

Global Fund Quality Assurance of Pharmaceutical Products: **Frequently Asked Questions (FAQs)**

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General principles

1. What is the difference between Quality Assurance (QA) and Quality Control (QC)?

Quality Assurance (QA) is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use.

Quality control (QC) includes all QA measures taken to verify that raw materials, intermediates, packaging materials and finished pharmaceutical products conform to established specifications for identity, strength, purity and other characteristics. It includes the setting of specifications, sampling, testing and analytical clearance.

2. Where can we find the Quality Assurance Policy of the Global Fund?

The full text of the Global Fund Quality Assurance Policy (for Pharmaceutical Products) can be found here: [Global Fund QA Policy](#), and a presentation explaining the policy is available [here](#).

3. What are the important basic requirements of the QA Policy?

The QA Policy requires that medicines purchased with Global Fund resources must meet the following requirements:

- Clinical standards:

Medicines must be listed in current standard treatment guidelines (STG) or essential medicines list (EML) of the recipient country and the World Health Organization (WHO). A justification is needed if medicines are listed in only one of these two sets of guidelines. (QA policy sections 3-6)

- Quality standards:
 - (i) All finished pharmaceutical products must be authorized for use in the recipient country (QA policy section 19) and in addition
 - (ii) Antiretrovirals, anti-TB products and antimalarials (“ATM medicines”) must be WHO-prequalified or authorized for use in a country with a stringent regulatory authority (SRA) OR ATM medicines which have passed a review by the Expert Review Panel (ERP) (QA policy section 7) can be purchased under certain circumstances (see Questions 11).
 - Selection criteria: WHO-prequalified product or SRA-authorized products should be procured in priority when at least 2 products of the same formulations meeting one of these criteria are available on the market. (QA policy sections 8 -9)
 - Quality monitoring all along the supply chain (QA policy sections: 24-30).

4. How is compliance with the QA policy monitored?

PRs must report all purchases of ATM medicines in the Global Fund Price and Quality Reporting Mechanism (PQR) as a condition for continued disbursement of funds. Non-compliances are monitored, and a compliance report is issued at regular intervals to Fund Portfolio Managers. Compliance with selection criteria is also reviewed during periodic review.

Compliance with quality monitoring requirements is monitored based on the PR’s periodic reporting.

5. What are A, B and ERP-reviewed products?

WHO-prequalified products have come to be known as “A”-products, and those authorized for use in a country with a [stringent regulatory authority](#) (a member, associate or observer of ICH) as “B” products, because of the paragraph numbering in the first QA Policy.

ERP-reviewed products are alternative products which do not comply with these standards, but which can be procured for 12 months under certain circumstances (for details see Question 11) if they have passed a technical review by the ERP (for details see Questions 19 to **Error! Reference source not found.**).

6. How do we know which products meet the quality standards of the QA Policy?

The Global Fund Secretariat maintains lists of [ARVs](#), [anti-TB](#) products and [antimalarials](#) which are WHO-prequalified, SRA-authorized or ERP-reviewed; a combined list in Excel is available [here](#). For SRA-authorized products, the Secretariat relies on information received from manufacturers. Principal Recipients should still verify the status of the products which they are intending to procure.

7. Can the PR purchase products not listed in the Global Fund list?

The list is not exhaustive and the PR can procure any product outside the list provided that the product complies with the Global Fund QA policy. In such case the PR should obtain the following documents as evidence of the product from the manufacturer to ensure that the product complies with Global Fund QA policy:

1. Copy of approval or registration certificate or marketing authorization from a stringent regulatory authority (SRA);

2. Copy of GMP (Good Manufacturing Practice) certificate issued by an [SRA](#), a [PIC/S](#) member or the WHO Prequalification Programme certifying the compliance of the manufacturing site with WHO GMP requirements.

8. What is WHO prequalification of products?

[WHO prequalification of medicines](#) is a service provided by WHO to assess the quality, safety and efficacy of medicinal products. Originally, in 2001, the focus was on medicines for treating HIV/AIDS, tuberculosis and malaria. In 2006, this was extended to cover medicines and products for reproductive health. In 2008, prequalification of zinc – for the management of acute diarrhoea in children – was added. Since 2001, over 370 medicines have been prequalified.

9. If there is only one WHO-prequalified or SRA-authorized product, do we have to select it?

No, it is not mandatory. If only one or no WHO-prequalified or SRA-authorized product is available on the market, PRs can consider one or more ERP-reviewed products and select the product with better advantage of lead time and or price.

10. If a product is prequalified by WHO, can we procure the same product with a packaging which is not listed in WHO List of Prequalified Medicinal Products?

No. WHO prequalification is valid for a specific product, with a specific strength, from a specific production line, in a specific packaging format and from a specific manufacturing site approved after GMP inspection. Therefore, only products listed on the website of [the WHO prequalification of medicines programme](#) are recognized as WHO-prequalified, with defined packaging. However in the case of blister/foil packaging, if a blister/foil pack with a specified number of units is prequalified, then the number of such blisters/foils per secondary pack does not change the PQ status.

11. Can ERP-reviewed products be procured in the same way as WHO-prequalified or SRA-authorized products?

No. The following processes should be respected.

(i) *Prioritization in selection process of a product:* If two or more WHO-prequalified (“A”) or SRA-authorized (“B”) products can be supplied in sufficient quantities within 90 days from order (or longer if this is acceptable for treatment programs), PRs must procure an A or B product. When only one or no WHO-prequalified or SRA-authorized product is available on the market, PRs can consider one or more ERP-reviewed products.

(ii) *Notification Process* for ERP pharmaceutical products: PRs must do the following before they can procure an ERP-reviewed product:

- Send a [notification](#) to the Secretariat justifying their choice (stating that only one or no WHO-prequalified or SRA-authorized product is available for that formulation);
- Receive a letter of no objection from the Secretariat (valid for one year); and
- Inform the Secretariat in advance of each purchase order using the [Notification of Additional Order](#) form, so that the Secretariat can organize pre-shipment quality control (QC) testing.

. For all pre-shipment QC testing arranged and paid by the Global Fund Secretariat, shipment of the product is subject to satisfactory QC testing results. (See also [FAQs on QC testing](#))

12. How long does the notification and testing process take?

The response to the notification is generally sent within 3 days after the receipt by the Global Fund Secretariat of the notification request.

The duration of the Quality Control testing depends on the nature of the product requested. On average, it takes about two months from receipt of a notification until the products are released for shipment.

13. When a PR decides to procure an ERP product, when should a notification be issued?

If as result of the bidding documents review (tender adjudication process) it appears that only one or no WHO-prequalified or SRA-authorized product is available, PR can consider procuring an ERP-reviewed product. A notification request, completed with all the relevant justification for the choice of the product, should be sent to the FPM before signing a contract with the supplier/manufacturer of the selected product.

14. If no finished product has been identified that is compliant with Global Fund QA standards for a needed medicine, what steps does the Global Fund Secretariat take?

The Global Fund Secretariat proactively invites manufacturers to submit dossiers of eligible products for ERP review. The Global Fund is working with WHO to address the problem of non-availability of any approved products, bearing in mind the need to maintain access to treatment for patients.

15. What happens if no finished product of a needed medicine meets the quality standards of the QA Policy?

When a product does not meet the Global Fund QA standards, the product cannot be procured with Global Fund resources. In such case the Global Fund encourages the PR to either identify an alternative medicine that complies with the QA Policy, or to fund the product from an alternative funding source.

16. The products which comply with the QA Policy are not authorized for use in our country. What should we do?

Pharmaceutical products purchased with Global Fund resources must at all times comply with national regulations and, where applicable must be authorized by the national drug regulatory authority in the country in which they are used, following its standard practices for registration (or other forms of authorization, such as authorizations for special use).

This means that the product should at least be authorized for use in the destination country. If a product is not registered, but the country needs to purchase it, then the manufacturer can be encouraged to seek accelerated registration of the product (for example through the mechanism described on the webpage of the [WHO Prequalification Programme](#) under “Collaborative registration”) or a registration waiver in recognition of the stringent assessment of the product by the WHO Prequalification Programme or by a [stringent regulatory authority](#) (QA Policy Section 19-21).

17. Some of the manufacturers say that we have to wait for six months before the products can be delivered. What can we do?

If a product is not available in sufficient quantities within the time required in the treatment programme (not more than 90 days from the time of order, unless longer lead times are acceptable to the PR), then PRs may consider other manufacturers. If as a result of non-availability fewer than two choices of A or B products remain for a certain formulation, then PRs can consider an ERP-reviewed product.

18. What if the manufacturer states that they can supply within 90 days, but then they do not?

Performance of suppliers should be monitored. Compliance with agreements should be taken into consideration in future procurement and short-listing of suppliers. This information should also be reported to the Global Fund Secretariat (FPM and Pharmaceutical Supply Management specialist) for the record.

Expert Review Panel

19. What is ERP?

The Expert Review Panel is a group of regulatory experts hosted by the WHO Department of Essential Medicines and Pharmaceutical Policies. Its role is to conduct quality risk assessments for antiretroviral, anti-TB and antimalarial products which are not yet WHO-prequalified or authorized by a Stringent Regulatory Authority (SRA).

20. What is the ERP members' professional expertise?

Members of the ERP have a wide range of expertise from working experience with regulatory and technical organizations around the world. According to the ERP's [Terms of Reference](#), each ERP Member shall have extensive professional experience in at least one of the following technical areas: (i) quality assurance of pharmaceuticals; (ii) quality control of pharmaceuticals; (iii) pharmaceutical regulatory affairs; (iv) disease control; (v) pharmaceutical manufacturing; and/or (vi) clinical and/or biopharmaceutics/ pharmacokinetics.

21. What is the difference between ERP review and WHO prequalification/SRA authorization?

ERP review is a quality risk assessment based on an abridged product dossier which follows a [questionnaire](#) format. ERP review is not a substitute for WHO prequalification or SRA authorization. Products which pass the ERP review are eligible for procurement (under certain conditions – see also Questions 6 and 7) for 12 months only. During this time the product is expected to progress to WHO prequalification or SRA authorization.

22. What types of products does the ERP review?

The Global Fund regularly publishes invitations for Expression of Interest (EOI) on its [Information for suppliers](#) webpage. The EOIs include antiretrovirals, first-line anti-TB medicines and antimalarials recommended in WHO and national treatment guidelines for which less than 3 WHO prequalified or SRA-authorized finished products have been identified according to information provided by manufacturers.

To be eligible for ERP review, products have to be under assessment by the WHO Prequalification Programme or by a stringent regulatory authority (SRA), and must be manufactured in compliance with Good Manufacturing Practice (GMP) as certified by one of the above organizations or by a PIC/S member. Certain established FPPs that are not invited for WHO Prequalification can be reviewed even if they are not under WHO or SRA assessment, as long as the second requirement (GMP compliance) is met. The criteria applicable to each formulation are mentioned in the respective EoI.

23. How can manufacturers submit their products for ERP review?

In response to Invitations for Expression of Interest posted on the “Information to suppliers” webpage on the Global Fund website, or in response to a specific request by the Global Fund to answer a country need, the manufacturers submit an appropriately filled [questionnaire](#) dossier and relevant technical documentation as listed on the last page of the questionnaire.

24. How does the ERP assess product dossiers?

The ERP performs a quality risk assessment based on major product attributes including GMP status of the manufacturing site, FPP manufacturing process and FPP specification, stability data, evidence of therapeutic equivalence, API source and API quality, as supported by the technical documentation submitted by manufacturers.

25. How long does it take to get a product reviewed by the ERP?

ERP reviews are organized twice a year, which gives manufacturers up to six months to prepare their submissions. The Global Fund Secretariat communicates the outcome of the ERP review within approximately ten weeks after the deadline of submission stated in the invitation for Expression of Interest.

26. How does the ERP state its conclusions?

The ERP gives advice to the Global Fund Secretariat by classifying products into four categories. Only products in categories 1 and 2 may be considered for procurement for 12 months and are included in the Global Fund’s [Lists of ARVs, anti-TB and antimalarial products](#) together with the time-limit of the validity. Details on the categorization are described [here](#). In exceptional cases, the ERP may request additional data if these might improve the outcome.

27. What happens if a product fails the ERP review?

Manufacturers will receive feedback on the reasons for categorization of a product into Categories 3 or 4. Improved dossiers may be resubmitted to a subsequent ERP review.

28. What happens when a product’s validity period ends?

The Global Fund will consider whether there is still a need for the product. If so, the Global Fund will invite manufacturers to submit a report on progress towards WHO-prequalification or SRA authorization, and to re-submit a product questionnaire dossier for assessment by the ERP. If it passes the review, it will be listed again on the Global Fund list (see Question 26) as “ERP-reviewed” for a maximum of 12 months.

Pre-shipment QC testing

29. What is quality control (QC)?

Quality control refers to all measures taken to verify that raw materials, intermediates, packaging materials and finished pharmaceutical products conform to established specifications for identity, strength, purity and other characteristics. It includes the setting of specifications, sampling, testing and analytical clearance.

30. Why should products be tested before shipment?

QC testing of samples evaluates whether batches of products supplied conform to the agreed requirements and specifications. Pre-shipment QC testing aims to avoid that batches which do not meet these requirements are shipped to countries.

31. Which types of products must be tested before shipment?

Pre-shipment QC testing is mandatory for all ERP products. Contracts for procurement of these products should therefore afford the Global Fund or its representative the right to access the manufacturing site or procurement agency's warehouse to take samples.

32. Will each batch of pharmaceutical products subject to pre-shipment QC be tested?

No. QC testing is mandatory for every purchase order, but not every batch will be tested. The contracted laboratory selects batches randomly in accordance with advice provided by the QA Officer at the Global Fund. For example, a high sampling frequency might be required for the first few batches procured, for products with a high risk of quality deficiencies, or for products with a recent history of non-compliance with specifications.

33. Who is responsible for pre-shipment QC testing?

It is the responsibility of the Global Fund Secretariat to order and pay for pre-shipment QC testing of products for which it has issued a “no objection” letter (in case of ERP-reviewed products) and received a [notification of order](#). The Global Fund has contracted independent QC laboratory services through a competitive process as recommended by the Global Fund Board.

34. Who performs pre-shipment sampling and QC testing?

The Global Fund has contracted two laboratories: SGS Netherland B.V. laboratory for pre-shipment inspection, sampling and quality control testing, and the National Institute of Drug Quality Control in Vietnam (a WHO-prequalified laboratory) for quality control testing.

35. How is pre-shipment QC testing organized?

Based on the notification submitted by PRs ahead of each purchase order, the Global Fund Secretariat makes arrangements for sampling and QC testing by the contracted QC laboratory. Once the Secretariat receives the laboratory report, it takes the final decision on whether to release the consignment.

36. Can the supplier dispatch any products to countries while pre-shipment QC testing is in progress, before receiving the Global Fund's decision?

No. All batches which are selected for testing must be kept by the supplier at the manufacturing site or by the procurement agent at the warehouse until testing is completed and the Global Fund QA officer has agreed in writing that the batches can be shipped to the destination country. The Fund Portfolio Manager in consultation with the QA team can grant exceptional arrangements in emergency situations to ensure timely delivery of products in country.

37. What analytical methods are used, and what parameters are tested?

Only pharmacopoeial methods published in the [International Pharmacopoeia](#) (Ph. Int.), the United States Pharmacopoeia (USP) or the British Pharmacopoeia (BP) are recommended. If no pharmacopoeial monographs exist in one of these three pharmacopoeias, manufacturers' methods will be used.

Usually the parameters tested include:

- a. appearance, identification, assay (quantitative estimation of active ingredients) and impurity control;
- b. dissolution or disintegration; content uniformity or weight variation (for tablets and capsules);
- c. pH and microbial limits (for solutions, if included in the specifications); and
- d. sterility and bacterial endotoxin test (for injectables).

38. How is the confidentiality of information provided by the manufacturers ensured?

The QC laboratory signs a confidentiality agreement as part of its contract with the Global Fund. Information received from the manufacturer will remain confidential.

39. What happens if a product fails pre-shipment QC testing?

Any out-of-specification results are handled in accordance with procedures described in the contract between the Global Fund and the laboratory.

If the results of the tests are confirmed to be outside the limits of the specifications, the batch will not be released for shipment, and the manufacturer will be asked to replace the batch with another one which will be tested for conformity with specifications.

40. Are the results of pre-shipment QC testing publicly available?

Yes, the Global Fund posts [results of pre-shipment QC testing](#) on its website. PRs should therefore include a clause in their tenders and contracts to reserve the right for the Global Fund to publish the outcomes of pre-shipment QC testing.

In-country quality monitoring

41. What does quality monitoring mean?

The Global Fund's QA Policy requires Principal Recipients (PRs) to adhere to best practice as described in interagency guidelines for a [Model Quality Assurance System for Procurement Agencies](#) (MQAS) when procuring, receiving, storing and distributing any pharmaceutical products in grant-funded programs. This requires defined quality assurance systems for procurement, warehousing at central medical stores, quality control testing, distribution, monitoring storage and distribution sites, and safe disposal of pharmaceutical products.

42. Who is responsible for post-shipment quality control (QC) testing of products in the country of use?

Testing of any pharmaceutical product after receipt in the country of use, according to the Global Fund's QA policy is the responsibility of the purchasing entity (PR or sub-recipient). The costs of testing should be included in the grant budget. The PR responsible for the grant must select the testing laboratory and should monitor the laboratory's performance according to best practice.

43. Which products should be tested in the country of use?

All pharmaceutical products (including WHO-prequalified, SRA-authorized or ERP-reviewed products) should be tested, but not all batches should be tested. It is recommended that PRs obtain the advice of the national medicines regulatory authority and/or the contracted QC laboratory to organize random testing, taking into account specific risk factors. These can be product-related factors such as recent date of licensing, known stability problems, complexity of product, high number of patients using the product and reports of quality problems during the past year, or supply chain-related factors, such as poorly controlled storage or distribution conditions

44. At what point should the products be tested?

Products should be sampled and tested at different points in the supply chain, from initial receipt of the FPPs in-country to delivery to end-users/patients. A testing programme should be designed to plan this testing in a way which strikes a balance between the benefits of testing and the expense of time and resources. More information can be found in the [Global Fund's guidance document on QC testing](#).

45. Where should the products be tested?

The laboratory contracted for testing must be either WHO-prequalified (see the list of prequalified laboratories on the website of the [WHO Prequalification Programme](#)), or ISO 17025-accredited for the required scope of testing. The laboratory should have sufficient capacity to conduct full pharmacopoeia testing, and to adopt manufacturer's specifications for products which do not have a monograph. A [list of qualified laboratories](#) is posted on the Global Fund website. If the national QC laboratory or a laboratory recognized by the national medicines regulatory authority is included in this list, it can be selected to do the testing.

46. What if there is no qualified laboratory available in the country?

PRs should identify a WHO-prequalified or ISO 17025-accredited laboratory in another country. The [list of qualified laboratories](#) on the Global Fund website can be used as a guide.

47. What happens if products fail post-shipment QC testing in countries?

Out-of-specification results should be validated according to the contracted laboratory's standard operating procedure. The PR and the supplier should be informed immediately.

If it is confirmed that the product does not meet specifications, the PR must inform the national medicines regulatory authority and the Global Fund. The PR should request the manufacturer to replace the products in accordance with the purchasing contract.

48. Should PRs report the results of in-country QC testing ?

Yes, Section 24 of the QA policy requires PRs to report to the Global Fund the results of quality control testing. This is part of periodic reporting by the PR.

49. How is quality monitoring enforced?

Local Fund Agents (LFAs) will verify that good practices are followed. Disbursements are subject to data verification and report-back by the LFA.

50. Where can we find guidance for in-country quality monitoring?

The [guidance on quality monitoring](#) posted on the Global Fund webpage on QA of pharmaceutical products provides further information and references to relevant technical guidelines.
