

Collaboration in Verification of Good Manufacturing Practices (GMP) Compliance Between WHO-PQT and Medicines Manufacturers Interested in Submitting for WHO Prequalification

One of the objectives of the World Health Organization is to make quality priority medicines broadly available. For this purpose the World Health Organization Prequalification Team (WHO-PQT) thoroughly assesses individual medicines and organizes inspections of manufacturers and contract research organizations (CROs). The inspections are normally organized only after submission of an application for prequalification of a medicine. However, WHO-PQT successfully piloted, in cooperation with the Nigerian government and manufacturers association, a scheme which suggests that verification of the compliance with the principles of Good Manufacturing Practices (GMP) before the submission for prequalification can facilitate the prequalification process. This also potentially increases assurance of the integrity of the data compiled in the dossier which will be generated under a confirmed GMP environment and reduces the risk of critical observations in inspections organized later during prequalification process. Therefore, to stimulate submissions of mature applications for prequalification of medicines produced in compliance with GMP, a process is proposed to help interested manufacturers in resource-limited countries to achieve assurance of GMP compliance earlier than would otherwise be the case.

The process recognizes the important role of national GMP inspectorates. Cooperation with national inspectorates in countries of manufacture can make an important contribution to building of these inspectorates' capacity.

Principles for organization of pre-submission inspections

Manufacturers in resource-limited countries developing a medicine for WHO prequalification can approach WHO-PQT with a request for pre-submission inspection (pre-inspection) under the following conditions:

1. The manufacturer is either producing, or at an advanced stage of development of a finished pharmaceutical product (FPP) invited for WHO prequalification,¹ United Nations Commission on Life-saving Commodities for Women and Children (UNCoLSC) project² or other WHO recognized projects of public health relevance.
2. There must exist a pre-submission plan for data development and completion of the dossier, as well as for achievement of GMP compliance, which provides a realistic chance for a prequalification submission in less than two years.

¹ http://www.who.int/prequal/info_applicants/eoi/FPPs_APIs_invited.xlsx

² <http://www.lifesavingcommodities.org/about/lifesaving-commodities/>

3. In order to optimize the use of WHO-PQT resources, the plan and existing status of GMP compliance should be verified either by the national medicines regulatory authority (NMRA), or another party with recognised expertise, which is assisting the manufacturer in the preparation for prequalification.

To consider a request for pre-inspection, WHO-PQT should be provided with the following documents:

1. A request for pre-inspection and confirmed agreement with the conditions under which the pre-inspection is provided. The manufacturer should identify the medicine(s) intended to be prequalified (should the company produce or plan to produce more medicines that are of WHO-PQT interest, these should also be identified). The manufacturer should also identify any external party(ies) by which it is or has been assisted to submit for prequalification. The request must be signed by a responsible representative of the company management entitled to make decisions and commitments in the company (*Annex 1*).
2. A plan summarizing the essential steps in the data development, completion of the dossier and achievement of GMP compliance for each product relevant for WHO-PQT according to the provided template (*Annex 2*). The plan has to be confirmed by management of the respective manufacturer. If some of the individual steps have already been implemented, the company should be prepared to share the relevant documentation with WHO-PQT.
3. A detailed current inspection report (in English) issued by national inspectorate stating the GMP standard against which the site was assessed and the compliance status. Some minor observations for which corrective action is pending may remain. In such a case, a plan of corrective and preventive actions (CAPAs) should be submitted as well. If the national inspectorate in the country of manufacture does not possess the capacity to conduct a GMP inspection, a detailed inspection report generated by GMP inspectors from another country should be provided. It is also possible to provide an audit report of independent expert(s), with recognised expertise, together with CV(s) of the expert(s).
4. Should the manufacturer be assisted by a third party (e.g. NGO, foreign government organization, experts under specific project), a statement from this party should be provided confirming preparation of the manufacturer to submit a specific product for prequalification, commenting on the feasibility of the product development plan and readiness of the manufacturer for the pre-inspection. This statement should be confirmed by the management of the respective manufacturer.

The request and information should be provided to WHO-PQT for the attention of Dr Milan Smid, Lead of PQT Technical Assistance and Laboratory Services Group by email: prequalreg@who.int.

The obtained information shall be treated as confidential. WHO-PQT reserves the right to request additional information from the manufacturer or the assisting party(ies) and to decide on individual cases depending on the priority of proposed medicine(s), available resources and other prioritized activities. If the decision is negative, WHO can arrange for additional technical assistance to rationalize the product and data development plan or to reduce the risk of negative inspection outcomes.

The manufacturer shall be informed about the WHO-PQT decision within 60 days, which does not include time by the manufacturer to respond to any request for additional information.

Organization of pre-submission inspections

If the organization of the pre-inspection is agreed, the planning and communication with the manufacturer shall be organized as for regular prequalification inspections. The pre-inspection will be conducted within six months from date of agreement. The manufacturer will be requested to submit the following information to the WHO-PQT inspectorate electronically, to facilitate the preparation for, and conduct of, the pre-inspection:

1. A site master file compiled according to WHO guidelines.³
2. Product master formula and batch formula.
3. Manufacturing process flow chart indicating major process steps, equipment, in-process control and scale (input and output). A blank or executed batch manufacturing record may be submitted in lieu of or in addition to the process flow chart.
4. Specifications of active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs).

The pre-inspection shall be system-oriented, with a focus on the production line(s) and manufacture of the medicine(s) planned to be submitted for prequalification. The respective NMRA shall be informed about the conduct of the pre-inspection and shall be invited to participate. The pre-inspection report shall be provided to the manufacturer and the respective NMRA. In the event that a CAPA plan is agreed, this can be monitored by correspondence in co-operation with the NMRA.

The cost of the pre-inspection shall be covered by the manufacturer (or by another party on behalf of the manufacturer) on a cost-recovery basis. Under specific circumstances (e.g. highly prioritized medicine), the pre-inspection cost may be waived.

The same principles for organization of pre-inspections shall be applied when the technical assistance to manufacturers is provided by parties external to WHO or by WHO-PQT itself.

Outcomes of pre-submission inspections

Should the pre-inspection conclude positively (taking into account implementation of corrective actions), the non-confidential part of the pre-inspection report shall be publicly posted in the form of a WHO Public Inspection Report (WHOPIR) to demonstrate GMP compliance of the pre-inspected manufacturer and the scope of the pre-inspection. The manufacturer is expected to notify WHO-PQT inspectorate about any changes or other occurrences that can affect the validity of the pre-inspection

³ http://www.who.int/prequal/info_applicants/info_for_applicants_sitemasterfile.htm

report and GMP compliance status. The pre-inspection report shall be considered invalid and shall be withdrawn from the WHO-PQT website within two years from the pre-inspection if the prequalification application for the intended medicine is not submitted to WHO-PQT within that period.⁴

Should the pre-inspection conclude negatively, no follow-up pre-inspection is organized. However the manufacturer retains the right to be involved in regular prequalification processes. In this situation, and also if the manufacturer is not seen yet prepared for the pre-inspection, it is possible to agree with WHO-PQT on provision of a technical assistance in order to achieve the required standards.

More information can be obtained by contacting prequalreg@who.int. Consultancies on provision of pre-inspection to specific manufacturers can be requested at the same address.

⁴ In case of UNCoLSC project and other projects the period of publication of the WHOPIR will be set individually.