



# Best medicine

Good-quality active pharmaceutical ingredients are vital to the production of good quality medicines. **Dr Antony Fake** and **Jacqueline Sawyer** explain how the World Health Organization's Prequalification of Medicines Programme facilitates access to quality medicines through assessment of products and inspection of manufacturing sites.

**G**ood-quality active pharmaceutical ingredients (API) are the building blocks of good-quality medicines. In their absence, commercialisation of good quality medicines is slowed and patient access to safe and efficient treatment is impeded.

The globalisation of markets compounds quality-of-medicines issues; for example, API manufacturers are increasingly based in China, whereas most manufacturers that have had finished pharmaceutical products (FPP) prequalified by the World Health Organization (WHO) are based and manufacture their products in India.

**“ API manufacturers who have not undergone SRA assessment can apply for API prequalification without having to submit an associated application for FPP evaluation. ”**

Information asymmetry, communication problems due to lack of a common language, and trade across different jurisdictions exacerbate difficulties in sourcing APIs of a high standard. These problems are acute for therapeutic areas such as tuberculosis (TB); manufacturers of anti-TB medicines complain increasingly that they cannot obtain good-quality APIs.

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Yet FPP manufacturers are responsible for ensuring the quality of their products, including that of the constituent APIs. Thus, having located an API source, an FPP manufacturer must also verify its quality, which includes verifying that the API is manufactured in compliance with good manufacturing practice (GMP).

This necessitates obtaining certificates of on-site inspections and conducting paper-based audits of technical documents. For manufacturers in developing countries, this task can be burdensome, if not impossible, particularly if an API has been purchased through a broker.

#### **Eliminating poor-quality APIs**

Experience has repeatedly shown that manufactured APIs may fail to comply with internationally accepted GMP. This is not surprising given that adoption of ICH GMP standards among API manufacturers is not yet equally widespread across all geographic regions.

In 2006, the International Conference of Drug Regulatory Authorities highlighted the need for high-level action aimed at improving API quality. The WHO responded by developing and

publishing a procedure for WHO prequalification of APIs. As the procedure notes: “A proper system of qualification of suppliers can promote the constant sourcing of active ingredients of appropriate quality and thereby safeguard public health interests.”

Taking this procedure as its starting point, the WHO Prequalification of Medicines Programme (see ‘The WHO/PQP celebrates a decade’, right) launched a project in 2010 to prequalify APIs by issuing its first invitation to API manufacturers to submit an expression of interest for evaluation. A second, more-extended expression of interest was issued by the WHO/PQP in March 2011. The WHO’s evaluation procedure is open to a variety of APIs used in medicines for treating HIV, TB and malaria, and for reproductive health (see Figure 1, opposite). APIs that are evaluated and found to be manufactured in compliance with WHO GMP are publicly listed.

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#### WHO prequalification of APIs: a unique service

The WHO/PQP is not replicating efforts made by national medicines regulatory authorities (NMRAs). Other regulatory schemes for API assessment exist, but these do not necessarily include those APIs that are urgently needed for the manufacture of FPPs in the aforementioned therapeutic categories. Moreover, many regulatory schemes assess an API only if it is submitted in relation to an application for medicine registration. Even if an NMRA does assess an API with respect to such an application, this does not necessarily include verification of compliance with GMP, or making public the details of the API if it receives approval. By assessing the quality of APIs, verifying the GMP standard of their manufacturers and publishing details of successful applications, the WHO/PQP is providing a unique service.

This does not mean that national regulators and the WHO/PQP are never called on to evaluate the same API. But this is not a common occurrence and the scope of the assessment is often different.

In any event, the WHO procedure takes this possibility into account by allowing for the findings of the assessment and inspection reports from stringent regulatory authorities (SRAs) to be incorporated into the WHO/PQP’s decision-making process.

#### How does the process work?

The principal components of the API prequalification evaluation process are assessment of the quality components of the application, and evaluation of the GMP standards under which the API is manufactured. Full details can be found on the WHO/PQP website at [www.who.int/prequal](http://www.who.int/prequal).

The quality assessment is based on an evaluation of the manufacturer’s Drug Master File, which covers the API information found in the ICH Module 3.2.S. (The Drug Master File is referred to

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### The WHO/PQP celebrates a decade

The WHO/PQP celebrated its tenth year in 2011. Located at the WHO headquarters in Geneva, Switzerland, the programme was launched in 2001 in response to uncertainty expressed by UN agencies and other organisations regarding the quality of medicines for treating HIV/AIDS, which were being procured in increasing numbers. Since then its scope has expanded to cover not only priority medicines for treating HIV/AIDS, but also those for malaria and tuberculosis, as well as influenza-specific antiviral medicines, zinc for managing acute diarrhoea and products for reproductive health.

The WHO/PQP’s guiding principle is ‘Good quality medicines for everyone’. It works towards attainment of this global public health goal by evaluating finished pharmaceutical products (FPPs) and quality control laboratories (QCLs), inspecting pharmaceutical manufacturing sites and QCLs, and building national capacity for the manufacturing, regulation and quality control of medicines.

FPPs and QCLs that meet the WHO requirements in terms of assessment of the submitted dossier and inspection of the sites involved are listed on the WHO List of Prequalified Medicinal Products and the WHO List of Prequalified Quality Control Laboratories, respectively. UN agencies and other organisations involved in the bulk purchasing of medicines use the list of prequalified medicines to guide procurement decisions.

The list of prequalified QCLs is of value to any organisation or treatment programme that wishes to test medicine quality using standards and expertise that are known to meet international criteria. In late 2010, the programme initiated the prequalification of active pharmaceutical ingredients to support manufacturers in manufacturing good-quality FPPs.

as an APIMF within WHO/PQP.) The recently published *Guideline on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product (FPP): Quality Part* describes the information that the WHO/PQP requires regarding APIs. If an API manufacturer has already submitted an APIMF in connection with evaluation of an FPP and the APIMF was found to be satisfactory, an abridged APIMF assessment is undertaken.

#### WHO procedure for prequalifying APIs

With respect to the evaluation of GMP, applicants can choose between submitting evidence of the GMP status of their manufacture of the API undergoing assessment or undergoing a WHO inspection. The evidence submitted must include:

- GMP certificates
- inspection reports
- corrective and preventive action reports
- site master files
- annual product review reports.

**Figure 1. APIs included in the second invitation to submit an expression of interest for API evaluation to the WHO/PQP programme – March 2011.**

Therapeutic category	Invited API
HIV	Abacavir, atazanavir, darunavir, didanosine, efavirenz, emtricitabine, etravirine, lamivudine, lopinavir, nevirapine, raltegravir, ritonavir, stavudine, tenofovir, zidovudine
Anti-malarial	Amodiaquine, artemether, artesunate, dihydroartemisinin, lumefantrine, mefloquine, piperazine, pyrimethamine, sulfadoxine
Anti-tuberculosis	Amikacin, capreomycin, cycloserine, ethambutol, ethionamide, isoniazid, kanamycin, levofloxacin, moxifloxacin, ofloxacin, para-aminosalicylic acid, prothionamide, pyrazinamide, rifampicin, streptomycin, terizidone
Reproductive health	Desogestrel, estradiol, ethinylestradiol, etonogestrel, levonorgestrel, medroxyprogesterone, mifepristone, misoprostol, norethisterone, norgestrel, oxytocin

Any evidence provided regarding GMP status must meet several important criteria with respect to the issuing authority, and the specificity and date of the inspection. If the evidence provided is considered to be insufficient in terms of establishing that GMP at the manufacturing site is acceptable, a WHO-led GMP inspection will be required, which will also be necessary if evidence of GMP is unavailable. In addition, an API manufacturer can request a WHO inspection of its manufacturing site.

Subject to acceptance of the APIMF, and verification that the API is manufactured in compliance with WHO GMP requirements, the API will be prequalified by the WHO. Information about the prequalified API will be added to the WHO List of Prequalified APIs, including:

- WHO application number
- international nonproprietary name
- name of applicant
- site(s) of API manufacture
- APIMF version number
- API specification version number
- primary and secondary packaging components
- assigned re-test period
- recommended storage conditions.

Further useful information will be obtainable from the WHO Public Inspection Report (WHOPIR). This will have been posted on the WHO/PQP website when the API manufacturing site(s) passed WHO inspection. WHOPIRs summarise inspection findings and are frequently consulted by procurement agencies that seek information about the operations of a manufacturer in general, as well as on a particular API.

The API manufacturer will be issued with a Confirmation of API-PQ document. This will specify the re-test period, storage conditions, API specifications, assay test methodology and related substance test methodology that were accepted as part of prequalification.

The API manufacturer may distribute this document to third parties and it can be submitted by FPP manufacturers

to NMRAs as supporting evidence of the quality of their API source.

Taken together, the information made publicly available and the information provided in the Confirmation of API-PQ document, provide recipients with the most important details of the API and the dossier on which the decision to prequalify was made.

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#### Who benefits from WHO prequalification of APIs?

WHO prequalification of APIs benefits API manufacturers, FPP manufacturers, the United Nations and other international procurers, and NMRAs. For FPP manufacturers, clear identification of APIs that have been evaluated and confirmed as being manufactured in compliance with WHO GMP standards – and for which quality regulatory documentation is maintained – is invaluable because it saves them time and money in locating and registering sources of API.

For API manufacturers, WHO prequalification will confirm that they are API manufacturers that prepare quality APIs, manufacture in compliance with GMP and maintain excellent regulatory documentation. Prequalification of APIs is of particular relevance to those API manufacturers that are currently supplying only their domestic markets, and who have limited or no experience of registering their products with SRAs.

For these manufacturers, working with the WHO/PQP is an opportunity to enhance their quality systems and regulatory documentation, and to assess their level of compliance with GMP. Evidently, a company must generally assume costs when improving its manufacturing standards. But the WHO/PQP does not levy either application or inspection fees. Moreover, for manufacturers producing APIs that are urgently needed, the WHO/PQP can organise assistance to resolve specific technical problems.

API manufacturers who have not previously undergone SRA assessment will be interested to know that they can apply for API prequalification without having to submit an associated application for FPP evaluation. This is generally not the case

### The first WHO-prequalified APIs

WHO/PQP has received a steady number of applications for API assessment since October 2010. Three APIs for antimalarial medicines – one lumefantrine API and two artemether APIs – have already been prequalified. Details can be found at on the WHO/PQP web site. Prequalification of further APIs is anticipated in the very near future.

with NMRAs. This could be an important point for API manufacturers that have not yet attracted an FPP manufacturer partner. Such manufacturers will not have been able to obtain approval of their API from an NMRA. Nevertheless, they will be keen for FPP manufacturers to be aware that their APIs meets SRA requirements. The WHO/PQP offers them a means of raising this awareness.

“ For manufacturers that are already manufacturing to international standards, WHO prequalifications will serve as further confirmation of quality assurance. ”

For manufacturers that are already manufacturing to international standards, WHO prequalification will serve as further confirmation of quality assurance. For medicines procurers, use of a prequalified API is a strong indicator that the overall quality of an FPP is acceptable, even if the FPP in question has not been prequalified by the WHO.

For NMRAs within developing countries, the benefits of WHO prequalification of APIs will be quickly apparent when they review an application for marketing authorisation for an FPP that uses a WHO-prequalified API. Full evaluation of an API

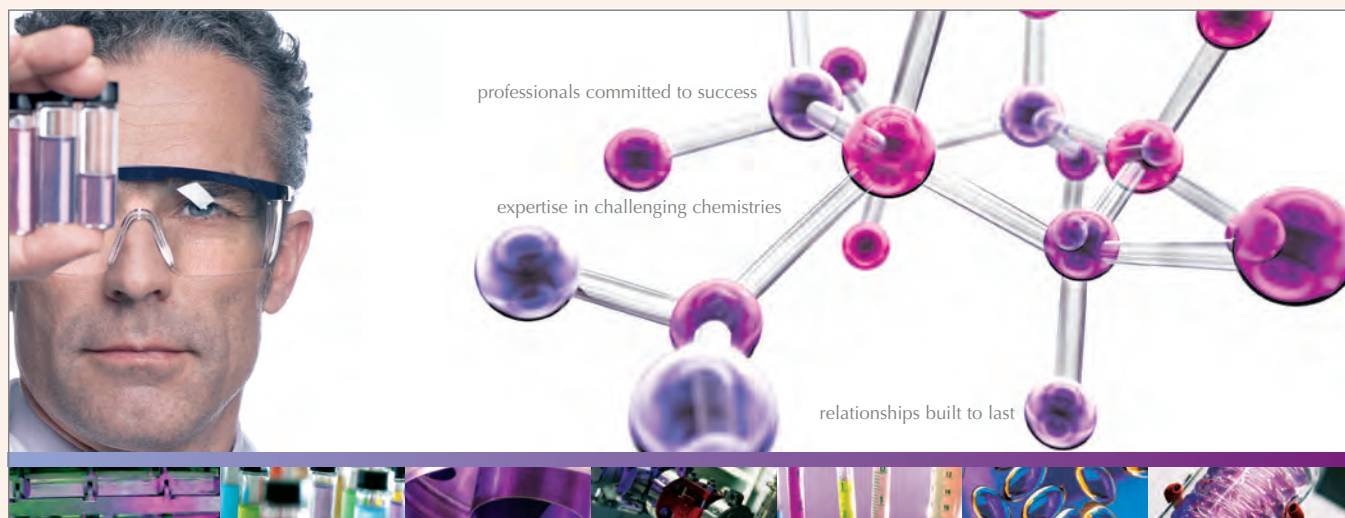
supplier is a cost-intensive and resource-demanding activity, which only a few NMRAs can afford to undertake. As a result, in-depth API assessment rarely forms part of the process of granting marketing authorisations to FPPs. This means that the quality and safety of marketed pharmaceutical products can be undermined: if an API is not assessed in depth, it will be registered with fewer details, meaning that control over the quality of the manufacture of that API will be less.

In some cases, the API manufacturer could make changes to the manufacturing process or sites without notifying the NMRA or without drawing the attention of the NMRA. This lack of information about an API makes it difficult for other NMRAs to verify whether an API supplier is legitimate.

The published details of WHO-prequalified APIs, together with the Confirmation of API-PQ document, will enable NMRAs to quickly identify whether the API details presented to them when an FPP is submitted to them for registration are identical to those relating to a WHO-prequalified API.

The WHO's API prequalification procedure also allows for sharing of assessment reports with NMRAs, subject to the protection of any commercially sensitive, confidential or proprietary information.

The primary and most important beneficiaries of the WHO-prequalification of APIs will be patients. Easier identification of sources of good-quality APIs by FPP manufacturers should facilitate enterprise between API and FPP manufacturers, and lead to increased volume and choice of medicinal products. ■



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