WHO Prequalification of Medicines Programme

Inspection of API manufacturing sites

The WHO Prequalification of Medicines Programme (PQP) aims to make quality priority medicines available for the benefit of those in need. This is achieved through evaluation of product dossiers, inspection of manufacturing sites and clinical research organizations (CROs), and by building national capacity for sustainable manufacturing and monitoring of quality medicines.

When the product dossier and all relevant manufacturing and clinical sites have been found acceptable, the product is prequalified and listed on the Prequalification Programme web site together with the applicant’s name and corresponding manufacturing site of the finished product. (http://apps.who.int/prequal). PQP embraces the concept that “good quality must be built into the product during its design and manufacturing process; it cannot be tested into the product afterwards” (1).

One of the most important components of a pharmaceutical product is the active pharmaceutical ingredient (API). Ensuring the quality of the API greatly contributes to achieving the objective of building the quality, safety and efficacy into the product. One of the strategies employed by PQP to achieve this is through inspection of API manufacturing sites to assess compliance with good manufacturing practices (GMP) and to verify data submitted in product dossiers.

PQP inspections

API manufacturing site inspections were initiated in 2003 as an element of finished product prequalification. In 2010, a procedure was initiated to prequalify APIs separately since many problems that PQP faces are related to quality. As part of the procedure, a separate application for APIs is available and they are assessed and inspected before being included in the WHO List of Prequalified Active Pharmaceutical Ingredients (http://apps.who.int/prequal). The list provides United Nations agencies, medicines regulatory authorities (MRAs) and others with information on APIs that have been found to meet WHO-recommended quality standards. Identification of sources of good-quality APIs will facilitate the manufacture of good-quality finished pharmaceutical products (FPP) that are needed for procurement by UN agencies and disease treatment programmes. A description of the procedure can be found at http://apps.who.int/prequal/info_applicants/API_introduction.htm. APIs eligible for prequalification are available at: http://apps.who.int/prequal/info_applicants/EOI-API_v1.pdf

The availability of a list of prequalified quality APIs is particularly valuable to manufacturers of finished dosage forms. This can also expedite prequalification of finished products when applicants have used quality prequalified APIs in their formulations. With information on sources of prequalified APIs, production of quality finished dosage forms of priority essential medicines is facilitated, increasing access to good quality medicines. API prequalification also assists MRAs by enabling them to verify the standard of APIs used to manufacture nationally registered medicines.

An inspection team normally consists of a WHO inspector based in Geneva and a
co-inspector appointed by WHO from a Pharmaceutical Inspection Cooperation Scheme (PIC/S) member inspectorate. An inspector(s) from the national medicines regulatory authority of the country, in which the manufacturing site is located is invited to participate as an observer.

Risk management principles are used to select the site to be inspected, the duration of the inspection and the frequency of inspection. In terms of priorities, inspection of sites for finished pharmaceutical products comes first followed by sites for APIs, CROs and quality control laboratories (QCL) in that order.

Table 1 sets out examples of relative risks associated with products.

More specifically, additional risk factors for APIs are considered. These parameters include:
- Polymorphism; solubility in water; complexity of the route of synthesis; solvents used; impurities; sterile versus non-sterile API; fermentation;
- Toxicity; activity/potency; particle size; other properties identified to be considered; site compliance information, e.g., from previous acceptable inspections, and type and number of FPPs in which the API is used.

The following order is provided for guidance in determining priorities:
- Sterile APIs.
- Re-inspection when it is more than 12 months past the re-inspection due date.
- A new API manufacturer when the product PQ process may be held up by lack of GMP evidence for the API manufacturer.
- The sole supplier of an API.
- The API is produced by fermentation.
- The API is used in paediatric PQ medicines.
- The API is used in a number of PQ products.

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<thead>
<tr>
<th>RELATIVE RISK CATEGORY</th>
<th>PRODUCT TYPE / ACTIVITY</th>
<th>Critical</th>
<th>High</th>
<th>Medium</th>
<th>Low</th>
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<td>Finished Products:</td>
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<td>Sterile finished products</td>
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<td>Non-sterile finished products</td>
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<td>APIs:</td>
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<td>Non-sterile APIs where there is a special risk (e.g. isomerism, polymorphism, special risk of harmful impurities, etc)</td>
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<td>Other non-sterile APIs</td>
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<td>QC Laboratories</td>
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All manufacturers of APIs used in pre-qualified medicinal products should comply with GMP. As a default, all manufacturers of APIs used in prequalified medicinal products should be inspected by the PQP. An inspection by the PQP may be omitted when other acceptable evidence of GMP compliance is provided by the API manufacturer. An inspection by another acceptable organization, such as the EDQM, a PIC/S member country, or the US FDA, may be considered in lieu of an on-site WHO PQP inspection when:

- The inspection was conducted within the last two years with a positive compliance outcome.
- The scope of the inspection covered the specific API in question.
- The API manufacturer submits a copy of the last inspection report for review by the PQP. The review must determine that the inspection was comprehensive and that the inspection report supports the final outcome.
- Irrespective of the above, the PQP reserves the right to inspect any API manufacturer if considered necessary on a risk basis.

Whether inspected by the PQP or when GMP compliance is based on an inspection by another acceptable organization, on-going GMP compliance must be confirmed at least every four years.

**Norms and standards used**

WHO norms and standards are used in the inspection of API sites. The WHO Expert Committee on Specifications for Pharmaceutical Preparations has revised the WHO GMP for APIs and has recommended a new text that follows closely the principles of ICH Q7 *Good manufacturing practice guide for active pharmaceutical ingredients* published by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). As a result the *WHO good manufacturing practices for active pharmaceutical ingredients* has been published in 2010 (2).

**Statistics**

Out of 126 API sites participating in PQ activities, 49 have been accepted based on approval by PIC/S inspectorates and/or ICH countries while 31 were inspected. Six of the inspected sites were found to
be operating at an unacceptable level of compliance with WHO GMP.

Most of the API sites were located in India and China and this is where most of the inspections have taken place. The sites inspected are those producing many APIs (average 4 APIs per site) mainly for HIV/AIDS, TB and malaria in that order.

According to the WHO PQ quality assurance system and procedure for prequalification, API sites should be re-inspected on a regular basis. Usually the interval between inspections is two to three years.

As noted in Figure 1, key observations of API inspections deficiencies noted during inspections of API sites have been mainly in materials management, documentation, cleaning and cross-contamination.

References
