Inspections

This section provides information on Inspection activities in the Prequalification Programme. The following topics are covered:

- General information on inspections
- Norms and Standards (e.g. GMP, GCP)
- Meetings with Inspectors - Meeting Request Form
- Training material
- Inspection reports and WHOPIRs
- Notice of Concern (NOC)
- GMP pre-inspections complementary to assistance to medicines manufacturers - pilot
- Collaborative procedure with National Medicines Regulatory Authorities (NMRAs) in inspection activities
- Points to consider for inspections of biowaiver data
- Frequently asked Questions and Answers

General information on inspections

The WHO prequalification team plans and coordinates the performance of inspections (announced or unannounced) of the site(s) of manufacture of selected Active Pharmaceutical Ingredients API(s), the Finished Pharmaceutical Product (FPP), and of selected clinical testing units or Contract Research Organization (CRO).

The inspections of the manufacturing site(s) are conducted to assess compliance with Good Manufacturing Practices (GMP) for Finished Pharmaceutical Products (FPPs) and GMP for Active Pharmaceutical Ingredients (APIs) as recommended by WHO. A Site Master File (SMF) submitted by the applicant will be reviewed before an inspection is performed. (Please note that a SMF should be submitted on a CD or DVD at the same time a product dossier is submitted for assessment. See Q&A). Data and information submitted in dossiers and SMFs will be verified during inspections.

The inspections of clinical testing units or organizations are carried out to assess compliance with GCP and GLP, and to perform data verification. (Please note that a Contract Research Organization Master File (CROMF) should be submitted on a CD or DVD upon request. See Q&A)

The inspections are performed by a team of inspectors consisting of experts appointed by WHO (preferably from drug regulatory authorities inspectorates, who act as temporary advisers to WHO) and WHO staff members. The inspectors have relevant qualifications and experience to perform such inspections, and are competent in areas such as production and quality control of pharmaceuticals, have appropriate experience in GMP and GCP or GLP. A representative of the drug regulatory authority of the country of manufacture would normally be expected to accompany the team to the manufacturing and testing facilities to assess the compliance with GMP and GCP or GLP.

The inspectors must comply with the confidentiality and conflict of interest rules of WHO. Each inspection team will perform the inspection and report on its findings to in accordance with SOPs established by WHO for that purpose so as to ensure a standard harmonized approach.

An inspection report listing all the observations and findings is prepared after the inspection and provided to the manufacturer or CRO as relevant. The manufacturer and or CRO has to take appropriate corrective and preventive action and submit a response to the inspection report for assessment by the inspectors. Follow-up inspections to verify the implementation of corrective and preventive actions can be done by WHO.

Norms and Standards

Manufacturers and CROs will be assessed though inspections (announced or unannounced), for compliance with WHO norms and standards including Good Manufacturing Practices (GMP), and Good Clinical Practices (GCP) and Good Laboratory Practices (GLP) as appropriate.

Good Manufacturing Practices (GMP):

- Active Pharmaceutical Ingredients (APIs)
- Finished Pharmaceutical Products (FPPs)

Good Clinical Practices (GCP):

- Guidelines for good clinical practice (GCP) for trials on pharmaceutical products, WHO Technical Report Series, No 850, Annex 3, 1995
- Good Clinical Practices (GCP) Handbook
- Additional guidance for organizations performing in vivo bioequivalence studies, WHO Technical Report Series No 937, Annex 9, 2006

Quality Control Laboratories (QCL):

- WHO Good Practices for Pharmaceutical Quality Control Laboratories
- WHO Good Practices for Pharmaceutical Microbiology Laboratories

Other WHO norms and standards may be applicable. For more details and related guidelines, please see the additional material on the following web links:

- Norms, standards and guidance for pharmaceuticals
- The WHO Expert Committee on Specifications for Pharmaceutical Preparations reports (Technical Report Series)
- Training Material

Transfer of Technology in Pharmaceutical Manufacturing:

- WHO Guidelines on transfer of technology in pharmaceutical manufacturing

Training Material

A CD-ROM is available containing training modules on basic good manufacturing practices as well as supplementary training material covering validation, water systems etc.

The contents are also available on the link below:

- Training Material

Training modules on quality control:

- Training Material

Presentations made at recent training workshops:

- Training Material

Inspection reports

Only manufacturers of FPPs meeting GMP requirements included in the list of prequalified products. Prior to listing, all the critical, major and other observations listed in the inspection report must be addressed and brought to a satisfactory level of compliance by the manufacturers.

In accordance with World Health Assembly Resolution WHA57.14 of 22 May 2004, WHO will – subject to the protection of any commercially sensitive confidential information – publish WHO Public Inspection Reports (WHOPIR(s)) on the manufacturers and CROs that were found to be in compliance with WHO-recommended guidelines and standards.

WHO Public Inspection Report (WHOPIR)

A WHOPIR reflects the inspection performed and gives a summary of the observations and findings made during the inspection, but excludes confidential proprietary information as well as all the individual observations that were communicated in the full inspection report. It also indicates the date and duration of the inspection as well as the scope of the inspection. WHOPIRs are listed below in alphabetical order.

- WHOPIRs

After a period of three years, WHOPIRs are moved to the section marked "Archived WHOPIRs". If a site is inspected and found to be non-compliant with GMP after a WHOPIR was issued following a previous inspection, that WHOPIR will be removed from the web site (as the site is then no longer considered compliant with GMP).

- Archived WHOPIRs

Notices of Concern (NOC)

In accordance with World Health Assembly Resolution WHA57.14 of 22 May 2004 – subject to the protection of any commercially sensitive confidential information – WHO is entitled to publish negative evaluation outcomes:

"3. (4) to ensure that the prequalification review process and the results of inspection and assessment reports of the listed products, aside from proprietary and confidential information, are made publicly available;"

What is an NOC?

An NOC is a letter that is issued to a manufacturer, contract research organization or quality control laboratory, by the WHO Prequalification of Medicines Programme.

When is an NOC issued?

An NOC is issued after an inspection was performed at a site where observations were made that result in concern regarding compliance of the site with specified standards such as Good Manufacturing Practices (GMP) or Good Clinical Practices (GCP) or Good Laboratory Practices (GLP).

An NOC may also be issued if the requested response to the observations noted in an inspection report, detailing the corrective actions taken or proposed to be taken, is not considered adequately robust and appears unlikely to deal with the underlying root cause of a critical or major observation.

An NOC may also be issued if the requested response to the observations noted in an inspection report, detailing the corrective actions taken or proposed to be taken, is not received by WHO on or before the due date (i.e. 30 days from the inspection date).

In addition, an NOC may be issued if a manufacturer refuses inspection of their manufacturing site.

What does an NOC contain?

An NOC states observations made during an inspection that are considered to be "critical" or "major" non-compliances with WHO norms and standards, that are of concern in relation to quality management or quality assurance; or "critical" or "major" non-compliances with WHO norms and standards that were not satisfactorily addressed in the response from the company to an inspection. For example in the GMP context:

Critical Deficiency – an observation that has produced, or may result in a significant risk of producing a product which is harmful to the user.

Major Deficiency – a non-critical deficiency which either:

- has produced or may produce a product which does not comply with its prequalification application (including variations); and/or
- indicates a major deviation from the GMP guide; and/or
- indicates a failure to carry out satisfactory procedures for release of batches; and/or
- indicates a failure of the person responsible for QA/QC to fulfill his/her duties; and/or
- consists of several other deficiencies, none of which on its own may be major, but which may together represent a major deficiency and should be explained and reported as such.

What is the purpose of an NOC?

An NOC is issued to remind a manufacturer, research organization or a laboratory of their obligations to quality assurance and to inform suppliers and procurement agencies of potential risks associated with a given product, manufacturer, organization or laboratory. It is not necessarily cause for public concern.

If WHO identifies a public health risk, appropriate additional steps will be taken to advise the public. These steps may include:

- suspension of products on the "List of prequalified products"; (See Notice of Suspension)
- a compulsory variation to temporarily or permanently suspend the use of a manufacturing site;
- recall of batches of products on the "List of prequalified products" that had been supplied by a manufacturer;
- rejection of applications submitted for assessment to the Prequalification Programme.

Is there a right of appeal?

Yes. An NOC contains the factual observations made during an inspection and these are discussed during the inspection and are listed in the inspection report. Normally the facts of the observations are not in dispute. However, a site may disagree with the risk posed by the observation, which is the basis of issuance of the NOC. Where the company disagrees with any aspect of the inspection report and subsequent NOC, the site should email the details to prequal@who.int "Attention: Coordinator, PQT" in the subject line. The matter will then be investigated and a response will be provided within 15 working days. Should the site not be satisfied with the response, the site is advised to email the Head, Regulation of Health products and Technologies (RHT) at RHTinfo@who.int including "Attention: Head, RHT " in the subject line. All feedback will be treated in-confidence and without prejudice.

When will an NOC be published?

If there are immediate public health concerns or if the inspection observations relate to misrepresentation of data, falsification or manipulation of data with the intent to deceive, the NOC will be immediately published on the Prequalification of Medicines Programme web site. **Note:** The WHO Prequalification of Medicines Programme has a zero tolerance policy in relation to such activities. it is usually an indicator of a serious quality system failure that needs to be addressed and it is regarded as a top management responsibility to ensure that it does not occur.

In other cases the NOC will be published after the corrective actions described in the response to the observations noted in the NOC have been reviewed and the review determines that the corrective actions are unsatisfactory (which may include not providing suitable objective evidence of corrective actions, if applicable). It may also be published if a response to the observations noted in the NOC is not received within 30 days from the date of the NOC, as requested.

How long is an NOC in effect?

An NOC will remain active on the WHO Prequalification of Medicines Programme web site until WHO is satisfied that the corrective actions taken are appropriate and have been effectively implemented.

How is an NOC lifted?

During the period that an NOC is in place the PQ Team Inspection Services will perform additional and more frequent inspections if the site is still supplying prequalified product. If the site has been suspended then the next inspection will be performed when the company advises that it considers that it has adequately dealt with the matters that led to the NOC. Following such follow up inspections and if satisfied that sufficient improvements have been made by the site, PQT **Inspection Services will recommend the lifting of the NOC and** that the site inspected may be named/continue to be named in the relevant dossiers under prequalification or already prequalified. If the NOC has been published on the website then the NOC is then removed from the website and placed in the archive.

In such cases a notice to this effect is placed on the WHO PQT website.

General advice to stakeholders

In all cases where a number of critical and/or a significant number of major observations have been made**, and particularly where an NOC was issued and subsequently lifted**, we remind sites that the improvements made and that their level of compliance with the relevant WHO issued guidelines must be sustained and continue to be improved.

In our risk based planning of inspections the next full WHO PQT inspection of such operations will therefore be performed at an earlier date than normal, and subsequent inspections performed more frequently until WHO PQT Inspection Services have evidence that the improvement implemented is permanent.

Supply chain audit and assurance systems are a key part of GMP and GCP. Organisations are expected to monitor their suppliers by a variety of means and take compliance into account as part of their supplier assurance programmes. WHO PQT therefore draws the attention of customers and other stakeholders that WHO PQT will expect them to take appropriate action when an NOC is issued and **where an NOC is subsequently lifted** continue to exhibit an enhanced level of due diligence and supervision of operations with a history of compliance issues, as part of their supply chain audit and assurance systems. WHO PQT will also verify that stakeholders seeking and or maintaining prequalification of their products have taken this advice seriously. Organisations supplying products and/or services from a site for whom an NOC has been lifted should therefore reasonably expect an enhanced level of supervision by their customers, and should plan to support this in the foreseeable future.

Notices of Concern

- Semler Research Center Pvt Ltd (12 April 2016), JP Nagar site, Bangalore - INDIA
- Svizera Labs Private Limited (02 September 2015), Navi Mumbai - INDIA
- Quest Life Sciences Pvt Ltd (30 June 2015), Chennai - INDIA
- Themis Medicare Limited (08 June 2011), Gujarat - INDIA

Notices of Concern - Vaccines

- Cadila Healthcare Limited (29 January 2016), Ahmedabad - INDIA

Collaborative procedure with NMRAs in inspection activities

- Guidance on collaborative procedure
  - Annex A - Invitation for expression of interest to participate in the procedure
  - Annex B - Expression of Interest Form
  - Annex C - Shared Inspection Schedule Form
  - Annex D - Nomination of Observer of Co-inspector
  - Annex E - Inspector Biodata Form
  - Annex F - Confidentiality Agreement
  - Annex G - Appointment of Observer or Co-inspector
  - Annex H - Appointment of Observer or Co-inspector - Template letter to Supervisor
- Collaborative procedure Questions & Answers

Questions and Answers (Q&A)

- HVAC systems: Questions and Answers
- Questions & Answers