

# Annex 11

## Collaborative procedure in the assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities

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## 1. Background information

Management of diseases known to be of major relevance to public health in countries with limited regulatory resources is often jeopardized by delayed access to new or needed therapies. Although many medicines successfully pass a regulatory review process conducted by internationally respected regulatory bodies, also known as stringent regulatory authorities (reference SRAs), or may in addition have been prequalified by the World Health Organization (WHO), local regulatory approvals tend to consume additional time and resources of national regulatory authorities (NRAs) before these therapies can be made available to patients.

To address this issue, WHO proposes a scheme for NRAs and pharmaceutical manufacturers to facilitate registrations of the vaccines and pharmaceutical products, including biotherapeutic products approved by reference SRAs.<sup>1</sup> WHO recognizes the scientific evaluation of medicines by reference SRAs as they apply similarly stringent standards for quality, safety and efficacy to those recommended by WHO.

Based on WHO experience with the Collaborative procedure of WHO-prequalified pharmaceutical products and vaccines,<sup>2</sup> it is possible to facilitate and accelerate national registration processes by provision of detailed assessment and inspection outcomes generated by respected regulatory bodies.<sup>3</sup> Assessment and inspection reports of reference SRAs made available in addition to the registration dossiers can facilitate the adoption of national regulatory decisions by assuring NRAs about the positive risk–benefit profile of a product and that its quality is identical with the product already approved elsewhere. Normally, publicly available versions of assessment and inspection outcomes do not provide all the necessary information in sufficient detail to enable regulatory decisions to be adopted. Therefore, detailed assessment and inspection outcomes that include commercially sensitive data must be shared. Whether to make such information sharing possible is up to interested pharmaceutical manufacturers, which

<sup>1</sup> In addition to medicines approved by the conventional marketing authorization process, the Procedure is applicable to special “approval” mechanisms like the scientific opinion process according to Article 58 of Regulation (EC) No. 726/2004, in the European Union (EU).

<sup>2</sup> 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), 263-304.

<sup>3</sup> Under the Collaborative procedure for WHO-prequalified pharmaceutical products and vaccines, the assessments and inspections are organized by WHO, although WHO cannot be considered as a regulatory body.

should provide consent to information exchange among reference SRAs and NRAs, to which a product is submitted for regulatory approval. Pharmaceutical manufacturers benefit from accelerated and facilitated regulatory processes. For their part, it is up to interested NRAs to provide sufficient assurance that shared data will be treated with necessary care and respect for confidentiality. Nonetheless, in some jurisdictions, publicly available information such as public assessment or inspection reports, and databases of compliance with good manufacturing practices (GMP) contain substantial summarized regulatory information that can facilitate the decision-making process in less well-resourced NRAs as well.

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

In addition to the 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 is applicable in principle to all types of medicines irrespective of whether the products are of an innovative or generic nature. The procedure is also applicable to biotherapeutic products and vaccines.

## 2. Glossary

For the purposes of this document, the following definitions and descriptions apply. They may have different meanings in other contexts.

**biotherapeutic.** A biological product with the indication of treating human diseases.

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

**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.

**medicine.** Any substance or combination of substances marketed or manufactured to be marketed for treating or preventing disease in human beings,

or with a view to making a medical diagnosis in human beings, or to restoring, correcting or modifying physiological functions in human beings.

**participating authority or participating national medicines regulatory authority.** National regulatory authority (NRA) that voluntarily agrees to implement this collaborative procedure and accepts the task of processing applications for registration of medicines approved by reference SRAs in accordance with the terms of the Procedure. A list of participating authorities is posted on the WHO Prequalification Team (WHO PQT) website (<http://www.who.int/prequal/>).

**participating manufacturer.** A manufacturer, which is a holder of a marketing authorization granted by a reference SRA for a medicine that is intended to be submitted, has been submitted or has been granted national registration by participating NRAs in line with principles of the Procedure.

**participating stringent regulatory authority.** A reference stringent regulatory authority that agrees to provide 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 the principles of the Procedure, support to other parties involved in the Procedure.

**pharmaceutical product.** Any substance or combination of substances marketed or manufactured to be marketed for treating or preventing disease in human beings, or with a view to making a medical diagnosis in human beings, or to restoring, correcting or modifying physiological functions in human beings.

**stringent regulatory authority.**<sup>4</sup> A regulatory authority which is:

- a) a member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), being the European Commission,<sup>5</sup> the US Food and Drug Administration and the Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency (as before 23 October 2015)); or
- b) an ICH observer, being the European Free Trade Association, as represented by Swissmedic, and Health Canada (as before 23 October 2015); or

<sup>4</sup> Clarification with respect to the definition of stringent regulatory authority. See WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-first report. Geneva: World Health Organization; 2017: (WHO Technical Report Series, No. 1003), pp 34–35; and WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-second report. Geneva: World Health Organization; 2018 (WHO Technical Report Series, No. 1010), Section 10.1).

<sup>5</sup> For the European Commission, products approved via the centralized procedure by the European Medicines Agency, decentralized procedure or mutual recognition in the European Union (EU) are eligible provided the respective NRA in the EU agrees to participate as a reference SRA in the Procedure.

- c) a regulatory authority associated with an ICH member through a legally binding, mutual recognition agreement, including Australia, Iceland, Liechtenstein and Norway (as before 23 October 2015).

**vaccine.** A biological preparation that improves immunity to a particular disease. A vaccine typically contains an agent that resembles a disease-causing microorganism and is often made from weakened or killed forms of the microbe, its toxins, one of its surface proteins or genetically-engineered material. The agent stimulates the body's immune system to recognize the agent as foreign, destroy it and "remember" it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters.

**variation.** A change to any aspect of a medicine, including but not limited to, the change of use of a starting material, a change to formulation, method and site of manufacture, specifications for the finished product and ingredients, container and container labelling and product information.

### 3. Principles of collaborative procedure

Principles of the procedure (same product or defined deviations, available assessment and inspection outcomes, bridging information facilitating assessment of risk–benefit profile in new target environment, post-authorization variations and commitments in line with the SRA) are applicable to any regulated product. Nonetheless, there is a difference in the nature and scope of documents to be shared for different product categories. At present, the process is applicable to reference SRA-approved (innovative and generic medicines) and vaccines. Products approved through special mechanisms such as conditional marketing authorization or under exceptional circumstances are eligible for the procedure if there is a high unmet medical need of public health importance because access to the reference SRA assessment reports would help participating NRAs to understand the acceptability of the risk–benefit profile of such products.

Participation of all parties is voluntary and should be performed in compliance with relevant applicable legislation. All reference SRAs, NRAs and holders of marketing authorization for products considered to be therapeutically important by participating NRAs are welcome to participate. WHO plays a facilitating role in this process and in monitoring of its use and refinement of the details of the conditions.

The general approach is similar to the principles of Collaborative procedure of WHO-prequalified products in terms of information sharing, utilization of shared information, management of confidentiality and time frame. Instead of the WHO PQT, reference SRAs are the generators of the basic regulatory expertise in this procedure.

The dossiers submitted for national registration are organized in line with the globally harmonized common technical document (CTD) format to maximize use of data already submitted to reference SRAs. In the case of generic medicines, the technical part of the dossier is equivalent to the WHO PQT prequalification dossier requirements. The open part of the active pharmaceutical ingredient (API) master file is considered sufficient, unless the manufacturer is informed otherwise by the respective NRA. For innovative products (i.e. new drug applications (NDAs), biologicals licence applications for vaccines or self-standing applications) the submitted dossier consists of a rather simplified version of the reference SRA dossier (unless otherwise requested by the respective NRA) to reduce the volume of submissions to a manageable level, while including all data essential for national assessments. Such pragmatic simplification also reduces the risk of unnecessary dissemination of highly sensitive commercial information and can make the process more acceptable for pharmaceutical manufacturers.

The key role in the process is assigned to the pharmaceutical manufacturers, which conduct the procedure and organize the provision of relevant regulatory information generated by reference SRAs to participating NRAs. The conditions under which individual reference SRAs agree to make available the assessment and inspection reports for this purpose have to be confirmed with each reference SRA. It is planned that WHO will summarize the positions of willing reference SRAs as regards the availability of assessment and inspection reports and post this information on its website, similarly to the list of NRAs that have agreed in principle to apply the piloted procedure. It is expected that the reference SRAs that issued the marketing authorization will provide a certain amount 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 reference SRAs in the proposed process is minimized.

It is up to the participating NRAs to recognize which individual medicines would be eligible for registration under this procedure, considering the relevance of the medicine concerned for public health and existing NRA capacity.

Confidentiality of shared data is assured by mechanisms applied by participating parties (NRAs, reference SRAs, manufacturers and WHO). Participating NRAs make a special commitment in the respect that any information and documentation provided to them by applicants and reference SRAs (possibly mediated by WHO) pursuant to this procedure will be treated as confidential and access to this information will be allowed only to persons involved in the individual registrations who are bound by confidentiality undertakings (Appendix 1). Authorities that make such a commitment and agree to apply the principles of the Procedure will be publicly listed by WHO.

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

### 3.1 Principal roles of the participating parties

**Participating NRAs** express their interest in participating in the Procedure, their commitment to respect the principles of the Procedure and their confirmation of confidential treatment of commercially sensitive information by forwarding to WHO a completed copy of Appendix 1 to this Procedure. A focal person for communication on issues relevant for the Procedure will be designated in each participating NRA. A list of participating authorities is posted on the WHO PQT website (<http://www.who.int/prequal/>). For GMP requirements for the procedure, the NRAs should refer to *Guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for marketing authorization of medical products* (WHO Technical Report Series, No. 1010, Annex 7, 2018). The guidelines provide the general approaches and best practices for desk assessment to verify and confirm compliance with GMP, good laboratory practices (GLP) and good clinical practices (GCP) of foreign facilities for manufacture of finished pharmaceutical products (FPPs) and APIs, quality control laboratories (QCLs) and contract research organizations (CROs)/clinical trial sites. The desk assessment of inspection reports is mostly sufficient to eliminate the need for site inspections.

**Participating reference SRAs** do not object to sharing their assessment and inspection reports with applicants or authorization holders to support access to needed medicines in line with the principles of the Procedure. Conditions and mechanisms by which the information will be shared, and the extent to which additional support can be offered to the participating NRAs are notified to WHO. A list of reference SRAs that agree to share the outcomes of their regulatory expertise in line with the principles of the Procedure and detailed conditions of information sharing are posted on the WHO PQT website (<http://www.who.int/prequal/>). An example of such a listing is provided in Appendix 2.

**Participating manufacturers** submit applications to NRAs and provide the assistance necessary to finalize the application in line with the Procedure. The participating manufacturers applying for registration have a major role in the national registration process and in the post-registration phase by carrying out the Procedure and providing any additional information requested. A primary obligation of the manufacturers is to inform the NRAs when a regulatory decision is taken by the reference SRA post-authorization, e.g. relating to non-compliance with GMP, withdrawal of the product, suspension of marketing authorization, or when the product is no longer authorized or marketed in the jurisdiction of the reference SRA.

WHO assists in the execution and maintenance of the Procedure, posts lists of participating NRAs and reference SRAs (including reference SRA conditions

for information sharing) on its website and collects information about the performance of the Procedure. Should the medicine be highly therapeutically relevant for WHO-supported treatment programmes, WHO actively facilitates information exchange among the reference SRAs involved and the participating NRAs. WHO provides information on products approved by participating NRAs through the facilitated registrations using the reference SRA procedure and makes it publicly available.

## 4. Medicines

Both innovative and generic medicines approved by reference SRAs are eligible for the Procedure. The medicines submitted for registration to the participating NRAs should be identical with medicines approved by reference SRAs. Within the context of this Procedure, identical products are characterized by the descriptions listed below. 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) and such deviations can be the reason for non-applicability of the Procedure.

For this Procedure, the same medicine is characterized by:

- the same qualitative and quantitative formulation;
- the same manufacturing site(s)<sup>6</sup> for API and FPP including specific block(s)/unit(s), chain, processes, control of materials and final product, and in the case of vaccines also by the same batch release scheme;
- the same specifications for excipient, API and FPP;
- the same essential elements of product information.<sup>7</sup>

<sup>6</sup> “Sameness” of the manufacturing sites for APIs and FPPs means that the specific site must be approved by the reference SRA for the specific product under consideration and included as part of the marketing authorization in the reference SRA country. Any additional sites, regardless of their GMP status, are not acceptable under this procedure. Any changes or variations to include additional sites should be approved by the reference SRA before inclusion in the submission to the participating NRAs.

<sup>7</sup> The essential elements of product information include 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 the applicant, language, format and degree of detail of the product information, labelling of primary, secondary and tertiary 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 the reference SRA.

## 4.1 Submissions format and content

- The dossiers submitted for national registrations are organized in International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) CTD format and contain data specified in Appendix 5. The scope of submitted technical data for innovators (i.e. NDAs or self-standing applications) represents a subset of the data submitted to reference SRAs that provides sufficient assurance about product identity, quality, safety and efficacy and meeting requirements for the NRAs. To the extent possible, API quality is confirmed by existing certification schemes (e.g. certificate of suitability (CEP)). The critical quality attributes of the excipients are taken into consideration and checked. In principle, only nonclinical and clinical summaries (ICH Module 2) are submitted instead of extensive full ICH Modules 4 and 5. However, the applicants are committed to submit these modules or specific nonclinical and clinical data if asked to do so by a participating NRA. The applicant should confirm with the respective NRAs whether full Modules 4 and 5 are required at the time of submission. It may be advantageous to submit, in addition to existing overviews, a “bridging report” that provides the summarized evidence on risks and benefits and justification of the relevance of the product for the countries for which marketing authorization is sought (Appendix 6).
- In the case of generic medicines the technical part of a dossier corresponds in Module 3 to the full scope of quality data on a finished dosage form (part 3.P) and data on the API correspond to the open part of the API master file (APIMF). Demonstrations of bioequivalence and biowaiver criteria are equivalent to the WHO PQT prequalification dossier requirements ([www.who.int/prequal](http://www.who.int/prequal)).
- In addition to technical data the applicants provide NRAs with:
  - valid assessment and inspection reports issued by reference SRAs;
  - quality information summary (QIS)-SRA(crp) (Appendix 4);
  - a declaration assuring the identity of the product with the medicine approved by the reference SRA, consent to communicate freely with the reference SRA on product-related matters, and additional commitments as specified in Appendix 7;
  - a declaration confirming same site and source including specific block(s) or unit(s) for API and FPP production;
  - commitment to conduct risk assessment or transport validation for supply of products to the NRA market, if such assessment or validation was not already covered as part of the dossier.

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

Translation of documents required in the national language is the responsibility of the manufacturer. The method and extent of verification of translation accuracy are a matter of decision of individual NRAs.

Samples, if required, should be used for checks on appearance or packaging. Laboratory testing of registration samples is not recommended and random sampling and testing should be planned in the post-registration period. Mock-ups showing the graphic design of package labelling are an acceptable way to present the texts and symbols on the packaging.

Note, 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 to align them with the Procedure and harmonize its requirements with the international format and content of a regulatory dossier. Specific national requirements should be made public.

## 4.2 Registration process according to the Procedure

The process flow of the Procedure is shown in Figure A11.1 and described briefly below.

1. *Pre-submission phase*
  - a. Manufacturers considering registrations according to the Procedure should familiarize themselves with the principles of the Procedure, which NRAs are prepared to participate in the Procedure, and the conditions under which reference SRAs that have authorized their medicine will agree to share information and provide additional prospective support.
  - b. It is recommended that a participating manufacturer should confirm with the participating NRA(s) its interest in applying the Procedure for the given medicine before the submission.
  - c. The manufacturer also needs to provide the reference SRA with its consent to share the relevant regulatory information with participating NRA(s). A model of the content of such consent has been proposed (Appendix 3A), but it is up to individual applicants and reference SRAs to agree on the details of the wording.
  - d. In the case that the manufacturer does not have valid assessment and inspection reports available, these should

be requested from the respective reference SRA. Should the manufacturer need to obtain the agreement of the reference SRA before sharing the assessment and inspection reports, such agreement should be requested. The model for the proposed content of the request is shown in Appendix 3B.

- e. In the case of medicines that are relevant for WHO-supported disease treatment programmes, the manufacturer should agree with WHO the extent of WHO's coordination and support.
  - f. The manufacturer prepares the quality information summary (QIS) reference SRA (QIS-SRA (crp)) (Appendix 4) and the QIS should be verified and endorsed by the reference SRA that issued the marketing authorization.
  - g. The reference SRA should provide the required documentation, e.g. assessment and inspection reports (where applicable) and endorsement of the QIS-SRA(crp) within 30 days from receipt of the request from the manufacturer or applicant. The individual reference SRAs are invited to notify WHO about their timelines and deadlines for these activities to be posted publicly on the WHO websites referenced in the Procedure.
2. *Submission for registration*
    - a. The manufacturer submits the registration application to the participating NRAs within 90 days from the date of receipt of documentation from the reference SRA. Specific national requirements must be respected, but it is up to the NRAs to minimize national deviations from the internationally acceptable dossiers to the greatest extent possible. Application fees may be charged in accordance with national requirements.
    - b. The registration dossier is organized in CTD format and consists of data sets as specified in Appendix 5, including valid assessment and inspection reports issued by the reference SRA and a manufacturer or applicant's declaration.
    - c. In the case of submissions coordinated with WHO, the manufacturer informs WHO about applications submitted to individual NRAs and comes to an agreement with WHO as regards access to the shared data (Appendix 8).
  3. *NRAs' acceptance of products for registration in line with the Procedure and registration phase*
    - a. The participating NRA validates the applications and documents submitted, decides whether or not to apply the

Procedure in each specific case, and informs the applicant of its decision within 30 days.

- b. Should the NRA have any doubts about the authenticity or validity of any of the assessment or inspection reports submitted, it can ask the respective reference SRA for confirmation. The way in which confirmation is organized can vary between reference SRAs. The practical way is to share recent assessment and inspection reports as archived by the reference SRA.
- c. The NRA processes an application, benefiting from shared reference SRA regulatory outcomes and assurance about the identity of the medicine with the one approved by the reference SRA. It is up to individual NRAs to decide to what extent they accept, verify or reassesses the information provided before coming to a decision. A pragmatic approach is to verify product identity and assess only those areas that relate to use of the product in the country concerned and where failure to comply with regulatory standards could pose specific health risks. For example, these might include: review of stability data for the climatic conditions appropriate to the participating NRAs, if these are different from those approved by the reference SRA; risk management plans (RMPs); bridging report; and labelling and product information for products approved for use in reference SRA countries. Note that product approval through mechanisms such as Article 58 of the Regulation of the European Commission, Health Canada Access Programme, United States Food and Drug Administration tentative approval, or the Swissmedic Marketing Authorization for Global Health Products Procedure is already designed to address such contextual issues in the receiving countries. Participating NRAs should avoid retesting samples prior to authorization. In the other areas, the outcomes of assessments by trusted authorities are proposed to be adopted.
- d. Participating reference SRAs can be approached to provide additional explanation or justification, depending on the extent of an individual reference SRA's commitment to support the process. In the case of medicines prioritized by WHO, the Organization can arrange for responses to questions, discussion via tele- or videoconferences or joint meetings with reference SRA experts to facilitate the process.

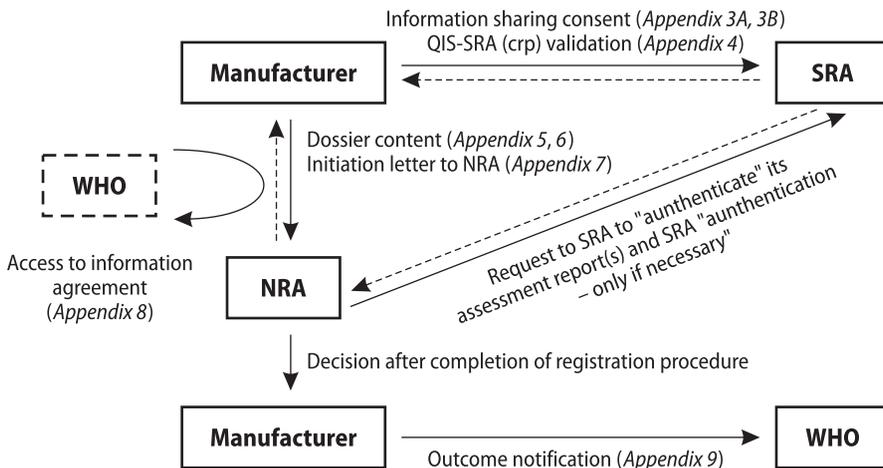
- e. Participating NRAs issue a decision within 90 calendar<sup>8</sup> days of regulatory time<sup>9</sup> from acceptance of the submission for processing according to the Procedure.
- f. Granting of registrations processed according to this Procedure is notified by the manufacturer to WHO to allow it to monitor the Procedure performance. Information about registered medicines, deviations from a reference SRA decision, dates of submission and experience is notified according to Appendix 9.

Figure A11.1

### A summary of the steps in the Procedure and corresponding documentation

#### Preconditions to initiate the national registration in line with the Collaborative procedure in assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities (SRAs)

- national regulatory authorities (NRAs) agree to participate and follow the principles of the procedure (*Appendix 1*)
- SRAs define conditions of their participation (*Appendix 2*)



QIS: quality information summary; NRA: national regulatory authority; SRA: stringent regulatory authority.

<sup>8</sup> Participating authorities should issue their national regulatory decisions at the earliest opportunity after being given access to the confidential information and documentation on a given product. If a participating authority does not issue its decision within 90 days of regulatory time, the reasons should be communicated to the applicant, and/or to the reference SRA, or to WHO, where applicable.

<sup>9</sup> Regulatory time starts after a valid application for registration according to the Procedure has been received and access to the confidential information has been granted (whichever is the later) and continues until the date of decision on registration. The regulatory time does not include the time granted to the applicant to complete missing parts of the documentation, provide additional data or respond to queries raised by NRAs.

## 5. Collaboration mechanisms for management of post-registration variations

### 5.1 General principles

The following principles are proposed to be respected during submissions of variations to medicines and vaccines registered or submitted for registration in line with the reference SRA Procedure. These principles take into account the existing reality of non-harmonized variation processes among NRAs that participated in the pilot reference SRA Procedure. The recommended approach to handling these variations is driven by the principle of non-interference with national legislation and decision-making while facilitating national decisions on variations by provision of essential information assuring that the medicine registered by the reference SRA procedure is of equivalent quality, and in line with the latest reference SRA decisions.

These guidelines focus on all variations relevant to countries that registered the product in line with the reference SRA Procedure. Variations that were submitted or notified to the reference SRA authority should be submitted to NRAs in participating countries to assure consistency of the regulatory status of the approved products between the reference SRA and NRAs over the product life-cycle. All variations that are approved by reference SRAs before an application for registration is submitted to the participating NRAs should be submitted and clearly identified in the initial submission to participating NRAs under this Procedure. It is not necessary to submit all changes, e.g. administrative changes that are relevant for the territory of the reference SRA only, or changes affecting the quality of the product that are specific to the reference SRA region. Variations that have local relevance in participating countries, which are not submitted or notified to the reference SRA should be submitted in line with national requirements.

The cover letter submitted with each variation should clearly indicate if a variation was submitted or notified to and approved or accepted by the reference SRA, or if a variation is only a national one.

Line extensions of already registered medicines (e.g. new formulations, additional strengths, new routes of administration, changes in active substance(s)), which were submitted to the reference SRA as a new application, are not considered as variations in this document.

At present, only variations are discussed. Management of other regulatory documents such as renewal submissions and outcomes, periodic benefit-risk evaluation report (PBRER) submissions and outcomes, submissions and outcomes concerning post-authorization measures and RMP updates will be the subject of future discussions. However, national guidance should be followed, should any of these documents and regulatory information already be required under existing national regulation.

## 5.2 Variations that are under assessment by reference SRAs at the time of submission of an application for registration to participating NRAs

All variations under the reference SRA assessment for which a decision is expected before finalization of the collaborative Procedure (registration process is expected to be complete within 90 days), should be identified in Appendix 4. Data supporting such variations should be included in the dossier submitted with the registration application.

The applicant should confirm and attest that the information submitted to the NRA is the same as that submitted to the reference SRA for the variation, where applicable.

The applicant should notify participating NRAs of the reference SRA's decision outcome(s) (and any conditions in the case of approval) within 30 days (preferably during exchange of questions and responses between the NRA and the applicant). If an assessment report is issued by the reference SRA, once the procedure is completed, a copy should be provided. In the case of variations not approved by the reference SRA, the applicant notifies NRAs about withdrawal (invalidation) of data related to the respective variation.

NRAs may consider reference SRA decisions on these variations during the registration process, thus avoiding the need to submit national variations immediately after the decision on registration is issued. In the case of variations not concluded by the reference SRA before the national registration is granted, the NRAs have the following options:

- consider these variations and grant registration, including conditional approval of not-yet reference SRA-approved variations; or
- defer the decision on registration until the reference SRA approval is obtained; or
- register the product based on the current reference SRA-approved conditions and await submission of variations according to section 4.3.

## 5.3 Variations approved by reference SRAs after national registrations are granted

Holders of registrations granted on the basis of the reference SRA Procedure are committed to keep NRAs informed about all variations or regulatory actions (e.g. urgent safety restrictions, suspensions of authorization) (Appendix 4, section 4b). The information should be provided in the form of the variation dossier submitted to the reference SRA. Holders of national registrations are

required to submit variations that have been approved (or accepted in the case of notification) by the reference SRA to relevant<sup>10</sup> participating authorities without delay at the latest 30 calendar days after the reference SRA's decision has been made. Should national legislation in a participating country require additional data or samples which are not practical to submit within 30 calendar days, the variation should be submitted as soon as possible, with a plausible explanation. There is no need to submit variations that have not been approved or accepted by the reference SRA.

The same data as submitted and approved by the reference SRA should be submitted to NRAs. The applicant should therefore confirm and attest that the information (variation dossier) submitted to the NRA is the same as that submitted to the reference SRA for the variation where applicable. In the case that an assessment report has been issued, this should be submitted with the copy of the reference SRA decision or other document confirming the final position of the reference SRA. In the case that the variation modifies information submitted to the NRA in the reference QIS-SRA (crp), a new updated reference QIS-SRA (crp) should be submitted. The reference SRA should provide the required documentation, e.g. assessment and inspection reports (where applicable), and endorsement of the QIS-SRA (crp) within 30 days from receipt of the request from the manufacturer or applicant.

The NRAs should rely on the decision of the reference SRA to the extent possible, using expedited review pathways similar to the initial marketing authorization process under the reference SRA collaborative procedure. National decisions on such variations submitted in line with the reference SRA Procedure should not be taken by participating NRAs later than 30 calendar days following submission.

If the NRA disagrees with a notification, it should communicate this to the manufacturer within 30 days following the submission. Otherwise the notification shall be deemed accepted.

Should a participating NRA receive an application from a manufacturer for a variation that has not been previously approved by the relevant reference SRA (and it is not a case of deviation as described below in section 4.4), the product could deviate from the reference SRA-approved version and such variation merits special attention from the NRA.

The NRAs should make every effort to align their decisions. WHO can assist in such situations and mediate in communication between the parties involved.

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<sup>10</sup> Relevant variations are those variations that could impact quality, safety and efficacy in the receiving country. Examples of non-relevant variations include addition of a manufacturing site only for the market in the SRA's region.

#### 5.4 **Variations in conditions of registration, which deviate from those approved by the reference SRA approval**

Deviations from the reference SRA's approved product characteristics, approved data and product information are possible provided the product is still considered – in principle – the same as the one approved by the reference SRA. All deviations from the conditions approved by the reference SRA should be identified in Appendix 4. All variations that differ from those approved by the reference SRA are subject to specific national variation guidelines in the participating countries. QIS: quality information summary; NRA: national regulatory authority; SRA: stringent regulatory authority.

# Appendix 1

## Agreement of the national regulatory authority to participate in the collaborative procedure in assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities

*Coordinated by the World Health Organization (WHO)*

### Details of national medicines regulatory authority (NRA)

Name of NRA: [Click here to enter text.](#) \_\_\_\_\_ (“the NRA”)

Postal address: [Click here to enter text.](#) \_\_\_\_\_

Country: [Click here to enter text.](#) \_\_\_\_\_

Telephone number (please include codes): [Click here to enter text.](#) \_\_\_\_\_

Email: [Click here to enter text.](#) \_\_\_\_\_

### Scope of agreement

Applicants for national registration of a pharmaceutical product or vaccine approved by a stringent regulatory authority (reference SRA) (hereafter referred to as “Applicants”) may express their interest to the NRA for the assessment and accelerated registration of this product (“the Product”) in the country under the “*Collaborative procedure in assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities*” (hereafter referred to as “the Collaborative procedure of reference SRA approved products” or “the Procedure”).<sup>1</sup>

Subject to the NRA agreeing to participate in the Procedure and conduct such assessment and consider such accelerated registration of the product under the Procedure, the NRA hereby confirms for each such product that it will adhere to, and collaborate with, the Applicant for marketing authorization of the product and if relevant with the respective reference SRA and WHO in accordance with the terms of the Procedure.

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<sup>1</sup> If the applicant for national registration is not the same as the reference SRA registration/marketing authorization holder, the reference SRA registration holder must confirm to the NRA with an authorization letter that the applicant is acting for, or pursuant to rights derived from, the reference SRA registration holder, and that the reference SRA registration holder agrees with the application of the Procedure in the country concerned.

## Confidentiality of information

Any information and documentation relating to the product and provided by the Applicant or reference SRA to the NRA under the Procedure may include but shall not necessarily be limited to:

- the registration dossier as defined by the Procedure
- the full reference SRA assessment and inspection outcomes (reports);
- information and documentation on variations, as well as information and documentation on any actions taken by the reference SRA after national registration of the Product;
- all such data, reports, information and documentation being hereinafter referred to as “the Information”.

As regards sharing the outcomes of assessments and inspections, full reference SRA assessment and inspection reports are shared by Applicants with participating NRAs with the agreement of the respective reference SRA. Should any data in the assessment and inspection report be hidden for whatever reason, the nature and scope of missing data will be clearly indicated. Sharing of any data by the reference SRAs is subject to consent of the data owner.

The Applicant and reference SRA agree to make the Information available to the NRA exclusively for the purpose of the assessment and accelerated registration of the Product in the Country and any post-registration processes that may be required, in accordance with and subject to the terms of the Procedure (“the Purpose”). The NRA agrees to treat any Information provided by the Applicant and reference SRA as aforesaid as strictly confidential and proprietary to the Applicant, parties collaborating with the Applicant and/or reference SRA as relevant. In this regard, the NRA agrees to use such Information only for the Purpose and to make no other use thereof. Thus, the NRA undertakes to maintain the Information received from the Applicant and reference SRA in strict confidence, and to take all reasonable measures to ensure that:

- the Information received from the Applicant or reference SRA shall not be used for any purpose other than the Purpose;
- the Information shall only be disclosed to persons who have a need to know for the aforesaid Purpose and are bound by confidentiality undertakings in respect of such information and documentation, which are no less stringent than those contained herein.

The NRA warrants and represents that it has adequate procedures in place to ensure compliance with its aforesaid obligations.

The obligations of confidentiality and restrictions on use contained herein shall not cease on completion of the Purpose.

The obligations of confidentiality and restrictions on use contained herein shall not apply to any part of the Information which the NRA is clearly able to demonstrate:

- was in the public domain or the subject of public knowledge at the time of disclosure by the Applicant or reference SRA to the NRA under the Procedure; or
- becomes part of the public domain or the subject of public knowledge through no fault of the NRA; or
- is required to be disclosed by law, provided that the NRA shall in such event immediately notify the reference SRA and the Applicant in writing of such obligation and shall provide adequate opportunity to the reference SRA and/or the Applicant to object to such disclosure or request confidential treatment thereof.

Upon completion of the Purpose, the NRA shall cease all use and make no further use of the Information disclosed to it under the Procedure, and shall promptly destroy the Information received from the Applicant and the reference SRA, which is in tangible or other form and is not archived in accordance with archival procedures established by the NRA. The Purpose for each product shall be deemed completed as soon as:

- the reference SRA authorization holder/Applicant discontinues participation in the Procedure for the particular product;
- the Product is deregistered by the NRA and/or ceases to be authorized by reference SRA.

The NRA agrees that it has no right in or to the Information and that nothing contained herein shall be construed, by implication or otherwise, as the grant of a licence to the NRA to use the Information other than for the Purpose.

Should WHO staff or external experts independent on the Applicant or NRA be provided with an access to the Information in order to coordinate the Collaborative reference SRA procedure or provide an expert opinion, an access to the Information shall be subject to a confidentiality undertaking.

## Timelines

In respect of each Product which the NRA accepts to assess and consider under the Procedure, the NRA undertakes to abide by the terms of the Procedure, including but not limited to the following timelines for processing each application:

- within 90 calendar days of regulatory time<sup>2</sup> after obtaining the assessment and inspection outcomes (reports) and validated QIS-SRA as well as receipt of validated submission, the participating NRA undertakes to take a final decision on the national registration of the Product;
- within 30 calendar days of regulatory time after obtaining the assessment outcomes (reports) and evidence of approval for variations and validated QIS-SRA (where applicable) as well as receipt of data submitted to the reference SRA for the variations, the participating NRA undertakes to take a final decision on the variation of the Product.

## Miscellaneous

The NRA agrees that WHO may list its name on the WHO-PQT website as a participant in the reference SRA Procedure. Except as provided hereinbefore, neither party shall, without the prior written consent of the other party, refer to the relationship of the parties under this Agreement and/or to the relationship of the other party to the Product, the Information and/or the Purpose, in any statement or material of an advertising or promotional nature.

This Agreement shall not be modified except by mutual agreement of WHO and the NRA in writing. The NRA furthermore undertakes to promptly inform WHO/PQT of any circumstances or change in circumstances that may affect the implementation of this Agreement and its participation in the Procedure. This Agreement can be invalidated by a written note from the NRA to WHO. Validity of this Agreement expires at termination of the Procedure, which will be publicly announced.

## Focal point(s) for communication

The NRA has designated the person(s) listed below to act as a focal point(s) for communication concerning the Procedure.

Title: \_\_\_\_\_

Name: \_\_\_\_\_

Position: \_\_\_\_\_

<sup>2</sup> Regulatory time starts after a valid application for the registration according to the Procedure has been received and access to the confidential information has been granted (whichever is the later) and continues until the date of decision on registration. The regulatory time does not include the time granted to the applicant to complete missing parts of the documentation, provide additional data or respond to queries raised by NRAs.

Email: \_\_\_\_\_

Telephone: \_\_\_\_\_

Title: \_\_\_\_\_

Name: \_\_\_\_\_

Position: \_\_\_\_\_

Email: \_\_\_\_\_

Telephone: \_\_\_\_\_

Agreed and accepted

For the NRA

Signature: Click here to enter text. \_\_\_\_\_

Name: Click here to enter text. \_\_\_\_\_

Title: Click here to enter text. \_\_\_\_\_

Place and date: Click here to enter text. \_\_\_\_\_



## Appendix 2

### Example of information included in the list of participating reference stringent regulatory authority(ies)

<p>Details of reference stringent regulatory authority (SRA) agreeing to proceed, in principle, in line with conditions of the Procedure</p>	<p>Provision of consent or “no objection statement” to share the assessment and inspection reports issued by the reference SRA</p>	<p>Agreement to authenticate the reference SRA-issued assessment and inspection reports on request of participating NRAs, which have received an application for registration according to the Procedure</p>	<p>Provision of additional explanation with scientific justification of granting authorization to NRAs, which have received an application for registration according to the Procedure</p>	<p>Reference SRA position on post-registration management of medicines registered by participating NRA using the Procedure</p>
<p>Name and address of reference SRA Focal point for communication in matters related to the Procedure</p>	<p>Example 1 (EMA – current situation) EMA does not object to MAHs of centrally authorized medicines and holders of scientific opinions according to European Union Article 58 using final assessment and inspection reports in support of national registrations.</p>	<p>Example 1 (EMA – current position) It is expected that requests for authentication of documents will be exceptional. Subject to previous agreement with MAH (see Appendix 3 of the Procedure) the EMA can provide to the requesting NRA the full assessment reports or other relevant assessment documents.</p>	<p>Possible, on the understanding that these situations are exceptional and that such a request is channelled by WHO or the respective NRA, not by the manufacturer.</p>	<p>For example, the EMA supports the obligation of MAHs to keep national regulators informed of due major variations or line extensions; however, for the Procedure the EMA would suggest to focus on initial applications.</p>

Table continued

<p>Details of reference stringent regulatory authority (SRA) agreeing to proceed, in principle, in line with conditions of the Procedure</p>	<p>Provision of consent or “no objection statement” to share the assessment and inspection reports issued by the reference SRA</p>	<p>Agreement to authenticate the reference SRA-issued assessment and inspection reports on request of participating NRAs, which have received an application for registration according to the Procedure</p>	<p>Provision of additional explanation with scientific justification of granting authorization to NRAs, which have received an application for registration according to the Procedure</p>	<p>Reference SRA position on post-registration management of medicines registered by participating NRA using the Procedure</p>
<p></p>	<p>However, when documents are provided to authorities in third countries by the MAH or holder of scientific opinion, personal information needs to be redacted. The “no objection statement” is provided by the EMA on request of individual MAHs. The request has to specify each NRA with which the assessment and inspection reports will be shared. The “no objection statement” is normally issued within 10 days.</p>	<p>As regards inspection reports, it is expected that the applicant will forward the latest inspection report(s) for the manufacturing site(s) to the participating NRA. Communication with the relevant Member State authority might be necessary to confirm authenticity of the inspection reports.</p>	<p></p>	<p></p>

Table continued

<p>Details of reference stringent regulatory authority (SRA) agreeing to proceed, in principle, in line with conditions of the Procedure</p>	<p>Provision of consent or “no objection statement” to share the assessment and inspection reports issued by the reference SRA</p>	<p>Agreement to authenticate the reference SRA-issued assessment and inspection reports on request of participating NRAs, which have received an application for registration according to the Procedure</p>	<p>Provision of additional explanation with scientific justification of granting authorization to NRAs, which have received an application for registration according to the Procedure</p>	<p>Reference SRA position on post-registration management of medicines registered by participating NRA using the Procedure</p>
	<p>Example 2 (hypothetical reference SRA) Reference SRA does not object to MAHs of centrally authorized medicines and holders of scientific opinions according to Article 58 using final assessment and inspection reports in support of national registrations. However, when documents are provided to authorities in third countries by the MAH or holder of scientific opinion, personal information needs to be redacted.</p>			

Table continued

<p>Details of reference stringent regulatory authority (SRA) agreeing to proceed, in principle, in line with conditions of the Procedure</p>	<p>Provision of consent or “no objection statement” to share the assessment and inspection reports issued by the reference SRA</p>	<p>Agreement to authenticate the reference SRA-issued assessment and inspection reports on request of participating NRAs, which have received an application for registration according to the Procedure</p>	<p>Provision of additional explanation with scientific justification of granting authorization to NRAs, which have received an application for registration according to the Procedure</p>	<p>Reference SRA position on post-registration management of medicines registered by participating NRA using the Procedure</p>
	<p>The general statement confirming reference SRA position and conditions for sharing of the final assessment and inspection reports are made publicly available at <a href="http://www.ema.europa.eu">www</a></p>			

EMA: European Medicines Agency; MAH: marketing authorization holder; NRA: national regulatory authority; SRA: stringent regulatory authority as stipulated by WHO.

## Appendix 3A

### Manufacturer's consent for information sharing with participating national regulatory authority(ies) and the World Health Organization

Date: \_\_\_\_\_ dd/mm/yyyy \_\_\_\_\_

To: \_\_\_\_\_

**RE: <SRA> sharing of non-public information concerning <Product> with the <NRA(s)> and the World Health Organization (WHO)<sup>1</sup>**

Dear [<SRA>],

On behalf of <manufacturer>, the <MAH> in <SRA country/region> of the above-referenced regulated product, I authorize the <SRA> to share the information described below (“Information”) only with <NRA focal point – contact person/function> and WHO <contact person/function> solely for the purpose of the *Collaborative procedure in assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities* <date; version>. Confidentiality agreements are in place between <manufacturer> and WHO.

I understand that the Information may contain confidential commercial or financial information or trade secrets that are exempt from public disclosure. I agree to hold <SRA> harmless for any injury caused by <SRA>'s sharing of the Information with the <NRA> and WHO under the terms set out herein.

Information authorized to be shared with the <NRA> and/or WHO:

- all available quality data on <Product>;
- all available nonclinical data on <Product>;
- all available clinical data on <Product>;
- any other document reasonably requested by the <NRA or WHO> during the evaluation procedure;

<sup>1</sup> During the *Collaborative procedure in national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities (WHO Technical Report Series No. 1010, 2018)* WHO plays a facilitating role.

- all other information regarding GxP inspections and <Product> assessment.

Authorization is given to <SRA> to provide the Information without deleting confidential, commercial or financial, or trade secret information.

As indicated by my signature, I am authorized to provide this consent on behalf of <manufacturer> and my full name, title, address, telephone number and email address are set out below for verification.

Yours sincerely,

Name: \_\_\_\_\_

Title: \_\_\_\_\_

Address: \_\_\_\_\_

\_\_\_\_\_  
Manufacturer: \_\_\_\_\_

Email: \_\_\_\_\_

Telephone number: \_\_\_\_\_

Fax number: \_\_\_\_\_

cc:

## Appendix 3B

### Manufacturer's request for stringent regulatory authority's (SRA's) permission for sharing SRA-owned non-public information with participating national regulatory authority(ies) and the World Health Organization

Date: \_\_\_\_\_ dd/mm/yyyy \_\_\_\_\_

<manufacturer>

**RE: Request to <SRA> for a permission to <manufacturer> to share <SRA>'s non-public information concerning <Product> with the <NRA(s)> and the World Health Organization (WHO)<sup>1</sup>**

Dear <reference SRA>,

<Manufacturer> as a <MAH> of the <SRA> authorized <Product>, hereby requests the <reference SRA's> permission to share <SRA>-owned non-public information concerning <Product> for the purpose of the *Collaborative procedure in assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities* assisted by WHO.

The information to be shared consists of

<SRA> final GxP inspection reports for Product <date; version>;

<SRA> Product assessment reports; and

<SRA> <other, please specify> documents/reports that may be needed in the context of this Procedure.

The information will be shared with the <NRA(s)> and WHO.

Yours sincerely,

Name: \_\_\_\_\_

Title: \_\_\_\_\_

SRA: \_\_\_\_\_

<sup>1</sup> During the *Collaborative procedure in national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities (WHO Technical Report Series No. 1010, 2018)*, WHO plays a facilitating role.

Address: \_\_\_\_\_

Email: \_\_\_\_\_

Telephone number: \_\_\_\_\_

cc:

## Appendix 4

### Quality information summary of the finished pharmaceutical product or vaccine approved by the reference SRA (QIS- SRA (crp))

#### Foreword

*Collaborative procedure in the assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities*

The WHO *Guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities* define a template for a simplified quality information summary (QIS) to outline the key quality parameters of a product approved by a stringent regulatory authority (reference SRA) for WHO prequalification. It was realized that this simplified QIS can be a useful instrument for sharing (under appropriate conditions of confidentiality) the essential quality parameters characterizing each medicine approved by SRAs in order to accelerate national decisions on registration. However, experience with the pilot-testing of the reference SRA *Collaborative procedure* revealed that the simplified WHO QIS does not contain certain data which would facilitate verification of “sameness” of the product for the purpose of the collaborative registration of reference SRA-approved medicines. Therefore the information content of the template was extended to the form of the “QIS-SRA (crp)”.

The QIS-SRA (crp) template should be completed by the applicant and verified by the reference SRA, ideally in the initial stage of the collaborative process, when the applicant (market authorization holder (MAH)) requests the reference SRA’s cooperation and grants consent to information sharing. Should data in the application for national registration deviate from data approved by the reference SRA, these should be clearly indicated and summarized in section B10. The QIS-SRA (crp) should be submitted as a part of the application for national registration together with other documents stipulated in the collaborative procedure for products approved by reference SRA. A copy should also be provided in Word format.

Whenever any variation to the approved product that affects the QIS-SRA (crp) has been approved by the reference SRA, the QIS-SRA (crp) should be revised (using track-changes mode) and resubmitted to the relevant regulatory authorities in Word format together with the regulatory letter or other relevant document confirming approval of the variation under consideration.

The QIS-SRA (crp) is specifically designed for the purpose of the SRA collaborative procedure and should not be confused with other formats of QIS that are used for the purpose of WHO prequalification.

When completing the QIS-SRA (crp) template, this covering *Foreword* should be deleted.

## QUALITY INFORMATION SUMMARY OF THE FINISHED PHARMACEUTICAL PRODUCT OR VACCINE APPROVED BY THE REFERENCE SRA (QIS-SRA(crp))

### A. Pharmaceutical product or vaccine subject to reference SRA collaborative procedure

**A1 Reference SRA**

**A2. Product registration/authorization number assigned by the reference SRA**

#### Information as currently approved by the reference SRA

**A3. Proprietary name of finished pharmaceutical product (FPP) in the reference SRA country/region**

**A4. Innovator or multisource (generic) FPP**

**A5. Name of the holder of the reference SRA marketing authorization and official address**

**A6. International Nonproprietary Name (INN) of active pharmaceutical ingredient(s) (API(s)), including form (salt, hydrate, solvate, etc.)**

**A7. Dosage form and strength**

**A8. Product description** (as in Product information, e.g. white, film-coated, capsule-shaped tablets debossed with "X" and score line on one side and plain on other side)

**A9. Primary and secondary packaging material(s) and pack size(s)** (all pack types)

**A10. Storage conditions** (as in Product information)

**A11. Shelf life of FPP** (including in-use periods, where applicable)

**A12. Names of all approved manufacturers of FPP, physical address(es) of manufacturing site(s)** (and unit if applicable), including intermediates, primary packaging site and release testing (indicate function of each site)

**A13. FPP storage conditions and duration over which stability, as reported to the reference SRA, was established** (e.g.  $30 \pm 2^\circ\text{C}/75 \pm 5\% \text{RH}$  for 24 months,  $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{RH}$  for 6 months):

Long-term (real time in months)	
Intermediate (duration in months)	
Accelerated (duration in months)	

**B. Information that is considered confidentialia****Information as currently approved by the reference SRA**

**B1.** Names of all approved API manufacturers, physical address(es) of manufacturing site(s) (and unit if applicable), including intermediates, contractors and release testing (indicate function of each site)

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**B2.** Active pharmaceutical ingredient master file/drug master file (APIMF/DMF version number(s) and date(s), if relevant)

Name of API	API manufacturer	APIMF/DMF version number(s) and date(s)

**B3.** API specifications of the FPP manufacturer

Standard (e.g. BP, Ph.Eur., Ph.Int., USP, in-house) <sup>a</sup>		
Specification reference number and version		
Test	Acceptance criteria	Analytical procedure (type/source/version)
Description		
Identification		
Impurities		
Assay		
Others, please specify		



Composition of all components purchased as mixtures (e.g. colourants, coatings, capsule shells, imprinting inks):

B6. FPP manufacture			
Master production document reference number and version			
B7. FPP specifications			
Standard (e.g. BP, Ph.Int., USP, in-house) <sup>a</sup>			
Specification reference number and version/ effective date			
Test	Acceptance criteria (release)	Acceptance criteria (shelf life)	Analytical procedure (type/source/version)
Description			
Identification			
Impurities			
Assay			
Others, please specify			
B8. Pharmacokinetic/safety/efficacy-related information used for reference SRA approval of <b>multisource</b> products. Indicate:			
Type of study	"X" in appropriate box	Comparator product	
Bioequivalence			
BCS-based biowaiver			
Other (specify)			
No study			
Notes/ clarifications			

<sup>a</sup> BP: British Pharmacopoeia; Ph.Eur: European Pharmacopoeia; Ph.Int.: The International Pharmacopoeia; USP: United States Pharmacopoeia.

<b>B9. List of variations pending in the reference SRA up to the date of verification</b>		
Variation number	Variation	Type of variation according to reference SRA regulations

<b>B10. Discussion of differences between national application and data approved by the reference SRA</b>		
Deviation reference no.	Data submitted for national registration which deviates from data approved by the reference SRA presented above. Mention also deviations in content of Product information, especially those related to indications, contraindications and posology.	Explanatory note

<b>C1. Confirmation of content and verification by the reference SRA</b>		
Date of completion by the applicant	Name of person representing the applicant who completed the QIS-SRA	Position in the organization
Date of verification by the reference SRA <i>Part B10 is exempted from verification</i>	Person representing the reference SRA who verified the QIS-SRA information	Position in the organization

## Change history to QIS-SRA (crp) and Product information

Date of revision (reported variation <sup>a</sup> )	Description of revision/variation

<sup>a</sup> Variations approved by the reference SRA **after** national registration of the FPP and affecting **only** the QIS-SRA and/or Product information should be reported in the change history.

## Appendix 5

### Proposed documentation for collaborative procedure for reference SRA-approved pharmaceutical products and vaccines

*Notes:*

The format of the documentation corresponds to common technical document (CTD) in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) format/content. For practical reasons nonclinical (Module IV) and clinical data (Module V) are replaced by summaries included in Module II. Should there be a need for more extensive data from Module IV and Module V, these are available on request.

Confidentiality of submitted data and non-disclosure to a third party is – in addition to relevant national legislation and organizational measures applied by national regulatory authorities (NRAs) participating in the Procedure – assured by a commitment on confidentiality that represents an integral part of the Procedure<sup>1</sup> (Appendix 1), is signed by representatives of participating NRAs and archived by WHO.

#### Adapted Module 1

	Documentation to be provided	Comments
1.0 Letter of application		Cover letter in English, French, or as applicable to the region
<b>Attachments to the letter:</b>		
Appendix 3A of the reference stringent regulatory authority (SRA) Procedure		

<sup>1</sup> Collaborative procedure in assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities, facilitated by WHO.

Table *continued*

	Documentation to be provided	Comments
Appendix 3B of the reference SRA Procedure		
Appendix 4	Includes information as specified in Commitment letter 1 (additional administrative data) and Commitment letter 2 (additional stability data for climatic zones). Any differences in the dossier submitted to the reference SRA should be explained, including differences in product information.	Submitted in English or French as applicable to the region
1.1 Comprehensive table of contents (TOC)	Comprehensive TOC including Module 1 information	
1.2 Quality information summary (QIS-SRA)	This will be included instead of a country-specific application form	Refer to Appendix 9 for the QIS-SRA template To be included in the adapted Module 1
<b>1.3 Product information</b>		
1.3.1 Package insert or summary of product characteristics	Product information as applicable for the region where the application will be submitted	Submitted in English or French as applicable to the region
1.3.2 Patient information leaflet or package leaflet	Mock-ups	Submitted in English or French as applicable to the region
1.3.3 Labelling	Mock-ups	Language and information to reflect national requirements

Table continued

	Documentation to be provided	Comments
<b>1.4 Marketing authorization from reference SRA</b>		
1.4.1 Marketing authorization from reference SRA	Yes	
1.4.2 Assessment report from reference SRA  (Access to the full assessment report from the reference SRA, if available)	Agreement from the manufacturer to allow reference SRA to share the report with WHO and national regulatory authorities (NRAs). Prior to sharing, the reference SRA and manufacturer should agree on the content of the document that is shared. If fully justified, sentences referring to highly confidential information and/or highly sensitive data and/or not related to the product assessment data could be masked.	Note that this type of document is available only for products registered in Europe, via the Centralized Procedure. Public reports are preferred as they already contain all useful information, except those considered to give a competitive advantage. The sharing process is facilitated by WHO, between reference SRA and NRAs.
<b>1.5 Good manufacturing practices (GMP) certification</b>		
1.5.1 Copy of the GMP certificate of the active pharmaceutical ingredient (API) supplier, if available	Yes If not available, statement signed by qualified person (QP) from the finished pharmaceutical product manufacturing site to be provided	Currently, this is not always available. No legalization is required.
1.5.2 Copy of the GMP certificate of the finished pharmaceutical product (FPP) manufacturer(s)	Yes	No legalization is required.

Table *continued*

	Documentation to be provided	Comments
1.5.3 GMP inspection report of the manufacturing site(s) (FPP) from any reference SRA	Agreement from the manufacturer to allow the reference SRA to share the report with WHO and NRAs. Prior to sharing, the reference SRA and manufacturer should agree on the content of the document that is shared. If fully justified, sentences referring to highly confidential information and/or highly sensitive data and/or not related to the product assessment data could be masked.	Public reports are preferred as they already contain all useful information, except those considered to give a competitive advantage. The sharing process is facilitated by WHO, between the reference SRA and NRAs.
<b>1.6 Other documentation</b>		
If generic dossier: <ul style="list-style-type: none"> <li>– full GCP inspection report of the bioequivalence study from any reference SRA, if any;</li> <li>– bridging report (where applicable) especially for innovative medicines (Appendix 6);</li> <li>– information on local representatives or distributor.</li> </ul>	Agreement from the manufacturer to allow reference SRA to share the report with WHO and NRAs. Prior to sharing, the reference SRA and manufacturer should agree on the content of the document that is shared. If fully justified, sentences referring to highly confidential information and/or highly sensitive data and/or not related to the product assessment data could be masked.	Public reports are preferred as they already contain all useful information, except those considered to give a competitive advantage. The sharing process is facilitated by WHO, between the reference SRA and NRAs.

## Module 2 summaries

Module 2 should be complete as submitted to the reference SRA.

*Note:* In the case of generic medicines for which a Clinical summary is not available, the Clinical overview (Module 2.5) should be included.

## Module 3 Quality documentation

Complete Module 3 as submitted to the reference SRA, except corresponding open part of the active pharmaceutical ingredient master file (APIMF) is submitted, unless indicated otherwise according to the requirements of the participating NRA. If climatic zone III–IV stability data are not available, the commitment and protocol should be provided for stability studies under the appropriate climatic conditions for the receiving country. Any preliminary data under the required climatic conditions for the participating NRA should be provided. The stability data should be assessed by the reference SRA, where applicable or possible.

Additional region-specific information for Module 3 should be provided, where applicable.

## Module 4 non-clinical documentation

Data to be provided only if required by the participating NRAs according to their national requirements, otherwise, these data are on request.

## Module 5 clinical documentation

For innovative medicines, data to be provided only if required by the participating NRAs according to their national requirements, otherwise, these data are available on request. For generic products, complete documentation on bioequivalence studies should be provided in the submission in-line with WHO Guidelines on registration requirements to establish interchangeability<sup>2</sup> and applicable national regulatory requirements for participating NRAs.

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<sup>2</sup> WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-first report. Geneva: World Health Organization; 2017: (WHO Technical Report Series, No. 1003, Annex 6), 181-236.

## Appendix 6

### Requirements for provision of a bridging report for reference SRA-approved pharmaceutical product and vaccines for consideration of registration in participating countries

It is expected and is general practice that medicines authorized for use by reference SRAs are approved for the conditions of use relevant for the respective reference SRA territory. When a reference SRA-approved product is submitted for the regulatory approval in a country where conditions of use or the benefit–risk profile of the medicine may differ, it is assumed that the applicant for registration (marketing authorization) is able to support the application by providing evidence of a positive benefit–risk profile for the proposed conditions of use for the country concerned. Since reference SRA assessments may not always account for specific circumstances that can significantly affected the benefit-risk of a medicine in countries/regions outside the SRA's region, , the reference SRA assessment reports can be considered incomplete to enable appropriate benefit-risk evaluation in those settings. Currently only the European Medicines Agency (EMA)'s scientific opinion according to Article 58 of Regulation (EC) No. 726/2004, in the EU, may be considered to extensively address these questions.

Differences in target population, epidemiology and other features of the disease, concomitantly used medicines and hence the interaction potential, local treatment and diagnostic modalities and other factors can substantially affect the benefit–risk profile of a medicine. There can also be issues related to certain quality parameters, especially in relation to the stability under different climatic conditions. Therefore, to provide regulators in target countries with information relevant to the use of the product in their countries it is proposed to develop a bridging report supplementing the reference SRA assessment report (quality, safety) and the quality and clinical overviews provided in Module 2 of the common technical document (CTD).

Such a bridging report should, in particular, provide the applicants with the justification of the:

- comparability of the studied population to the target population (e.g. ethnicity, gender representation, age groups) as regards demonstration of safety and efficacy;
- relevance of reference SRA-approved conditions of use as regards epidemiology and disease pattern in the target countries as well

as other implications for efficacy and safety, e.g. feasibility of monitoring and precautionary measures (e.g. resistance testing or therapeutic drug monitoring);

- interactions with food and with other medications relevant in the target countries that are not discussed in the reference SRA's assessment report;
- 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.

Such a report is justified where the reference SRA assessment report does not sufficiently cover these elements of assessment. Provision of a bridging report should not be mandatory, but can substantially facilitate conduct of the regulatory assessment, reduce the number of potential regulatory questions and shorten the duration of the regulatory approval process. Such a report can be valid for more than one country, where conditions of use of the medicine are considered, in principle, to be similar. Similarly to the the case of overviews submitted in Module 2, the bridging report may be prepared by the applicant, or by expert(s) contracted by an applicant, who will attach their professional CV(s).

# Appendix 7

## Expression of interest to national regulatory authority

Date: \_\_\_\_\_ dd/mm/yyyy \_\_\_\_\_

To: \_\_\_\_\_

**RE: declaration to the <national regulatory authority (NRA)> to initiate and proceed with registration of <Product> in line with the Procedure**

Dear <NRA>,

On behalf of <manufacturer>, the <marketing authorization holder (MAH)> in <stringent regulatory authority (reference SRA) country/region> of the <Product> that is registered with the <reference SRA> under the <reference number>, and solely for the purpose of the “*Collaborative procedure in the assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities*” (The Procedure – <date; version>) organized by WHO.

I, <manufacturer representative name> certify that:

1. The product submitted for registration is identical in all aspects of manufacturing and quality to that currently approved by the <reference SRA> under the <reference number>, including formulation, method and site(s) of manufacture, sources of active and excipient starting materials, quality specifications and control methods of the product and starting material, packaging, shelf life and product information.

If applicable:

The only exception(s) to the conditions approved by the <reference SRA> are:

<Deviations from current reference SRA approval, explanations and related commitments>.

2. Submitted assessment and inspection reports are complete reports as issued by the <reference SRA>. The <reference SRA> has been authorized by the <manufacturer> to share with <NRA focal point> all <Product> related regulatory information, including information

of a confidential nature. A copy of the authorization letter to the <reference SRA> is attached as <Appendix No. 1>.

If applicable:

The only data hidden in the assessment and/or inspection report of the <reference SRA> concern <nature and scope of missing data> and are hidden because of <reason>.

3. Information included in the registration dossier is identical with data currently approved by the <reference SRA>. As for the purpose of the Procedure, Module IV of the registration dossier in CTD format containing nonclinical data and Module V containing clinical data are replaced by respective summaries included in Module II, the <manufacturer> commits to submit without delay the non-submitted data on request of the <NRA>.
4. On behalf of <manufacturer>, the <MAH> in <SRA country/region> of the above-mentioned SRA regulated product, I hereby commit to
  - a. Supplying any additional information in accordance with local regulations or upon request from the <NRA> as soon as possible during the process.
  - b. Should the registration be granted, submitting in accordance with local regulations without delay all relevant variations as approved by the <SRA country/region>.
  - c. Supplying in accordance with local regulations any information about <SRA> regulatory actions relevant to the <Product>, including suspension or termination of registration, should it happen for whichever reason.

Signature

<Appendix No. 1>: Copy of the authorization letter to the <SRA (reference SRA)>

If appropriate:

- Current storage conditions approved by the <SRA country/region> are <storage conditions approved by reference SRA>. On behalf of <manufacturer>, the <MAH> in <SRA country/region> of the above-referenced regulated product, I hereby commit to supplying within <time period> results of stability data applicable to Zones III-IVa or IVb should any of these stability zones be applicable to your country.

In addition, <NRA> will be informed of any out-of-specification (OOS) results during the study and protocol for the relevant applicable zones.

- The WHO focal person (s) <name/s> has/have been provided with the <Product> dossier to facilitate the Procedure and is/are authorized by the <manufacturer> to communicate on the Product-related issues with <NRA representatives >. By this letter the <NRA> is authorized to share with WHO all <Product> related regulatory information and communicate for the purpose of the Procedure on the <Product> related regulatory issues, including exchange of confidential information.
- Should the local applicant be a different legal entity from a holder of reference SRA marketing authorization or from a holder of scientific opinion in the case of European Union Article 58 procedures, the relationship should be clarified and agreements assuring information flow should be adjusted to this situation.

# Appendix 8

## Confidential disclosure agreement

This Agreement, effective as from the last date of signature, is between: \_\_\_\_\_  
\_\_\_\_\_, of the one part,

and

WORLD HEALTH ORGANIZATION (“WHO”), 20 Avenue Appia, 1211 Geneva 27, Switzerland, of the other part.

WHEREAS, \_\_\_\_\_ has developed certain information and data relating to \_\_\_\_\_ which it considers to be confidential and its proprietary property (such confidential information and data being hereinafter collectively referred to as the “Information”).

WHEREAS, \_\_\_\_\_ is willing to release the Information to WHO, to enable WHO to assess such Information and conduct activities relating to the Collaborative procedure in assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities, including but not limited to collaboration with \_\_\_\_\_ (the “Purpose”), provided that WHO undertakes to regard the Information as confidential and the property of \_\_\_\_\_, and release it only to persons who are bound by like obligations of confidentiality and non-use, as are contained in this Agreement.

NOW IT IS HEREBY AGREED as follows:

1. The Parties hereto agree that any disclosure of Information by \_\_\_\_\_ to WHO will be subject to the following terms and conditions.
2. Any Information which is supplied directly by \_\_\_\_\_ in written or other tangible form shall be marked by \_\_\_\_\_ as “confidential”. Any Information which is supplied indirectly by \_\_\_\_\_, such as from a Stringent Regulatory Authority with \_\_\_\_\_’s consent, need not be marked “confidential”. Any Information which is disclosed by \_\_\_\_\_ in oral form shall be confirmed by it in written summary form within 30 days from the date of oral disclosure.

3. In accepting the Information, WHO agrees with \_\_\_\_\_ as follows:
- a) WHO shall regard the Information disclosed by \_\_\_\_\_ as confidential and the property of \_\_\_\_\_. In this regard, WHO agrees to use such Information only for the Purpose (as defined above) and to make no other use thereof, unless and until a further agreement is executed with \_\_\_\_\_ governing the use thereof;
  - b) nothing in this Agreement shall prevent \_\_\_\_\_ from disclosing the Information to any third party; and
  - c) WHO has no right in or to the Information of \_\_\_\_\_.
4. WHO undertakes to maintain the Information received from \_\_\_\_\_ in confidence. In connection with the foregoing, WHO shall take all reasonable measures to ensure that the Information received from \_\_\_\_\_ shall not be used for any purpose other than the Purpose (as defined above) and shall not be disclosed to any person who does not have a need to know for the aforesaid Purpose and is not bound by similar obligations of confidentiality and restrictions on use as contained in this Agreement.

For the avoidance of doubt, WHO shall be entitled to disclose the Information to third parties collaborating with WHO in connection with the Purpose (including, without limitation, with the relevant regulatory and other authorities of WHO Member States), provided that such third parties are bound by similar obligations of confidentiality and restrictions on use as contained herein.

The obligations of confidentiality and restrictions on use contained in this Agreement shall continue for a period of five (5) years from the date of disclosure by \_\_\_\_\_ to WHO.

5. The obligations of confidentiality and restrictions on use contained in this Agreement shall not apply to any part of the Information which WHO is clearly able to demonstrate:
- a) was lawfully in its possession and known to it prior to disclosure by \_\_\_\_\_ hereunder, as evidenced by documents antedating the date of disclosure; or
  - b) was in the public domain or the subject of public knowledge at the time of disclosure by \_\_\_\_\_ hereunder; or
  - c) becomes part of the public domain or the subject of public knowledge through no fault of WHO; or
  - d) becomes available to WHO from a third party not in breach of a legal obligation of confidentiality to \_\_\_\_\_ in respect thereof; or

- e) was subsequently and independently developed by or on behalf of WHO, as shown by written records, by persons who had no knowledge of such Information; or
  - f) is required to be disclosed by law, provided that WHO shall in such case immediately notify \_\_\_\_\_ in writing of such obligation and shall provide adequate opportunity to \_\_\_\_\_ to object to such disclosure or request confidential treatment thereof (provided always, however, that nothing contained herein shall be construed as a waiver of the privileges and immunities enjoyed by WHO and/or to submit WHO to any national court jurisdiction).
6. WHO undertakes that it will disclose the Information only to those persons who need to receive the Information of \_\_\_\_\_ for the Purpose (as defined above).
  7. WHO undertakes to ensure that all persons who receive the Information disclosed to WHO hereunder shall be bound by similar obligations of confidentiality and restrictions on use as contained in this Agreement.
  8. Nothing contained in this Agreement shall be construed, by implication or otherwise, as an obligation to enter into any further agreement relating to any of the Information or as the grant of a licence to WHO to use the Information other than for the Purpose (as defined above).
  9. Upon completion of the aforesaid Purpose and in the absence of any further written agreement between the Parties, WHO shall cease all use, shall make no further use of the Information disclosed to it hereunder, and shall, upon written request from \_\_\_\_\_, promptly return to \_\_\_\_\_ all of the Information received which is in tangible form, except that WHO may retain one copy of the Information in its files to determine any continuing obligations hereunder.
  10. This Agreement constitutes the entire understanding of the Parties hereto with respect to the subject matter hereof and shall not be modified except by mutual agreement in writing.
  11. Without the prior written consent of the other Party, neither Party shall, in any statement or material of an advertising or promotional nature, refer to the relationship of the Parties under this Agreement, or to the relationship of the other Party to the Information and/or the Purpose.
  12. Any matter relating to the interpretation or the execution of this Agreement which is not covered by its terms shall be resolved by reference to the laws of Switzerland. Any dispute relating to the interpretation or application of this

Agreement shall, unless amicably settled, be subject to conciliation. In the event of failure of the latter, the dispute shall be settled by arbitration. The arbitration shall be conducted in accordance with the modalities to be agreed upon by the Parties or, in absence of agreement, with the rules of arbitration of the International Chamber of Commerce. The Parties shall accept the arbitral award as final. It is agreed furthermore that nothing contained in this Agreement shall be construed as a waiver of any of the privileges and immunities enjoyed by WHO under national and international law, and/or as submitting WHO to any national court jurisdiction.

Made in two (2) original copies,

\_\_\_\_\_

**World Health Organization**

By: \_\_\_\_\_

By: \_\_\_\_\_

Title: \_\_\_\_\_

Title: \_\_\_\_\_

Date: \_\_\_\_\_

Date: \_\_\_\_\_



## Appendix 9

### Notification of an outcome of the national registration provided by the participating manufacturer to the World Health Organization

#### Details of pharmaceutical manufacturer using the Procedure<sup>1</sup>

Manufacturer: Click here to enter text. \_\_\_\_\_

Country: Click here to enter text. \_\_\_\_\_

Address: Click here to enter text. \_\_\_\_\_

Focal point: Click here to enter text. \_\_\_\_\_

Telephone number (please include codes): Click here to enter text. \_\_\_\_\_

Email: Click here to enter text. \_\_\_\_\_

#### Details of pharmaceutical product or vaccine (the Product) subject to the Procedure

Name of the Product: Click here to enter text. \_\_\_\_\_

Active pharmaceutical ingredient (s): Click here to enter text. \_\_\_\_\_

Strength: Click here to enter text. \_\_\_\_\_

Dosage form: Click here to enter text. \_\_\_\_\_

#### Course of the Procedure

Country: Click here to enter text. \_\_\_\_\_

Regulatory authority: Click here to enter text. \_\_\_\_\_

Date of submission of the application: Click here to enter text. \_\_\_\_\_

Date of acceptance of the application (if different from submission date): Click here to enter text. \_\_\_\_\_

Date of issuance of a decision: Click here to enter text. \_\_\_\_\_

Length of process interruption/clock-stop (if applicable):<sup>2</sup> Click here to enter text. \_\_\_\_\_

<sup>1</sup> Collaborative procedure in assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities – facilitated by WHO.

<sup>2</sup> Time provided by NRA to the applicant to complete data or respond to regulatory questions.

## Decision on registration

Granted, rejected, withdrawn: [Click here to enter text.](#) \_\_\_\_\_

Registration number (if applicable): [Click here to enter text.](#) \_\_\_\_\_

Registration granted in line with the reference SRA decision or with deviations, please comment: [Click here to enter text.](#) \_\_\_\_\_

## Compliance with the Procedure, other observations and recommendations

In the course of the Procedure the following deviations were observed and recorded: [Click here to enter text.](#) \_\_\_\_\_

Any other observations and recommendations: [Click here to enter text.](#) \_\_\_\_\_

\_\_\_\_\_

For the manufacturer

Signature:

Name: [Click here to enter text.](#) \_\_\_\_\_

Title: [Click here to enter text.](#) \_\_\_\_\_

Place and date: [Click here to enter text.](#) \_\_\_\_\_

