decisions on needed medicines and faster access to patients, the process also represents an avenue for harmonization of regulatory requirements and capacity building.

The Procedure and pilot are designed for chemical medicines, irrespective if these are of innovative or generic nature. Extension to other categories of medicines can be considered in future.

3. Principles of facilitated registration

Abstract

The process is applicable both to SRA approved innovative and generic medicines. Participation of all parties is voluntary and should be performed in compliance with relevant applicable legislation. All SRAs, NMRAs and holders of authorization for medicines considered to be therapeutically important by participating NMRAs are welcome to participate.

During the pilot phase WHO plays a facilitating role in process testing. Should the principles of the process appear to be workeable, WHO will focus on monitoring of its use and improvement of detailed conditions.

The general approach is similar to principles of Collaborative Registration of WHO-Prequalified Pharmaceutical Products in terms of information sharing, utilization of shared information, management of confidentiality and timeframe. Instead of the WHO Prequalification Team, SRAs are the generators of the basic regulatory expertise in this procedure.

The dossiers submitted for national registrations are organized in globally harmonized format (CTD) to maximize use of data already submitted to SRAs. In case of generic medicines the technical part of dossier is equivalent to the WHO/PQP prequalification dossier requirements. For innovative products (i.e. NDA or self-standing applications) submitted dossier consists of rather simplified version of SRA dossier in order to reduce the volume of submissions to practically manageable extent, but include all data essential for national assessment. Such pragmatic simplification also reduces the risk of unnecessary dissemination of highly sensitive commercial information and can make the process more acceptable for pharmaceutical companies.

The key role in the process is given to the pharmaceutical companies to carry on the procedure and organize provision of relevant regulatory information generated by reference SRA to participating NMRAs. Conditions, under which individual SRAs agree with availability of assessment and inspection reports for this purpose have to be confirmed with each SRA. It is planned that WHO will summarise positions of willing SRAs as regards availability of assessment and inspection reports and post it on its website, similarly like the list of NMRAs that agreed to apply the piloted procedure in principle. It is expected, that SRAs that issued the reference marketing authorization will provide certain degree of support and cooperation, if necessary (e.g. authentication of submitted documents in case of doubt). In general, to save the resources of reference authorities, the role of SRAs in the proposed process is minimized.

It is up to participating NMRAs to recognize individual medicine as being eligible for the registration under this procedure considering relevance of the respective medicine for public health and existing NMRA capacity.
Confidentiality of shared data is assured by mechanisms applied by participating parties (NMRAs, SRAs, companies, WHO). Participating NMRAs provide a special commitment in the respect that any information and documentation provided to it by applicants and SRAs (possibly mediated by WHO) pursuant to this procedure will be treated as confidential and an access to this information will be allowed only to persons involved in the individual registrations who are bound by confidentiality undertakings (Annex 1). Authorities that provided such a commitment and agree to apply the principles of the Procedure will be publicly listed by WHO.

After initiation of the Procedure, switch to normal registration process is possible, provided that involved parties inform each other well of this decision.

**Principal roles of the participating parties**

**Participating NMRAs** express their interest to participate in the Procedure, their commitment to respect principles of the Procedure and their confirmation of confidential treatment of commercially sensitive information by forwarding to WHO a completed Annex 1 to this procedure. A focal person to communicate on issues relevant for the Procedure will be designated in each participating NMRA. A list of participating authorities is posted on the WHO/PQT web site ([http://www.who.int/prequal/](http://www.who.int/prequal/)).

**Participating SRAs** do not object to share their assessment reports and inspection reports with applicants/authorization holders to support access to needed medicines in line with principles of the Procedure. Conditions and mechanisms, by which the information will be shared, and what can be an extent of additional support to participating NMRAs are notified to WHO. A list of SRAs that agree to share outcomes of their regulatory expertise in line with principles of the Procedure and detailed conditions of information sharing are posted on the WHO/PQT web site ([http://www.who.int/prequal/](http://www.who.int/prequal/)). Example of such listing is provided in Annex 2.

**Participating companies** submit applications to NMRAs and provide assistance necessary to finalize the application in line with the Procedure. The participating companies applying for registration have a major role in the national registration process and in the post-registration phase by carrying on the procedure and providing additional requested information.

**WHO Prequalification Team** (WHO-PQT) assists in execution and maintenance of the Procedure, posts lists of participating NMRAs and SRAs (including SRA conditions with information sharing) on its website and collects information about performance of the Procedure. Should the medicine be highly therapeutically relevant for WHO supported treatment programs, WHO actively facilitates information exchange among involved SRAs and participating NMRAs.

**Pharmaceutical products**

Both innovative and generic medicinal products approved by SRAs are eligible for the procedure. The products can be prequalified by the WHO SRA-prequalification route, but non-prequalified medicines are also eligible. The medicines submitted for registration to participating NMRAs should be identical with medicines approved by SRAs. Within the context of this procedure, identical product is characterized by descriptions listed below. It is important to note that should there be any deviations from this definition of ‘sameness’, these must be notified (e.g. different supply chain, specifications, stability or medical claims etc.) and such deviations can be the reason for non-applicability of the Procedure.

The same medicinal product for the purpose of the Procedure is characterised by
- the same manufacturing chain, processes, control of materials and final product;
- the same active pharmaceutical ingredient (API) and finished pharmaceutical product (FPP) specifications;
• the same essential elements of product information\textsuperscript{5}

**Submissions format & content**

- The dossiers submitted for national registrations are organized in ICH CTD format\textsuperscript{4} and contain data specified in Annex 4. Scope of submitted technical data for innovators (i.e. NDA or self-standing applications) represents subset of data submitted to SRAs that provides sufficient assurance about product identity, quality, safety and efficacy and is pragmatic for NMRAs. As much as possible API quality is confirmed by existing certification schemes (e.g. CEP). In principle, only non-clinical and clinical summaries (ICH Module 2, parts 2.6 and 2.7) are submitted instead of extensive full ICH modules 4 and 5. However, the applicants are committed to submit these modules or requested non-clinical and clinical data if asked by participating NMRA.\textsuperscript{6}

- In case of generic medicines the technical part of dossier corresponds in module 3 to full scope of quality data on finished dosage form (3.P part) and data on active pharmaceutical ingredients correspond to an open part of API master file. Demonstration of bioequivalence and biowaiver criteria are equivalent to the WHO-PQT prequalification dossier requirements (www.who.int/prequal).

- In addition to technical data the applicants provide NMRAs with
  - valid assessment and inspection reports issued by SRA and
  - a declaration assuring about the identity of the product with the medicinal product approved by SRA\textsuperscript{7}, consent to communicate in the product related matters freely with the reference SRA and additional commitments as specified in the Annex 5.

Should the local applicant be different legal entity from a holder of SRA marketing authorization (or scientific opinion), the relationship should be clarified and agreements assuring information flow should be adjusted to this situation.

Translation of documents required in national language is under responsibility of individual company. The method and extent of verification of translation accuracy is a matter of decision of individual NMRAs.

Samples, if required, should be used for control of appearance or packaging. Laboratory testing of registration samples is not recommended and random sampling and testing should be rather planned in the post-registration period. Graphical design of package labelling (mock-up) is an acceptable way for presentation of texts and symbols on the packaging.

It should be noted, however, that participating authorities may require applicants to comply with specific additional national requirements. Each participating authority is encouraged to reduce the scope of specific national requirements for the sake of the Procedure and harmonize with international format and content of regulatory dossier. Specific national requirements should be made public.

---

\textsuperscript{5} The essential elements of product information include in particular the indications, contraindications, posology (dosing), special warnings and precautions for use, adverse reactions, storage conditions, primary packaging and shelf-life. For pharmaceutical products differences in brand name, the name of applicant or prequalification holder, language, format and degree of detail of the product information, labelling of internal and external packaging among others, are not considered essential for the purposes of this procedure. The language of the product information may be different as long as the information content is the same as that approved by SRA.

\textsuperscript{6} It may be advantageous to submit in addition to existing overviews a ‘bridging report’ which discusses data relevant for the countries of submission if SRA assessment report does not cover these elements to sufficient extent – see Annex 8.

\textsuperscript{7} Same product – as defined above.
Collaborative Procedure in the Assessment and Accelerated National Registration of Pharmaceutical Products Approved by Stringent Regulatory Authorities – pilot assisted by the WHO Prequalification Team.

Registration process according to the procedure

1. Pre-submission phase:
   a. Companies considering registrations according to the Procedure select familiarize themselves with principles of the Procedure, NMRAs that are prepared to participate in the procedure and conditions, under which SRA that have authorized their medicinal product agrees with information sharing and provides additional prospective support.
   b. Best, if a participating company confirms with participating NMRA(s) its interest to apply the Procedure for the given medicine before the submission.
   c. In case that the company does not have available valid assessment and inspection reports, these should be requested from the respective SRA. Should the company need to obtain an agreement of SRA before sharing the assessment and inspection reports, such agreement should be requested. The model content of the request is proposed (Annex 3B).
   d. The company also provides reference SRA with its consent to share the regulatory relevant information with participating NMRA(s). The model content of the consent is proposed (Annex 3A), but it is up to individual applicants and SRAs to agree on detailed wording.
   e. In case of medicines that are relevant for WHO treatment programmes during the pilot phase of the Procedure, the company agrees with WHO the extent of WHO co-ordination and support.

2. Submission for registration
   a. The company submits the registration application to participating NMRA. Specific national requirements must be respected, but it is up to NMRAs to minimize national deviations from the internationally acceptable dossiers as much as possible. Application fees are applicable according to national requirements.
   b. The registration dossier is organized in CTD format and consists of data sets as specified in the Annex 4, including valid assessment and inspection reports issued by SRA and a company/applicant's declaration.
   c. In case of submissions co-ordinated with WHO, the company informs WHO about applications submitted to individual NMRAs and comes to an agreement with WHO-PQT as regards access to the shared data (Annex 6).

3. NMRAs acceptance of product for registration in line with the Procedure and registration phase
   a. Participating NMRA decides whether or not to apply the procedure for each specific case and informs promptly the applicant in this respect.
   b. Should NMRA have doubts about authenticity or validity of submitted assessment and inspection reports, it can ask respective SRA for a confirmation. The way by which the confirmation is organized can vary between SRAs. The practical way is to share recent assessment and inspection reports as archived by SRA.
   c. The NMRA processes an application, benefiting from shared SRA regulatory outcomes and assurance about the identity of the medicine with the one approved by SRA. It is up to individual NMRAs to which extent accept, verify or re-asses the provided information before coming to a decision. A pragmatic approach is to verify product identity and assess only those areas which relate to use of the product in the country concerned and where failure to comply with regulatory standards could pose specific health risks. In the other areas, the outcomes of trusted authorities are proposed to be adopted.
   d. Participating SRAs can be approached for additional explanation or justification, depending on the extent of individual SRA's commitment to support the process. In case of medicines prioritized by WHO, WHO can organize responses to questions,
discussion via tele- or video-conferences or joint meetings with SRA experts to facilitate the process.
e. Participating NMRAs issue a decision within 90 days from acceptance of the submission for processing according to the Procedure.
f. Achievement of registrations processed according to this procedure is notified by the company to WHO in order to monitor the Procedure performance. Information about registered medicine, deviations from SRA decision, dates of submission and experience is notified according to Annex 7.

4. Post-registration management
   a. Participating companies commit to inform NMRA(s) concerned about relevant variations or regulatory actions and submit corresponding applications for variations in line with national requirements.
   b. Notification of completion of post-authorization commitments agreed with reference SRA, conduct of specific risk-management plans and pharmacovigilance is subject to specific agreements with individual participating NMRAs.
   c. Concerned NMRAs are entitled to approach reference SRAs in case of doubt for the most updated information about the conditions of SRA product approval.

Summarizing scheme of steps in the Procedure and corresponding documentation

Annexes:
   Annex 1: Agreement of NMRA to participate in the pilot of the SRA collaborative registration procedure
   Annex 2: Example of information included in the list of participating SRAs
   Annex 3A: The model content of the company consent to SRA with information sharing
   Annex 3B: The model content of the request to SRA to agree with assessment and inspection reports sharing
   Annex 4: Standard document package to be submitted to NMRA for the purpose of national registration in line with the Procedure
Annex 5: Declaration of the applicant to the NMRAs to initiate registration in line with the Procedure
Annex 6: Confidential disclosure agreement among participating company and WHO-PQT to access the data shared by company with participating NMRAs
Annex 7: Notification of an outcome of the national registration provided by the participating company to WHO-PQT
Annex 8: Concept Note: Requirements for provision of a ‘bridging’ report for SRA-approved medicines for consideration of registration in non-SRA settings