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Guidance on

**In-country quality monitoring of  
pharmaceutical products in Global Fund  
supported programs**

Revision, Version 1  
January 2014

**Foreword** ([Go to Contents](#))

Medicines of assured quality are essential for impact in Global Fund-financed health programmes. The risk of substandard medicines is high in most grant-recipient countries. The Global Fund is committed to safeguarding the quality of the pharmaceutical products procured with its finance, as per the Global Fund Quality Assurance Policy for Pharmaceutical Products<sup>1</sup> (referred to as QA Policy in this document).

This guidance document was developed in 2010 to support the implementation of the QA Policy for Pharmaceutical Products. It was revised in 2013 to provide more explicit guidance to principal recipients (PRs) on minimum quality assurance (QA) measures, risk-based quality control (QC) testing and reporting requirements.

The document was written with input from Global Fund PSM Specialists with long-standing working experience in pharmaceutical supply management in grant-recipient countries. It is based on internationally recognized technical guidance, listed as [References](#) at the end of the document.

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<sup>1</sup> [www.theglobalfund.org/documents/psm/PSM\\_QApharm\\_Policy\\_en/](http://www.theglobalfund.org/documents/psm/PSM_QApharm_Policy_en/)

**Purpose of this guide** ([Go to Contents](#))

This guide provides guidance on quality monitoring activities which Principal Recipients (PRs) must undertake ensure that grant-funded pharmaceutical products meet their specifications until they reach the end users. These activities should be included in the concept note and in the procurement and supply management (PSM) arrangements agreed during grant making. If any gaps are identified, PRs should plan complementary activities to minimize the quality risks to pharmaceutical products as proposed in this guide.

**How to read this guide**

The essential points are outlined in brief at the beginning of the guide, followed by questions that point to more information provided in the remainder of the guide.

**Links shown in blue can be clicked to navigate within the PDF file.**

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## Foreword - Purpose of this guide

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## THE MAIN POINTS IN BRIEF

### Essential QA measures

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According to the Global Fund QA Policy PRs must adhere to the principles of the WHO Model Quality Assurance System (MQAS) for procurement agencies (1) in procuring grant-funded medicines. The MQAS provides guidance on QA measures all along the supply chain. The main elements of QA in grant supported programmes are:

- ✓ Sourcing of products in accordance with the Global Fund QA Policy and approved procurement methods;
- ✓ Secured storage systems at all levels;
- ✓ Secured distribution systems; and
- ✓ A batch traceability system throughout the supply chain.

#### More information (see Pages 9 ff.)

1. An MIS and SOPs should be in place throughout the supply chain – what are those?
2. What are the main QA principles in procurement?
3. What are the main QA principles on receipt of products?
4. What are the main QA principles in storage of products?
5. What are the main QA principles in distribution of products?
6. What steps should be followed if a quality issue is detected?

### Quality monitoring requirements

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According to the sections on “MONITORING PRODUCT QUALITY” of the Global Fund QA Policy (see Attachment 1), PRs must organize quality control testing of grant-funded pharmaceutical products samples all along the supply chain and report the results to the Global Fund.

However, quality cannot be “tested into” a pharmaceutical product. For successful quality monitoring PRs should implement proactive QA measures all along the supply chain. QC testing is that part of QA that serves to verify whether products meet the technical specifications that have been set for them.

| Quality assurance:                     |  |
|--|--|
| ✓ Procure good quality products        | → Define specifications meeting international quality standards                  |
| ✓ Accept only good quality batches     | → Do the products meet the agreed specifications on receipt?                     |
| ✓ Ensure safe storage and distribution | → Do the products continue to meet specifications until they reach the end user? |

#### More information (see Page 12):

7. What are the objectives of quality monitoring in grant-funded programmes?

## The role of national systems

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National medicines regulatory authorities (NMRAs) are legally responsible for overseeing the quality of pharmaceutical products in countries.

PRs must:

- ✓ Ensure that products are authorized for use in the destination country at the time of delivery (see Section 19 of the Global Fund QA Policy)
- ✓ Inform the NMRA of any quality issues as per national regulations, for example in case of complaints, recalls and QC testing failures.

If the national QC laboratory is WHO-prequalified or ISO 17025-accredited then it can be contracted to perform QC testing of grant-funded products.

In addition, PRs should support existing national systems for post-market surveillance and pharmacovigilance whenever possible.

### **More information (see Page 13)**

8. [What can be done to facilitate registration or authorization?](#)
9. [How can PRs support existing surveillance and pharmacovigilance systems?](#)

## Quality risk management in the supply chain

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Pharmaceutical supply chain management in today's globalized pharmaceutical environment is challenging. As supply chains evolve over time, quality risks should be monitored on an ongoing basis. PRs should identify gaps in the supply chain and take measures to address these risks as far as these are under their control. Available resources should be prioritized to deal with the most significant risks first.

### **More information (see Pages 14 ff.)**

10. [What are some examples of quality risks, and how should they be monitored?](#)
11. [How is quality risk management different from the periodic assessment of PSM risks by the Global Fund and LFAs?](#)
12. [What measures can be envisaged to manage the risks?](#)

## Managing quality monitoring

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It is recommended that PRs work with a pharmacist with relevant supply chain management experience to develop and maintain a quality monitoring plan for pharmaceutical products used in Global Fund supported programs. This plan is complementary to the PSM arrangements and focuses on addressing product quality risks through quality assurance and quality control activities during grant implementation.

### **More information (see Pages 16 ff.)**

13. [What quality monitoring activities should be planned?](#)
14. [What expertise is needed to manage quality monitoring activities?](#)
15. [Is there a timeline for implementing quality monitoring?](#)
16. [What approximate amount can be budgeted for quality monitoring activities?](#)
17. [Can grant funds be used to test medicines that are not financed by the Global Fund?](#)
18. [What costs can be budgeted for capacity-building?](#)

## QC laboratory

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The QA Policy requires that PRs organize QC testing by a laboratory which is WHO-prequalified or ISO 17025-accredited.

PRs must select one or more QC laboratories meeting these requirements to perform the testing. It should be ensured that adequate laboratory resources will be available for the required type and amount of testing.

### **More information (see Pages 18 ff.)**

19. [What is the role of laboratories that are not WHO-prequalified or ISO 17025-accredited?](#)
20. [How can PRs identify a laboratory that meets the required standards?](#)
21. [When should more than one laboratory be selected?](#)
22. [How should costs be evaluated?](#)

## QC testing plan

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PRs should develop a pre-defined QC testing plan in consultation with the contracted QC laboratory. The QC testing plan should focus on the products and locations with the greatest quality risks. Accordingly it should define the number of batches to test, both on receipt and in the supply chain. All products should be tested at the rate of least once batch every 3 years. It is recommended to phase in the testing activities to build capacity for sampling and testing while addressing logistic challenges.

### **More information (see Pages 19 ff.)**

23. Which products should be prioritized for testing on receipt?
24. Which products should be prioritized for testing in the supply chain?
25. What information will the laboratory need to advise PRs on a QC testing plan?
26. What methods should be used for QC testing?
27. What QC tests should be performed?
28. Can screening technologies be used to test pharmaceutical products?
29. Should products of the same batch be tested more than once?

## Sampling

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Once a QC testing plan is established, PRs should organize sampling of products on receipt and in the supply chain in accordance with the pre-defined QC testing plan and an adequate SOP. In addition, QC testing can be organized “by exception” if products with suspected quality problems are found in the supply chain.

To obtain valid QC testing results the samples must be handled in such a way to prevent damage and mix-ups until they reach the laboratory. Samples should only be taken by trained and qualified staff in accordance with written instructions.

### **More information (see Pages 23 ff.)**

30. Should batches be quarantined if they are sampled in the supply chain?
31. What is “a sample”?
32. What is random sampling?
33. How many dosage units should be collected per sample?
34. How should the dosage units for the sample be selected?
35. Should bulk packs be sampled?
36. What documentation should be included with the sample?
37. What should be considered when preparing samples for transport?
38. Where can PRs find technical guidance on sampling?

## Interpreting QC testing results

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It is important to ensure that QC testing results are confirmed before they are reported further. Wrongly interpreted results may lead to wrong decisions, which can be costly and can cause reputational damage to the PR, the treatment programme and the manufacturer. A standard operating procedure must therefore be agreed with the QC laboratory to confirm results that are outside defined specification limits.

**More information (see Pages 26 ff.)**

- [39. How to read a QC testing report](#)
- [40. What is the difference between the manufacturer's CoA and an analytical report from an independent laboratory?](#)
- [41. What happens if a sample does not meet specifications?](#)

## Reporting QC results to the Global Fund

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For grant-funded products received in country from 1 January 2013, PRs should report results of QC testing performed by the approved contracted QC laboratory as part of periodic reporting, for verification by the LFA.

All QC testing results should be kept on record by the PR until at least one year beyond the expiry date of the product.

**More information (see Pages 27 ff.)**

- [42. Is there a recommended format for reporting of QC results to the Global Fund?](#)
- [43. Should PRs report the results of QC testing done by a laboratory that is not WHO-prequalified or ISO 17025-accredited?](#)
- [44. What should be reported if no QC testing was organized?](#)

## MORE INFORMATION

### Essential QA measures

#### 1. An MIS and SOPs should be in place throughout the supply chain – what are those?

**Management information system (MIS):** An MIS to keep track of products throughout the supply chain is essential for product recalls and will also help to prevent fraud. However, computerized systems do typically not extend beyond the central level. At peripheral level, some other system such as stock cards and local computer records must be maintained to trace products, batches and quantities.

Supporting documentation must be kept for all stock movements and related action taken, from order and release into the supply chain through storage and distribution to end users, or rejection and disposal of products.

**Standard operating procedures (SOPs):** The 2013 revision of the WHO MQAS (1) offers a list of suggested SOPs in each of its Modules (Purchasing, Receiving, Storage and Distribution). It also provides instructions and examples of how to write an SOP, and how to keep track of changes whenever the SOP is updated. Staff should be trained in using SOPs. ([Back](#))

#### 2. What are the main QA principles in procurement?

QA in procurement sets the quality standards and specifications that will subsequently be monitored in the country. If a prequalification system is in place to select products of assured quality, the risk of quality failures in the supply chain will be reduced. The most important QA-related building blocks in procurement are:

- Technical specifications for products, packaging and shelf life in line with QA policy requirements
- A list of products and suppliers identified for purchasing<sup>2</sup>
- QA-related contract provisions, e.g. a Certificate of analysis (CoA) to be supplied with each batch, permission for Global Fund to publish the results of independent QC testing, and action to take if supplied products do not meet agreed specifications, e.g. replacement at the manufacturer's cost
- A system to monitor supplier performance

► Relevant guidelines: 1 (MQAS - Module III) ([Back](#))

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<sup>2</sup> For ARVs, antimalarials and anti-TB products the Global Fund maintains lists of products classified by their quality status as per the requirements of its QA Policy. See

<http://www.theglobalfund.org/en/procurement/quality/pharmaceutical/#Lists>

### **3. What are the main QA principles on receipt of products?**

QA measures on receipt at the port of entry or central point of delivery aim to ensure to clear goods safely and promptly from the port of arrival, to verify that what was received is what was ordered, and to ensure that only products meeting specifications are authorized for release into the supply chain. All consignments must be quarantined on arrival. The goods and related documentation must be inspected and the findings documented in a goods inspection report.

To check compliance with specifications, PRs should organize QC testing of selected batches according to a pre-defined QC testing plan and “by exception” in case of suspect products. The goods should be kept in quarantine until the results are received. For the remaining batches, PRs should review the manufacturer’s CoA (see also Questions **39** and **40**) as part of goods inspection on arrival. Trend analysis of CoA results for specific products can be performed in consultation with the QC laboratory, and in case of out-of-trend results the QC testing frequency can be increased.

► Relevant guidelines: **1** (MQAS - Module IV) ([Back](#))

### **4. What are the main QA principles in storage of products?**

QA measures during storage at central warehouses, peripheral stores (regions, districts) and health facilities (hospitals, health centres, clinics) aim to protect the products from damage and tampering and to ensure that products are not close to expiry when they reach the patients. This is achieved mainly through temperature and humidity control, access control at the storage site, and regular checks of stock and expiry dates.

► Relevant guidance: References **1** (MQAS Module IV) and **2**. For further reading on waste management, see Reference **3**. ([Back](#))

### **5. What are the main QA principles in distribution of products?**

QA in distribution aims to get products that meet agreed specifications safely and promptly to authorized recipients. As in storage, temperature control (including cold chain) and security are the main issues.

► Relevant guidance: References **1** (MQAS Module V) and **4**. ([Back](#))

### **6. What steps should be followed if a quality issue is detected?**

Quality issues must be handled in such a way that products which are suspected or confirmed not to meet specifications will not be distributed to end users or diverted for resale. The main steps are:

- Quarantine the product as “NOT FOR USE”. Depending on the nature of the problem, quarantine the whole batch, including at other sites if necessary.
- Confirm the quality issue: Organize QC testing or re-testing by the contracted laboratory if needed. Some quality failures may be obvious and may not need further confirmation.

- If quality issues are confirmed, inform the Global Fund, the NMRA and the marketing authorization holder in writing and obtain authorizations for further action.
- Return or recall the product in collaboration with the manufacturer and the NMRA.

► Relevant guidance: **1** (MQAS, see Module IV, “Rejected materials”). For information on safe disposal of pharmaceutical products see Reference **3**.  
([Back](#))

## Quality monitoring requirements

### 7. What are the objectives of quality monitoring in grant-funded programmes?

Quality monitoring aims to ensure that Global Fund-financed medicines meet quality standards as defined in the QA Policy until they reach the end users.

Provided that essential QA measures are in place all along the supply chain, the results of QC testing will enable the PR to:

- (1) provide evidence that the medicines reaching patients in grant-funded programmes do generally meet the specifications that are set for them,
- (2) identify products or batches not meeting specifications and remove them from the supply chain, and
- (3) obtain information to support gap analysis and risk management in the supply chain. ([Back](#))

## The role of national systems

### **8. What can be done to facilitate registration or authorization?**

It is the responsibility of manufacturers to obtain marketing authorization for their products in countries. Some national regulatory authorities have mechanisms in place to fast-track registration of WHO-prequalified and/or SRA-authorized products, or to waive the registration requirements altogether. Where this is not the case, the WHO collaborative registration procedure can be considered in countries participating in this initiative. Under this procedure WHO will share prequalification assessment information confidentially at the request of the manufacturer, and if NMRAs accept to collaborate for a specific product they will issue their registration decision within 90 days from receiving access to the shared information.<sup>3</sup> ([Back](#))

### **9. How can PRs support existing surveillance and pharmacovigilance systems?**

PRs should support existing national systems for post-market surveillance and pharmacovigilance whenever possible.

Post-market surveillance aims to detect quality issues with products circulating in countries. It should take into account both formal complaints as well as reports on medicines quality problems from the community, for example health care workers or patient support groups. These actors have an important role to play in detecting quality issues, including those caused by fraud (see Reference 5 for further reading).

Pharmacovigilance aims detect adverse effects or any other possible drug-related problems. It is critical when pharmaceuticals – including new medicines – are deployed for large scale use. PRs can support pharmacovigilance by participating in the worldwide pharmacovigilance network known as the WHO Programme for International Drug Monitoring (6).

The country dialogue process should be used to encourage integration of quality monitoring processes into existing national programmes. Guidelines and formats available at national level should be used as much as possible. ([Back](#))

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<sup>3</sup> [www.who.int/prequal](http://www.who.int/prequal) - “ Collaborative registration”

## Quality risk management in the supply chain

### 10. What are some examples of quality risks, and how should they be monitored?

Not all risks should be investigated by QC testing (see also under “QC testing plan”). In many cases, questions and indicators observed for example at monitoring visits will be sufficient to identify the gaps to be addressed. An example is shown below, followed by an overview of possible quality risks and possible strategies if QC testing is to be organized. ([Back](#))

#### Example

**Risk:**  **Poorly controlled storage conditions at peripheral level**

▶ **Questions:** Is the temperature at peripheral stores monitored? Is the monitoring reliable? Are actions taken in case of temperature excursions?

▶ **Indicator:** How many temperature excursions were recorded at each store each month in the last 6 months?

Training and/or upgrading measures should be considered where temperature control is a problem.

▶ **QC testing** (if planned – see also Question [24](#)): How many samples fail QC testing at the five stores with the most frequent temperature excursions?

|                                 | <b>Quality risks may arise in case of:</b>   | <b>Possible QC strategies*</b>  |
|---------------------------------|--|---|
| <b>Procurement</b>              |  Decentralized procurement channels<br> Frequent emergency orders<br> Poorly defined specifications ... etc. (see Question <a href="#">23</a> ) | ▶ Sample products on receipt, focus on occurrence-related risks   |
| <b>Port clearance</b>           |  Long shipping routes, many stops<br> Frequent delays at port<br> Doubtful port storage conditions ...etc.                                      | ▶ Sample on receipt to detect damage and tampering  |
| <b>Storage</b><br>Central level |  Large buffer stocks<br> Seasonal peaks or campaigns<br> Repackaging or relabeling done <sup>4</sup> ...etc.                                    | ▶ Sample products with long storage history and sensitive stability   |
| Peripheral level                |  Many different stores<br> Poorly controlled storage conditions<br> Poor stock management ...etc.   | ▶ Sample strategically to diagnose the problem  |
| <b>Distribution</b>             |  Complex distribution chains<br> Private or contracted-out systems<br> Frequent emergency deliveries ...etc.                                    | ▶ Sample close to patient level, pursue upstream as needed  |
| <b>Vigilance</b>                |  No post-market surveillance system<br> No adverse reaction reporting  | ▶ Sample close to patient level, focus on exposure- and harm-related risks (see Question <a href="#">23</a> ) |

Note: \* Not all risks need to be investigated by QC testing (see also under “QC testing plan”).

<sup>4</sup> Repackaging and relabelling should be minimized as much as possible. Where it cannot be avoided it must be performed with the permission of the marketing authorization holder and under WHO, PIC/S or SRA GMP conditions.

**11. How is quality risk management different from the periodic assessment of PSM risks by the Global Fund and LFAs?**

The procurement and supply management (PSM) arrangements are assessed by LFAs and the Global Fund at a certain point in time, sometimes only through desk review of documents. This assessment will not capture all the complexities of QA and QC systems in practice as they evolve over time.

Ongoing quality risk management should aim to capture these complexities, and to identify and address any gaps. ([Back](#))

**12. What measures can be envisaged to manage the risks?**

The principle of risk management is to prioritize available resources to address the most urgent risks first. Some risks may be outside the control of PRs, while others may be relatively minor and may not need to be addressed as a priority. For example if sourcing of quality-assured pharmaceuticals is a major problem PRs can consider to upgrade the procurement systems or to use pooled procurement services. If there are issues with storage conditions, PRs can consider to upgrade the stores and/or to review the distribution strategy to minimize the storage times of products under inadequate conditions. ([Back](#))

## Managing quality monitoring

### 13. What quality monitoring activities should be planned?

Planning for quality monitoring should include risk-based QA and QC activities as outlined in this guide as far as they are not already covered in the PSM plan. An illustrative template is shown below. The items to include depend on the context and priorities identified for each grant. ([Back](#))

#### Quality monitoring timelines, budgets and expenditure

(illustrative, adapted from: Reference 7, Annexes 9 and 10)

|   | Year 1 |    |    |    | Year 2 |    |    |    |
|---|--------|----|----|----|--------|----|----|----|
|   | Q1     | Q2 | Q3 | Q4 | Q1     | Q2 | Q3 | Q4 |
| <b>General</b> E.g. coordinator, staff time, training, MIS, SOPs... (specify) |        |    |    |    |        |    |    |    |
| <b>Purchasing</b> (list items as appropriate ...)                             |        |    |    |    |        |    |    |    |
| <b>Receipt and port clearance</b> (...)                                       |        |    |    |    |        |    |    |    |
| <b>Storage</b>  |        |    |    |    |        |    |    |    |
| <i>At central level (...)</i>   |        |    |    |    |        |    |    |    |
| <i>At peripheral level (...)</i>  |        |    |    |    |        |    |    |    |
| <i>At health facility level (...)</i>   |        |    |    |    |        |    |    |    |
| <b>Distribution</b> (...)   |        |    |    |    |        |    |    |    |
| <b>Other</b> – e.g. Pharmacovigilance (...)                                   |        |    |    |    |        |    |    |    |
| <b>QC testing</b>   |        |    |    |    |        |    |    |    |
| Method transfer at laboratory   |        |    |    |    |        |    |    |    |
| Routine testing   |        |    |    |    |        |    |    |    |
| Training on sampling  |        |    |    |    |        |    |    |    |
| Visits to facilities for sampling   |        |    |    |    |        |    |    |    |
| Transport of samples  |        |    |    |    |        |    |    |    |
| Reporting   |        |    |    |    |        |    |    |    |
| Record-keeping for batch traceability   |        |    |    |    |        |    |    |    |
| (...)   |        |    |    |    |        |    |    |    |

The activities should be implemented according to a work plan with a budget and defined indicators. Progress should be monitored. ([Back](#))

### 14. What expertise is needed to manage quality monitoring activities?

It is recommended that the person appointed by the PR to coordinate quality monitoring activities and liaise effectively with the NMRA should have experience in pharmaceutical procurement and quality assurance. In countries where there is more than one PR managing pharmaceutical products, quality monitoring activities for all the Global Fund-financed pharmaceutical supply management activities should be coordinated.

If the NMRA has adequate capacity and resources, it can be involved in quality monitoring activities such as inspection of consignments, sampling, interpretation of out-of-specification results, monitoring of storage facilities or medicines disposal. ([Back](#))

**15. Is there a timeline for implementing quality monitoring?**

The essential QA measures outlined in this guide should be implemented from the start of the grant and should be maintained and strengthened thereafter on an ongoing basis. Contracting a QC laboratory may take up to six months in most cases; thereafter QC testing can be phased in as agreed with the laboratory.

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**16. What approximate amount can be budgeted for quality monitoring activities?**

The cost of quality monitoring activities depends on the medicines procured and on the quality risks present in the particular grant. Guidance developed for UNDP-managed Global Fund grants (7) suggests to budget 2-3% of the total value (Ex-Works) of the medicines procured for quality-related activities – 2% in case of high procurement value and 3% in case of low procurement value. [\(Back\)](#)

**17. Can grant funds be used to test medicines that are not financed by the Global Fund?**

No, only the cost of QC testing of products procured with Global Fund grant funds will be covered. [\(Back\)](#)

**18. What costs can be budgeted for capacity-building?**

Funding of capacity building-measures will be considered on a case-by-case basis as part of the country dialogue process, and will be validated by consulting with WHO or other technical partners as part of this process. Capacity-building measures are most beneficial if they contribute to improving national health systems. Examples include:

- Capacity-building at national QC laboratories or any other national entities involved in quality monitoring
- Upgrading of national QC laboratory or other public sector laboratories (if any) to WHO- or ISO 17025 standards
- Upgrading of national stock management systems and processes (e.g. storage, warehousing, distribution, documentation, reporting)

Complementarity should be ensured, i.e. there should be no duplication of funding from different sources for the same activities. [\(Back\)](#)

## QC laboratory

### 19. What is the role of laboratories that are not WHO-prequalified or ISO 17025-accredited?

Laboratories that do not meet the Global Fund requirements cannot be contracted for QC testing using Global Fund finance. Such laboratories may be encouraged to work towards ISO-accreditation or WHO prequalification<sup>5</sup>. The cost and benefits of achieving and maintaining these standards should be considered. Regional cooperation can be considered for cost-effective use of QC testing expertise and resources. ([Back](#))

### 20. How can PRs identify a laboratory that meets the required standards?

A [list of QC laboratories](#) that meet the Global Fund's minimum requirements for QC drug testing laboratories is maintained on the Global Fund's website. It includes WHO prequalified laboratories and those ISO 17025 laboratories that have been determined by the Global Fund to meet its minimum requirements. PRs that identify additional ISO 17025 laboratories, not yet listed on the Global Fund's website, can provide details to the QA officer at the Global Fund by completing the required [questionnaire](#) and submitting the necessary documents.

If a laboratory meets the required standards it will be added to the list on the Global Fund website.

Apart from complying with the standards required by the Global Fund QA Policy, the laboratory should offer the required type of tests according to product specifications (see Question [27](#) about tests to be performed). For example not all laboratories undertake microbiological testing. ([Back](#))

### 21. When should more than one laboratory be selected?

Selecting a single QC laboratory that can perform all required tests is preferable in most cases, as working with two laboratories will add logistic challenges. If this is not possible, PRs can contract a second laboratory. In some situations, the selected QC laboratory may subcontract another laboratory to do specific types of tests, such as microbiological testing. In this case, the subcontracted laboratory must also be WHO-prequalified or ISO 17025-accredited, and its details must be provided to the Global Fund. ([Back](#))

### 22. How should costs be evaluated?

If PRs have a choice between several qualified laboratories they should request quotations specifying the routine cost per batch required for complete testing of the product and the cost of method transfer for products that require testing as per the manufacturer's method. ([Back](#))

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<sup>5</sup> See [www.who.int/prequal](http://www.who.int/prequal)

## QC testing plan

### 23. Which products should be prioritized for testing on receipt?

QC testing on receipt should focus on those product categories that do not need to be WHO-prequalified or SRA-authorized under the Global Fund QA Policy, such as medicines to treat opportunistic infections. ERP-reviewed products do not need to be tested on receipt since they have been tested by an independent laboratory before shipment, nor do batches manufactured up to 3 months earlier need to be tested on receipt unless specific risks related to transport have been identified.

Batches should be selected randomly for testing (see also Question 32). The frequency of testing should be highest for the products with the greatest risks, as shown below. (Back)

### Product-related quality risks and illustrative testing frequencies

**Illustrative only**, to be discussed with the QC laboratory

**Legend:** ●●● Test all batches | ●● Test 20-50% of batches | ● Test 10-20% of batches  
○ QC testing not a priority unless a specific risk factor justifies the testing

| Types of risk<br>Types of products   | Testing frequency |
|--|-------------------|
| <b>Occurrence-related risk: The risk of quality defects occurring</b>  |                   |
| <b>Stability</b>   |                   |
| Products requiring storage below 8°C<br>Products containing an unstable API<br>Products with a total shelf life < 2 years<br>Liquids   | ●●                |
| <b>Complex formulation, challenging to manufacture</b>   |                   |
| Products with a biological active substance  | ●●                |
| Fixed-dose combinations (FDCs)<br>Tablets or capsules with less than 5mg dose<br>Products requiring sterile production or sterile APIs | ●                 |
| <b>Unknown or unstable manufacturing quality</b>   |                   |
| Products with quality problems reported during the past year, or WHO alert published on WHO website <sup>6</sup>                       | ●●●               |
| No stringent GMP certificate   | ●●●*              |
| Recently licenced, not previously procured   | ●●                |
| Another product of the same manufacturer had a documented quality issue in the past year   | ●                 |
| Products containing an API that is in global short supply  | ●                 |
| <b>Risk of illicit product infiltrating the supply chain</b>   |                   |
| High price differentials, high-value products  | ●                 |
| <b>Exposure-related risk: The extent of harm if a failure occurs</b>   |                   |
| Large numbers of patients treated<br>High product value  | ●                 |
| <b>Harm-related risk: The severity of harm if a quality defect occurs</b>  |                   |
| e.g. Life-saving medicines, emergency medicines  | ●                 |

\* Products produced at a site that does not comply with GMP as certified by WHO, an SRA or PIC/S are not recommended to be procured with Global Fund finance. (Back)

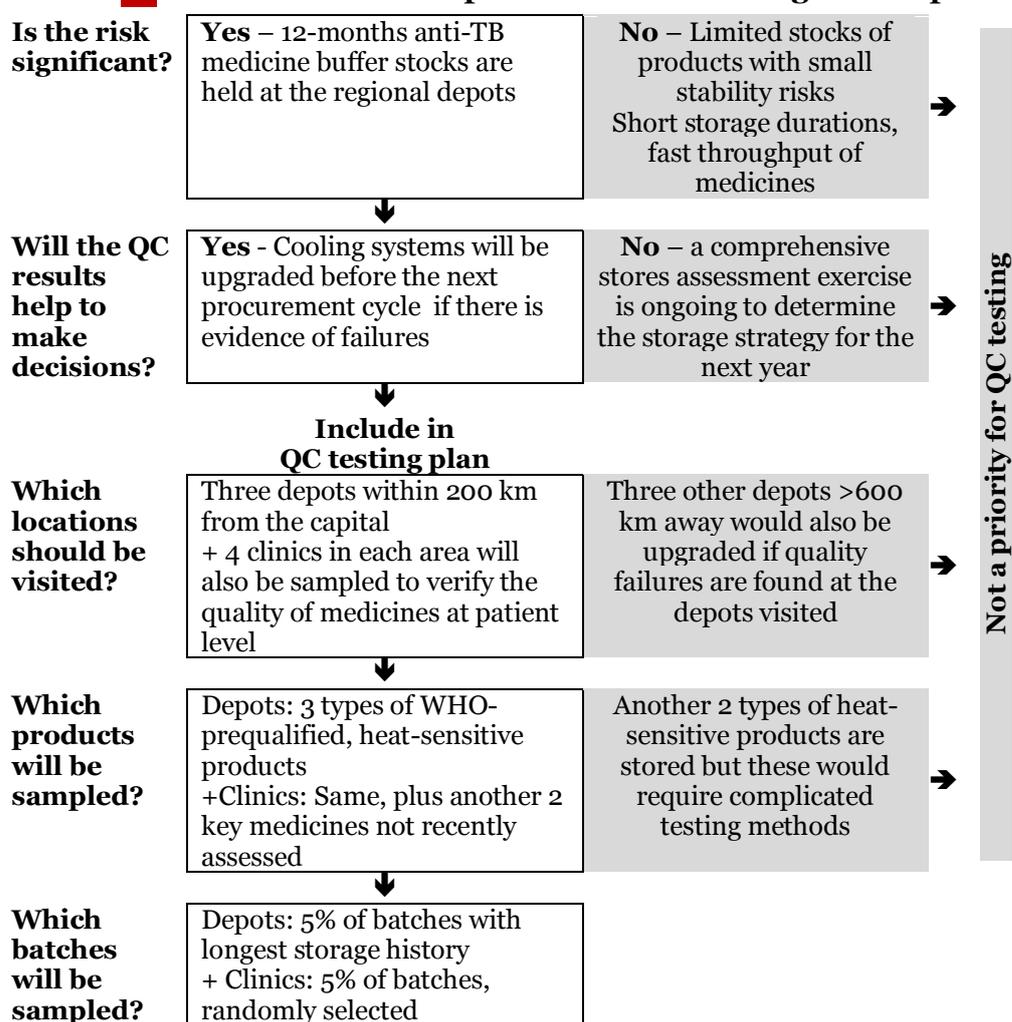
<sup>6</sup> WHO drug alerts: <http://www.who.int/medicines/publications/drugalerts/en/>

## 24. Which products should be prioritized for testing in the supply chain?

QC testing in the supply chain should be done on all types of medicines, including WHO-prequalified, SRA-authorized and ERP-reviewed medicines. The quality monitoring coordinator should discuss with the QC laboratory which products should be sampled at which locations under the the QC testing plan. Supply chain-related risks (see Question 10) as well as product-related risks (see Question 23) should be considered. Testing could be organized to explore the magnitude of a problem and/or the impact of corrective measures. An example is shown below. (Back)

### Example:

#### Risk: ? Less-than-ideal temperature control at regional depots



(Back)

## 25. What information will the laboratory need to advise PRs on a QC testing plan?

PRs should provide the QC laboratory with a list of products procured with Global Fund resources, including their quality status, quantities and other relevant information as shown in the example below. ([Back](#))

### Example of product-related information to provide to the QC laboratory

|   |   |
|---|---|
| Product:                                | Ampicillin, 500 mg vial for injection   |
| Manufacturer:                           | XXX Co. Ltd   |
| Storage requirements:                   | Store below 25°C, in a dry place  |
| Global Fund QA Policy classification:   | Not classified (not WHO-prequalified, SRA-authorized or ERP-reviewed)                         |
| Registered or authorized by NMRA:       | Registered  |
| Previously procured from this supplier: | No  |
| Total annual procurement:               | 1.250.000 vials   |
| Usage:                                  | Used at 45 treatment sites  |
| Remarks:                                | Reports of quality issues with other products from XXX Co Ltd in 2009, subsequently addressed |

In addition, a list of sites can be provided where the products are stored and used. Information on location will be relevant in terms of distance from the laboratory and climatic conditions. Any specific risks in the supply chain that may justify QC testing should also be discussed (see Question [24](#)).

## 26. What methods should be used for QC testing?

The contract should require the use of monographs in the latest editions of the International Pharmacopoeia (Ph. Int)<sup>7</sup>, British Pharmacopoeia (BP) or US Pharmacopoeia (USP), if available. If the product requires testing according to the method provided by the manufacturer, the method transfer process should be performed to ensure that the manufacturer's method gives valid results at the contracted laboratory. ([Back](#))

<sup>7</sup> Freely available at [www.who.int/medicines/publications/pharmacopoeia/en/index.html](http://www.who.int/medicines/publications/pharmacopoeia/en/index.html)

## 27. What QC tests should be performed?

The recommended tests are listed below. The final decision on tests to perform should be agreed with the laboratory. ([Back](#))

| Type of test  | On receipt* | In the supply chain* |
|---|-------------|----------------------|
| Appearance, Identification  | ✓           | ✓                    |
| Related substances, water content   | ✓           | ✓                    |
| Assay (quantitative estimation of active ingredients)   | ✓           | ✓                    |
| Dissolution or disintegration test (for solid dosage forms)   | ✓           |                      |
| Uniformity of weight (for solid dosage forms)   | ✓           |                      |
| pH (for solutions)  | ✓           |                      |
| Microbial limit tests (for non-sterile products)<br>Sterility test (for sterile products)<br>Bacterial endotoxins test (for large volume parenterals) | ✓           |                      |

\* See Questions [23](#) and [24](#) on prioritizing products for testing on receipt and in the supply chain.

Additional tests may be requested on a case-by-case basis for example to detect counterfeiting, based on prior experience of the NMRA and/or the PR. Flexibility should be provided in the contract for the laboratory to adapt its charges on a case-by-case basis by prior agreement with the PR if additional tests are needed, or if testing methods change. ([Back](#))

## 28. Can screening technologies be used to test pharmaceutical products?

The use of mobile QC laboratories (such as Minilab®) and other screening technologies may provide a first quick check to detect basic quality problems, but can by no means replace full QC testing. ([Back](#))

## 29. Should products of the same batch be tested more than once?

Products of the same batch can be considered uniform, and duplicate testing should be minimized. More than one sample of the same batch can be taken for example in the following situations:

- In case of specific quality complaints;
- At different locations, to determine the effect of climatic and storage conditions on the quality of the product; and/or
- At different times, to determine the effect of continued storage on product quality. However, this will require a very good back-track system. ([Back](#))

## Sampling

### 30. Should batches be quarantined if they are sampled in the supply chain?

While batches identified for testing on receipt should be quarantined and released only once positive results from the QC laboratory are received, batches sampled for routine testing in the supply chain need not be quarantined and can be used in parallel to the testing. Batches sampled “by exception”, i.e. due to a suspected quality issue, should be quarantined as appropriate in the specific situation. ([Back](#))

### 31. What is “a sample”?

A sample means a specimen of a specific finished product collected at a specific site. All units of one sample must be of the same batch. This means that two specimens of the same batch collected at two different sites represent two samples. ([Back](#))

### 32. What is random sampling?

Random sampling is done in such a way that the chance to be selected is the same for each batch, and that the choice is not foreseeable by the supplier. For example, if 5% of batches are to be sampled on receipt, a table of 100 numbers in random sequence can be consulted. If the first five numbers are 73, 50, 95, 43 and 20, then the 20<sup>th</sup>, 43<sup>rd</sup>, 50<sup>th</sup>, 73<sup>rd</sup> and 95<sup>th</sup> batch in order of arrival will be sampled. ([Back](#))

### 33. How many dosage units should be collected per sample?

The contracted QC laboratory will define the number of dosage units to sample for each product, allowing for validation or method transfer if applicable, testing as per the agreed method, confirmative testing in case of out-of-specification results, and retention samples. ([Back](#))

#### Indicative quantities to be sampled per batch for routine tests

| Dosage form  | Packaging (typical)                             | Number of dosage units or multidose packs to be sampled <b>per batch</b>         |
|--|---|--|
| Tablets and capsules (immediate or modified release, chewable, dispersible etc.) | Blisters, co-blisters, bottles                  | Approx 100 units.<br>For co-packaged products: approx. 100 units of each product |
| Oral solutions/ suspensions, powder for oral solution/suspension                 | Multidose bottles                               | At least 5 bottles   |
| Injections, powder for injection   | Multidose vials                                 | At least 10 vials  |
| Powders for oral solution/suspension; Injections or powders for injection        | Single dose sachets, bottles, vials or ampoules | At least 15 units (20 units if the dose per unit is below 50 mg)                 |

**34. How should the dosage units for the sample be selected?**

Whole, intact original packages with package inserts should be sampled. All the units in a sample must be of the same batch. Only products without apparent quality problems should be taken for routine testing. Samples should have at least six months' remaining shelf life to allow for completion of testing before the product expires. ([Back](#))

**35. Should bulk packs be sampled?**

PRs may decide not to test products supplied in bulk packs (500 or more units per jar/bottle), as sampling whole packages will significantly reduce the stock level available at the site. If bulk packs or other medicines with small stock levels are to be tested, the order quantity should be adjusted beforehand to avoid shortages. ([Back](#))

**36. What documentation should be included with the sample?**

The following documents should accompany each sample to the laboratory.

- A sample collection form (see Annex 2 of Reference 8 for a suggested format, to be adapted as appropriate).
- A checklist of information present on the packaging and in the patient leaflet, if this is to be verified as part of the testing<sup>8</sup>.
- A copy of the manufacturer's batch analysis certificate
- A written request for QC testing with reference to the contract with the QC laboratory
- If samples are to be shipped outside the country, a written statement to facilitate customs transit, indicating that the samples are sent for laboratory testing purposes only, will not be used on humans or animals, have no commercial value and will not be placed on the market. ([Back](#))

**37. What should be considered when preparing samples for transport?**

Each sample should be marked on the outer packaging with the site where the sample was taken, the type of product and the date of sample collection. A simple

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<sup>8</sup> The following information must be present on packaging and labelling:

External (secondary) packaging: Product name, INN, Strength, Dosage form, Batch number, Manufacturing date, Expiry date, Storage conditions, Contents by weight or volume or unit, Name and address of manufacturer/ marketing authorization holder

Primary packaging: Product name, strength, batch number, expiry date, contents by weight or volume or unit

Package leaflet: Indication, pharmacology, dosage & administration, contraindications, warning and precautions, side effects, drug interactions, composition, storage conditions, name and address of manufacturer/marketing authorization holder

This list has been provided by the WHO technical officer in charge of prequalification of QC laboratories.

coding system may be used for this purpose (for example: Kenya/Clinic16/EFZ600mg/21-04-2009).

Samples must be packed in such a way that they can always be identified. For example, each sample can be placed into a plastic zip lock bag with a label showing all information about the sample and the name of the person who did the sampling. If these instructions are followed it is not necessary to mark the primary packing (e.g. blister foil). The plastic bag and the accompanying documents can be placed into a labelled envelope to keep out the light.

The storage conditions for the product indicated on the label, including any cold chain requirements, must be followed throughout transport. The fastest available method of transport should be used. Fast courier service is recommended where hand delivery is not possible. Any anomalies observed on arrival should be recorded on the sample collection form. ([Back](#))

### **38. Where can PRs find technical guidance on sampling?**

Information on organizing in-country sample testing surveys is provided in Reference **8**. Guidelines on sampling in the regulatory context are found in Reference **9**, some of the general principles are also appropriate for sampling by procurement agencies and buyers of pharmaceutical products. ([Back](#))

## Interpreting QC testing results

### 39. How to read a QC testing report

The QC laboratory will issue an analytical test report with a description of the tests done, specifications and limits used, detailed results, conclusions whether or not the sample was found to be within the limits of the specifications used, and a discussion (see Reference **10** for details). A routine check of the report should be done to verify that the specifications and methods are reflected correctly, and that the conclusions are consistent with the acceptance limits and results stated in the report. ([Back](#))

### 40. What is the difference between the manufacturer's CoA and an analytical report from an independent laboratory?

The manufacturer's CoA reflects the QC testing results obtained at the manufacturing site upon release of the batch, using the manufacturer's in-house methods described in the approved regulatory dossier of the product.

An independent QC testing report shows the QC testing results obtained by a laboratory independent of the manufacturer at any stage in the supply chain. Publicly available (compendial) testing methods are typically used if available for the specific product. ([Back](#))

### 41. What happens if a sample does not meet specifications?

**Confirm:** The QC laboratory must have an SOP to investigate and confirm the results.

**Reject the product:** If the out-of-specification result is confirmed, the PR should inform the NMRA, the Global Fund and the manufacturer, and discuss the actions to be taken to reject or recall the product if deemed necessary (see Question **6** for the main steps to follow).

**Address the root cause:** The QC laboratory can advise PRs on possible causes of quality failures, taking into account the nature of the failure, the history of the product and other QC results reported for the same batch (e.g. from other buyers or from testing of retention samples). PRs should then take corrective measures within their control. For example if the failure is attributed to a manufacturing issue the PR could impose pre-shipment testing, change suppliers or explore possibilities for the manufacturer to improve production processes. If products are degraded the PR can upgrade the storage facilities or reconsider the distribution strategy. If illicit products are found, security measures in the supply chain may need to be strengthened. ([Back](#))

## Reporting QC results to the Global Fund

### 42. Is there a recommended format for reporting of QC results to the Global Fund?

The PR should report the results of independent QC testing of Global Fund-financed pharmaceutical products as part of periodic reporting to the Global Fund. A suggested reporting format is given below. CoAs should be attached in case of out-of-specification results. ([Back](#))

### Suggested format for reporting of QC results to the Global Fund

Grant number: .....Period of reporting: .....

#### 1. Summary of QC testing of Global Fund-financed pharmaceutical products organized during the reporting period

Name and address of contracted laboratory: .....

| Name, description and manufacturer of finished product tested | Number of batches received during reporting period | QC testing on-receipt    |  | QC testing in the supply chain |  |
|---|--|--------------------------|--|--------------------------------|--|
|   |  | Number of batches tested | Number of batches with confirmed out-of-specification results* | Number of batches tested       | Number of batches with confirmed out-of-specification results* |
|   |  |                          |  |                                |  |
|   |  |                          |  |                                |  |
|   |  |                          |  |                                |  |
|   |  |                          |  |                                |  |

\* Please complete details under 2. for each batch counted in this column.

#### 2. Out-of-specification results observed and action taken

(Please repeat this section for each confirmed quality failure observed during the reporting period)

Medicine (INN, strength and dosage form).....

Batch number.....

Out of specification result(s) – please attach CoA:.....

Action taken to confirm .....

Action taken after confirmed failure .....

#### 3. Comments

In case of delays or deviations in implementing the QC testing plan, please include a brief description of the reasons, challenges, progress and timelines for implementation or adaptation of the QC testing plan as applicable.

.....  
 .....  
 .....

([Back](#))

**43. Should PRs report the results of QC testing done by a laboratory that is not WHO-prequalified or ISO 17025-accredited?**

No, only results of testing done by WHO-prequalified or ISO 17025-accredited laboratories should be reported. Use of grant funds for testing by other laboratories will be considered as non-compliance with Global Fund requirements. ([Back](#))

**44. What should be reported if no QC testing was organized?**

If no testing was done, the reasons for this should be documented, and progress and expected timelines for implementing a QC system should be reported to the Global Fund. Deviations from the pre-defined QC testing plan should also be documented and the plan should be adapted as needed to ensure that it remains realistic and implementable. ([Back](#))

## **ATTACHMENT 1:**

# **Relevant extracts of the Global Fund QA Policy**

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The full text of the [QA Policy](#) is available on the Global Fund website<sup>9</sup>

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### **MONITORING PRODUCT QUALITY**

24. The quality of the Finished Pharmaceutical Products (FPPs) procured with Global Fund grant funds must be monitored. The cost of conducting QC activities may be budgeted for in the Global Fund grant. PRs must submit to the Global Fund the results of QC tests, which may be made publicly available by the Global Fund.

For all FPPs

25. In collaboration with National Drug Regulatory Authorities (NDRAs), PRs must ensure that random samples of FPPs are obtained at different points in the supply chain - from initial receipt of the FPPs in-country to delivery to end-users/patients - for the purpose of monitoring the quality of such FPPs (including QC testing).

26. Such samples must be sent to NDRA laboratories or NDRA Recognized Laboratories or WHO Prequalified Laboratories or Global Fund contracted laboratory(ies) for QC testing.

27. To ensure the NDRA Laboratories or NDRA Recognized Laboratories have adequate capacity for full pharmacopoeial testing, they must meet one of the following criteria:

(i) Prequalified by the WHO prequalification Programme , or

(ii) Accredited in accordance with ISO 17025

28. The Global Fund will, based on the advice of WHO, provide protocols and SOPs that may be used for QC testing and reporting of results.

29. The Global Fund will request Local Fund Agents to verify whether PRs have complied with the process described in Sections 25 and 26.

30. Technical assistance aimed at strengthening NDRA Laboratories or NDRA Recognized Laboratories may be included in Global Fund proposals.

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<sup>9</sup> [www.theglobalfund.org/documents/psm/PSM\\_QApharm\\_Policy\\_en/](http://www.theglobalfund.org/documents/psm/PSM_QApharm_Policy_en/)

## REFERENCES

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### Notes:

Updated versions of **WHO guidelines on medicines quality assurance** are found at [www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/guidelines/en/index.html](http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/index.html). Guidelines under revision are published for comment in the Section titled “Current projects”.

A series of **QC laboratory training modules** based on WHO guidelines and related guidance is found at

[http://www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/quality\\_control\\_training/en/index.html](http://www.who.int/medicines/areas/quality_safety/quality_assurance/quality_control_training/en/index.html)

The WHO Prequalification Programme for QC laboratories maintains a list of relevant **guidelines on QC** and other useful links on its website at

[http://apps.who.int/prequal/info\\_applicants/qclabs/prequal\\_quality\\_control\\_labs.htm](http://apps.who.int/prequal/info_applicants/qclabs/prequal_quality_control_labs.htm)

- 1 WHO Model Quality Assurance System For Procurement Agencies (MQAS).** Revision. Working document QAS/12.508/Rev.1. To be published as Annex 3 to the WHO Technical Report Series, 2014 (in preparation). The revised working version and related documents are available at [www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/projects/en/index.html](http://www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/index.html)
- 2 WHO Technical Report Series 908. Annex 9: Guide to good storage practices for pharmaceuticals.** Geneva, World Health Organization, 2003.  
[http://www.who.int/entity/medicines/areas/quality\\_safety/quality\\_assurance/GuideGoodStoragePracticesTRS908Annex9.pdf](http://www.who.int/entity/medicines/areas/quality_safety/quality_assurance/GuideGoodStoragePracticesTRS908Annex9.pdf)
- 3 WHO. Guidelines for Safe Disposal of Unwanted Pharmaceuticals in and after Emergencies.**  
[http://www.who.int/water\\_sanitation\\_health/medicalwaste/unwantpharm.pdf](http://www.who.int/water_sanitation_health/medicalwaste/unwantpharm.pdf)
- 4 WHO Technical Report Series No. 957. Annex 5: WHO good distribution practices for pharmaceutical products.** Geneva, World Health Organization, 2010.  
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- 5 US Institute of Medicines (IOM) Committee on Understanding the Global Public Health Implications of Substandard, Falsified, and Counterfeit Medical Products. Countering the Problem of Falsified and Substandard Drugs.** February 2013.  
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- 6 WHO Uppsala Monitoring Centre. **Guidelines for Setting up and Running a Pharmacovigilance Centre.** UMC, 2000.  
<http://www.who-umc.org/graphics/24747.pdf>  
See also the webpage of the Uppsala Monitoring Centre at  
[www.who-umc.org/DynPage.aspx?id=97218&mn1=7347&mn2=7252](http://www.who-umc.org/DynPage.aspx?id=97218&mn1=7347&mn2=7252)
- 7 UNDP: **Quality Assurance Plan for medicines funded by the Global Fund: Information collection.** Available from PSM specialists at the Global Fund Secretariat.
- 8 WHO. **Proposal for a procedure on sampling and market surveillance survey.** Working document QAS/12.510. Draft for comments.  
[http://www.who.int/entity/medicines/areas/quality\\_safety/quality\\_assurance/Samplingprocedure-QAS12-510\\_31082012.pdf](http://www.who.int/entity/medicines/areas/quality_safety/quality_assurance/Samplingprocedure-QAS12-510_31082012.pdf)
- 9 WHO Technical Report Series, No. 929. Annex 4: **WHO guidelines for sampling of pharmaceutical products and related materials.** Geneva, World Health Organization, 2005.  
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- 10 WHO Technical Report Series No. 957. Annex 1: **WHO good practices for pharmaceutical QC laboratories.** Geneva, World Health Organization, 2010.  
[http://www.who.int/medicines/publications/TRS957\\_2010.pdf#page=95](http://www.who.int/medicines/publications/TRS957_2010.pdf#page=95)